E-ISSN 2228-8082
Volume 75, Number 5, May 2023

135 Years Siriraj

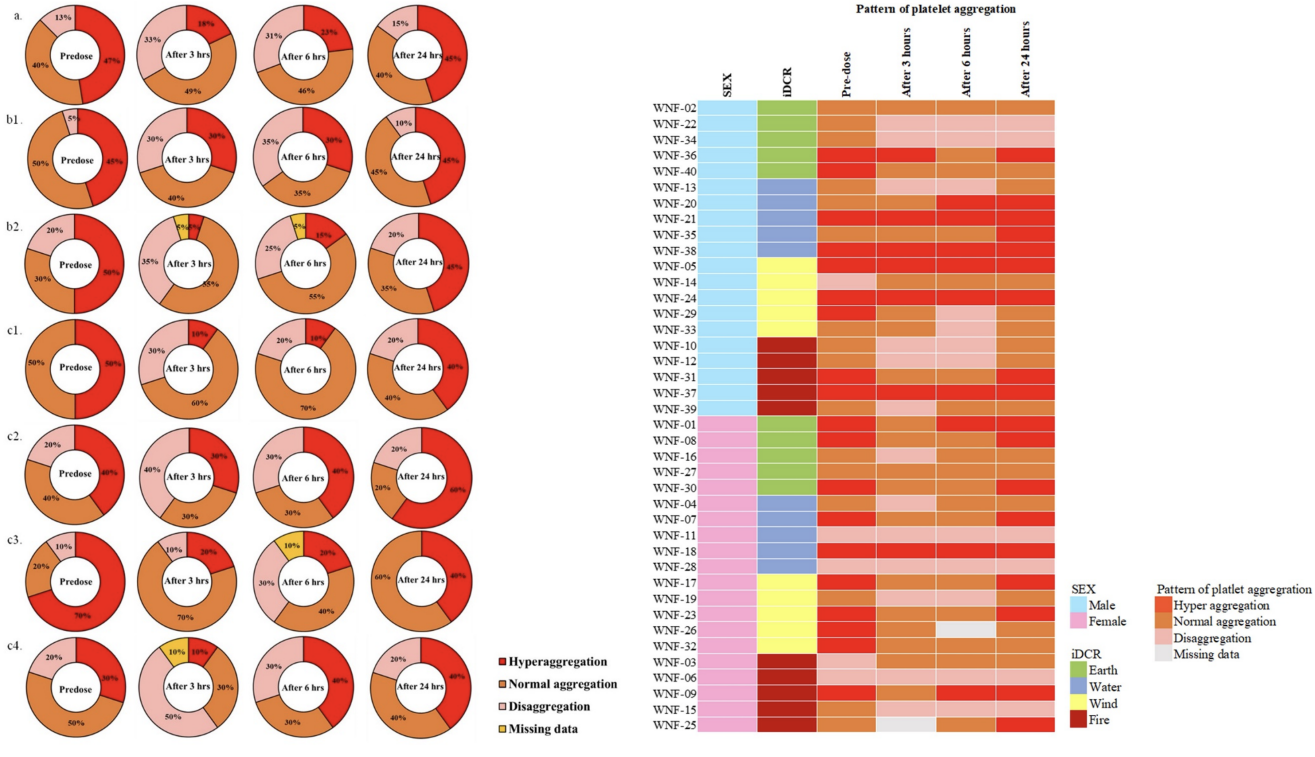
SMJ

Siriraj Medical Journal

The world-leading biomedical science of Thailand

MONTHLY

ORIGINAL ARTICLE



By Suveerawan Limsuvan, et al.

Indexed by Scopus®

Siriraj International Conference in Medicine and Public Health

THAILAND SECTION 1954

https://he02.tci-thaijo.org/index.php/sirirajmedj/index
E-mail: sijournal92@gmail.com

Siriraj Medical Journal SMJ

Volume 75, Number 5, May 2023

ORIGINAL ARTICLE

REVIEW ARTICLE

SIRIRAJ MEDICAL JOURNAL

https://he02.tci-thaijo.org/index.php/sirirajmedj/index

Office: His Majesty the King's 80th Birthday Anniversary 5th December 2007 Building (SIMR), 2nd Fl., Room No.207
Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand Tel: 02-419-2888 Fax: 02-411-0593
E-mail: sijournal92@gmail.com

The effect of the Thai Herbal Wattana Formula on Platelet Aggregation and the Relationship with Innate *Dhatu Chao Ruean*

Suveerawan Limsuvan, M.Sc.*, Titchaphorn Palo, M.Sc., Dollaporn Mamaethong, B.ATM. *, Nut Yuthanarat, B.ATM. *, Suksalin Booranasubkajorn, Ph.D.*, Natchagorn Lumlerdkij, Ph.D.*, Kamonchanok Maneechai, B.ATM *, Pravit Akarasereenont, M.D., Ph.D.*,****

**Center of Applied Thai Traditional medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, **Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.*

ABSTRACT

Objective: To investigate the effects of the Thai Herbal Wattana formula (WNF) on platelet aggregation and find a link between Innate *Dhatu Chao Ruean* (iDCR) factors and platelet aggregation.

Materials and Methods: Forty healthy volunteers with different iDCRs (Earth, Water, Wind, and Fire) received a single dose of 1,000 mg WNF. A blood sample was taken before and after the WNF administration at 3, 6, and 24 hours for analysis of platelet aggregation by aggregometry. Epinephrine, adenosine diphosphate (ADP) and collagen were used as platelet agonists.

Results: The WNF affects platelet aggregation in some subjects, especially females with an Earth iDCR or Wind iDCR with hyperaggregation patterns at baseline. The result after WNF treatment revealed that the percentage of platelet aggregation significantly changed downward at 3 hours and then recovered to pre-dosing levels after 24 hours. Additionally, it also did not have any relationship to iDCR. There were no reported adverse drug events.

Conclusion: WNF should be used with caution in patients with blood diseases and a close eye should be kept on herb-drug interactions such as with aspirin or other NSAIDs.

Keywords: Thai Herbal Wattana formula; WNF; Herbal medicine; Platelet aggregation; innate *Dhatu Chao Ruean*
(Siriraj Med J 2023; 75: 321-329)

INTRODUCTION

New trends regarding good health have generated interest in young people in society. Recently, the use of herbal medicine as an alternative or complementary therapy has increased dramatically in many parts of the world. Thai Traditional medicine refers to the knowledge, skills, and practices passed down from generations of folk healers from many cultures and is used to help maintain health against age-related deterioration, as well as prevent and treat various diseases. As a basic theory, Thai traditional medicine considers the imbalance of four elements (Earth, Water, Wind, and Fire) as an illness. In each person, there will be one element that is more dominant. Innate *Dhatu Chao Ruean* (iDCR) is the dominant body element at birth. It is analyzed by the month of birth and is divided as follows: Earth, from September to November, Water, from June to August, Wind, from March to May, and Fire, from December to February.[1]

Corresponding authors: Pravit Akarasereenont
E-mail: pravit.auk@mahidol.edu
Received 25 February 2023 Revised 20 March 2023 Accepted 21 March 2023
ORCID ID:http://orcid.org/0000-0001-9768-8347
https://doi.org/10.33192/smj.v75i5.261536

The Thai Herbal Wattana formula (WNF) has been used for over 40 years. It is used to help maintain health, and prevent age-related problems, such as muscle pains, loss of appetite, weaknesses, digestion, and gastrointestinal problems. The 18 medicinal plant components in the formula are *Boesenbergia rotunda* (L.) Mansf, *Saussurea lappa* C.B. Clarke., *Ligusticum sinense* Oliv. cv. Chuanxiong, *Cinnamomum illicioides* A. Chev., *Carthamus tinctorius* L., *Mallotus repandus* (Willd.) Muell. Arg., *Cladogynos orientalis* Zipp. ex Span., *Derris scandens* (Roxb.) Benth., *Cryptolepis buchanani* Roem. & Schult., *Tinospora crispa* (L.) Hook.f. & Thomson, *Caesalpinia sappan* L., *Piper nigrum* L., *Ferula assa-foetida* Regel, *Drypetes roxburghii* (Wall.) Hurusawa, *Aegle marmelos* (L.) Corrêa, *Citrus sinensis* (L.) Osbeck, *Terminalia chebula* Retz. and, *Cyperus rotundus* L. The recommended dose is 3-5 pills (200 mg/pill), 3 times per day before meals. The indication of this drug is older people (aging in Thai traditional medicine is defined as aged 32 and over). Moreover, the WNF has been investigated by many scientific studies to explain its pharmacological activities relating to age degeneration, including anti-oxidation[2], immunomodulatory[3,4] anti-neurodegenerative,[5] and anti-inflammatory properties.[6] Anti-inflammation is one effect linked to WNF's ability to ease muscle pain compared to diclofenac in OA knee patients.[7] The WNF may work similarly to NSAID inhibition. NSAIDs provide a COX inhibition that prevents synthesis of thromboxane A2. It is also effective at inhibiting platelet aggregation.[8] Understanding antiplatelet medications that balance anti-thrombotic potential with the danger of bleeding is still a concern. Therefore, this study aimed to investigate the impact of the Thai Herbal Wattana formula on platelet aggregation in healthy volunteers. This will help understand the safety of the WNF and any potential unwanted side effects. Moreover, it will be interesting to investigate the relationship between factors of innate *Dhatu Chao Ruean* and the impact of platelet aggregation on herbal drugs to better understand specific responses to provide personalized health care.

MATERIALS AND METHODS

Study drugs

WNF pills (200 mg) and powder were manufactured under GMP PIC/S (Good Manufacturing Practices) by the Manufacturing Unit of Herbal Medicines and Products, Center of Applied Thai Traditional Medicine (CATTM), Faculty of Medicine Siriraj Hospital, Mahidol University. The experiments used the same batch of WNF pills in the study. All WNF pills were authenticated and qualified by quality control, including the FTIR method, UPLC method, physical properties, and microbial contamination. WNF pills and powder were stored and preserved at room temperature in dry conditions.

Subject design

This controlled pre-post intervention study was conducted at the Faculty of Medicine Siriraj Hospital, Bangkok, Thailand. The protocol was approved by the Siriraj Institutional Review Board (COA no. Si 756/2019) and registered in the Thai Clinical Trials Registry (TCTR20221213002). Before enrolling in the study, participants were provided necessary information, including the risks and benefits and signed an informed consent form. For the pilot study, 40 healthy volunteers with four different innate *Dhatu Chao Ruean* (Earth, Water, Wind and Fire) were recruited. The following criteria was used for inclusion: 1) Thai male or female ≥ 32 years old at time of enrollment; 2) body mass index (BMI) between 18-24 kg/m^2 ; 3) in good health as confirmed by blood chemistry, or an AST ≤ 40 U/L (male), ≤ 32 U/L (female); ALT ≤ 41 U/L (male), ≤ 33 U/L (female); ALP ≤ 141 U/L (male), ≤ 105 U/L (female) and GFR ≥ 60 ml/min/1.73m^2. The exclusion criteria were: 1) evidence of allergic reactions from herbal medicine; 2) habitual smoking with no ability to abstain from cigarettes during the study; 3) history of excess alcohol ingestion without ability to abstain from alcohol during the study or drug abuse; 4) pregnant or breastfeeding; 5) history of blood donation or transfusion within 3 months of the study. The volunteers who had an adverse event caused by WNF or believed to have had an event as were withdrawn as per physician agreement. All participants received advice to prepare themselves prior to the study and were informed to abstain from caffeine, alcohol and intake of vitamins, dietary supplements, and foods containing any of the 18 components of the WNF for at least two weeks. Moreover, other information or concerns from volunteers was followed up on and proper advice provided. On experiment day, blood samples were drawn and kept in sodium citrate vacutainer (Greiner Bio-one GmbH, Austria) at pre-dose for baseline, 3, 6, and 24 hours after administration of 1,000 mg WNF. Moreover, vital signs and all reported adverse events were evaluated and recorded by study physicians.

Platelet aggregation assay

Platelet aggregation was determined using light transmission (LTA) and Born's technique in an aggregometer (AggRAM, Helena, USA). LTA is the gold standard for determination of platelet aggregation by measuring the change in absorbance as platelet-rich plasma (PRP) is

agitated with reagents. Epinephrine (Epi), adenosine diphosphate (ADP), and collagen (Col) were used as a panel of platelet agonists.[9] All platelet aggregation assays were run within 3 hours of blood collection. Citrated whole blood was centrifuged at 250g for 10 minutes at 25°C to prepare PRP. Some PRP was centrifuged at 4500g for two minutes at 25°C to prepare platelet-free plasma (PFP) to set as a blank. PRP was incubated at 37°C for 3 minutes before being induced with 1μM Epi, 25 μM Epi, 5 μM ADP and 1 μg/ml Col while stirring at 600 rpm. The reaction was allowed to proceed for 5 minutes. The difference between light transmissions of aggregated PRP and PFP was used to calculate the maximal amplitude of platelet aggregation as a percentage. Moreover, the platelets count was measured by using a non-metalized haemocytometer (Helena, USA).

Platelet status classification

There is still a need for a formally accepted standard for measuring platelet function. The previous method classified the function into 3 categories of aggregation based on how platelets responded to various epinephrine concentrations.[10,11] The primary phase of platelet aggregation, caused by 25 μM epinephrine, is defined by the "disaggregation pattern". In contrast, platelet aggregation caused by 1 μM epinephrine and expressed as the secondary phase of aggregation is known as the "hyperaggregation pattern". Therefore, the concentration-dependent response of platelets to 1 μM and 25 μM epinephrine was labeled as the "normal aggregation pattern".[10,11]

Statistical analysis

All data was presented as mean ± standard deviation (SD). Statistical analyses were performed with SPSS, version 18 (SPSS Inc., Chicago, IL, USA). Platelet aggregation data was evaluated for normality using the Kolmogorov–Smirnov and Shapiro-Wilk tests. Group comparisons were performed by a nonparametric Mann-Whitney U test (between gender) and the Kruskal-Wallis test (between iDCR). Time-dependent changes (before and after WNF administration) in groups were assessed by the nonparametric Friedman test; pairwise post hoc comparisons. Moreover, the chi-square statistic was used for categorical variables. Analyses were declared significant for a *P-value* <0.05.

RESULTS

Demographic characteristics

Forty healthy volunteers were enrolled in this study from March 2020 to August 2020. All subjects completed the study. The average age of the male group and female group was 36.3±3.9 and 39.1±5.9, respectively. The baseline characteristics, clinical chemistry, and hematologic screening of all subjects were normal. All data was homogeneous at the baseline. There was no difference between the sex groups (Table 1).

Platelet status pattern before dosing

Before WNF treatment, 47% of the total 40 subjects exhibited the hyperaggregation pattern while 40% and 13% exhibited the normal and disaggregation pattern (Fig 1a). A comparison of, male and female platelet aggregation status before dosing did not significantly differ between the two groups (Figs. 1b1-1b2). Among the iDCR group, more than half of the subjects in the Wind group (70%) exhibited the hyperaggregation pattern (Fig 1c3). However, platelet status patterns of subjects in the Wind, Earth, Water and Fire group were not significantly different (Figs 1c1-c4).

Effect of WNF on platelet aggregation

To assess the impact of the WNF on each subject, each individual subject's pattern of platelet aggregation stratified to sex, and iDCR is shown in Fig 2. The total result after WNF treatment revealed that the pattern of platelet aggregation status changed at 3 and 6 hours, and then recovered to pre-dosing levels after 24 hours. In the female group, especially those in the Earth or Wind iDCR, the hyperaggregation pattern was almost downward (Fig 2). The percentage of platelet aggregation for each agonist is shown as a heat map in Fig 3. The average of the percentages of aggregation decreased at 3 and 6 hours and then reverted to pre-dosing levels after 24 hours (Fig 4). However, the WNF also revealed an interesting trend of increased platelet aggregation classified as disaggregation status (Figs 4c1-3). In this study, platelet aggregation did not have any link to gender (Figs 4b1-4b2). Additionally, it also did not have any relationship to iDCR even if platelet aggregation in the Earth and Fire group significantly decreased after WNF treatment (Figs 4d1-4).

At each investigation time point, the average platelet counts were within an acceptable range (150-750 x 10^9 cells/L) and did not impair LTA experiments.[12] The average platelet count of 40 PRP subjects at pre-dose, 3, 6, and 24 hours after WNF administration were 366 x 10^9 cells/L, 298 x 10^9 cells/L, 307 x 10^9 cells/L, and 369 x 10^9 cells/L, respectively. The results showed a decreasing trend at 3 and 6 hours of dosing before reverting to pre-dosing levels after 24 hours.

TABLE 1. Demographic data and baseline laboratory values with reference range criteria.

Topic	Mean + SD		Reference range	
	Male (n=20)	Female (n=20)	Male	Female
Age (years)	36.3±3.9	39.1±5.9	≥ 32	
iDCR (4 elements)				
EARTH (Sep-Nov)	5	5		
WATER (Jun-Aug)	5	5	-	
WIND (Mar-May)	5	5		
FIRE (Dec-Feb)	5	5		
Vital sign				
Temp (°C)	36.5±0.3	36.3±0.3	-	
Pulse rate (/min)	69.0±7.6	73.1±7.4	-	
Respiratory rate (/min)	18.3±0.7	18.1±0.4	-	
Blood pressure (mmHg)				
Systolic	112.8±10.4	110.7±11.6	-	
Diastolic	70.7±11.6	68.9±9.5	-	
Body weight (kg)	65.1±8.3	53.8±5.5	-	
Height (cm)	171±0.1	159±0.05	-	
Body mass index (kg/m^2)	22.1±1.9	21.2±1.7	18-24	
Hb (g/dL)	14.9±0.9	12.5±1.1	12.70-16.90	12.0-14.90
Hct (%)	44.7±2.3	38.2±2.8	40.30-51.90	37.0-45.70
WBC (x 10^3/uL)	5.7±1.3	6.0±1.5	4.50-11.30	4.40-10.30
Platelet (x10^3/uL)	270.2±49.8	246.2±42.1	160-356	179-435
FBS (mg/dL)	86.7±6.0	87.2±5.1	74-99	
BUN (mg/dL)	12.2±2.9	10.7±2.8	6-20	
Creatinine (mg/dL)	1.0±0.1	0.7±0.1	0.67-1.17	0.51-0.95
eGFR	98.9±13.2	109.9±12.4	≥60	
Total cholesterol (mg/dL)	186±28.9	193.7±29.5	<200	
Triglyceride (mg/dL)	96.7±37.8	77.2±50.7	<150	
HDL (mg/dL)	54.5±11.9	65.5±14.9	>40	
LDL (mg/dL)	112.3±27.8	112.8±27.5	<130	
Total bilirubin	0.9±0.4	0.5±0.3	0.00-1.20	
AST (U/L)	21.2±6.6	17.5±3.1	0-40	0-32
ALT (U/L)	19.4±6.6	12.8±4.4	0-41	0-33
Alkaline (ALP)	66.3±17.9	57.4±13.8	40-129	35-105

Data were determined by Mean±SD

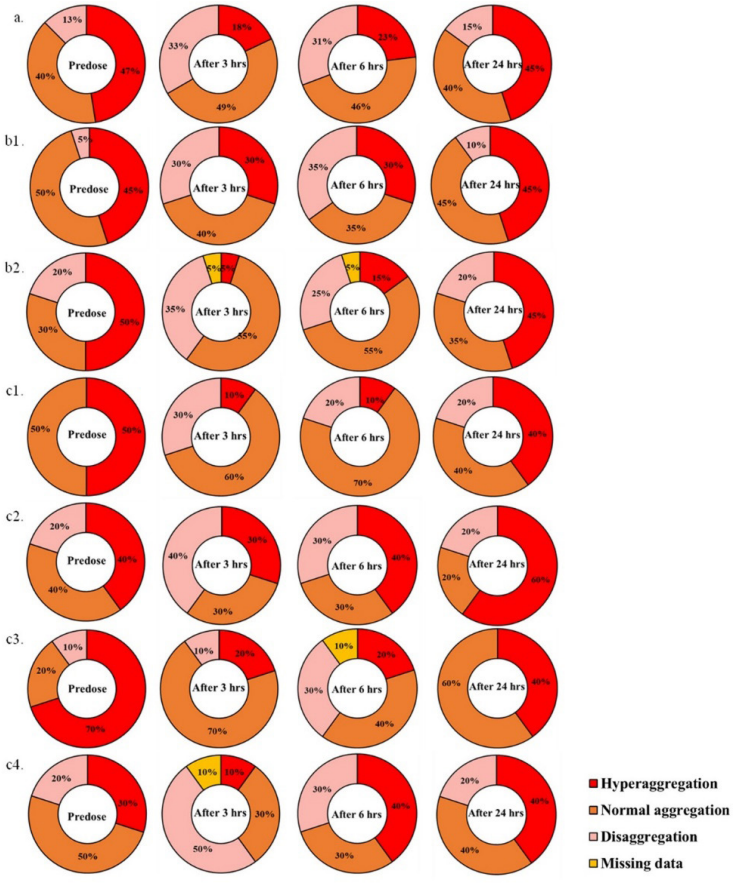


Fig 1. Platelet aggregation pattern before and after 3, 6 and 24 hours of WNF dosing in 40 healthy volunteers (a), grouping with sex (Male: b1, Female: b2) and iDCR (Earth: c1, Water: c2, Wind: c3 and Fire: c4)

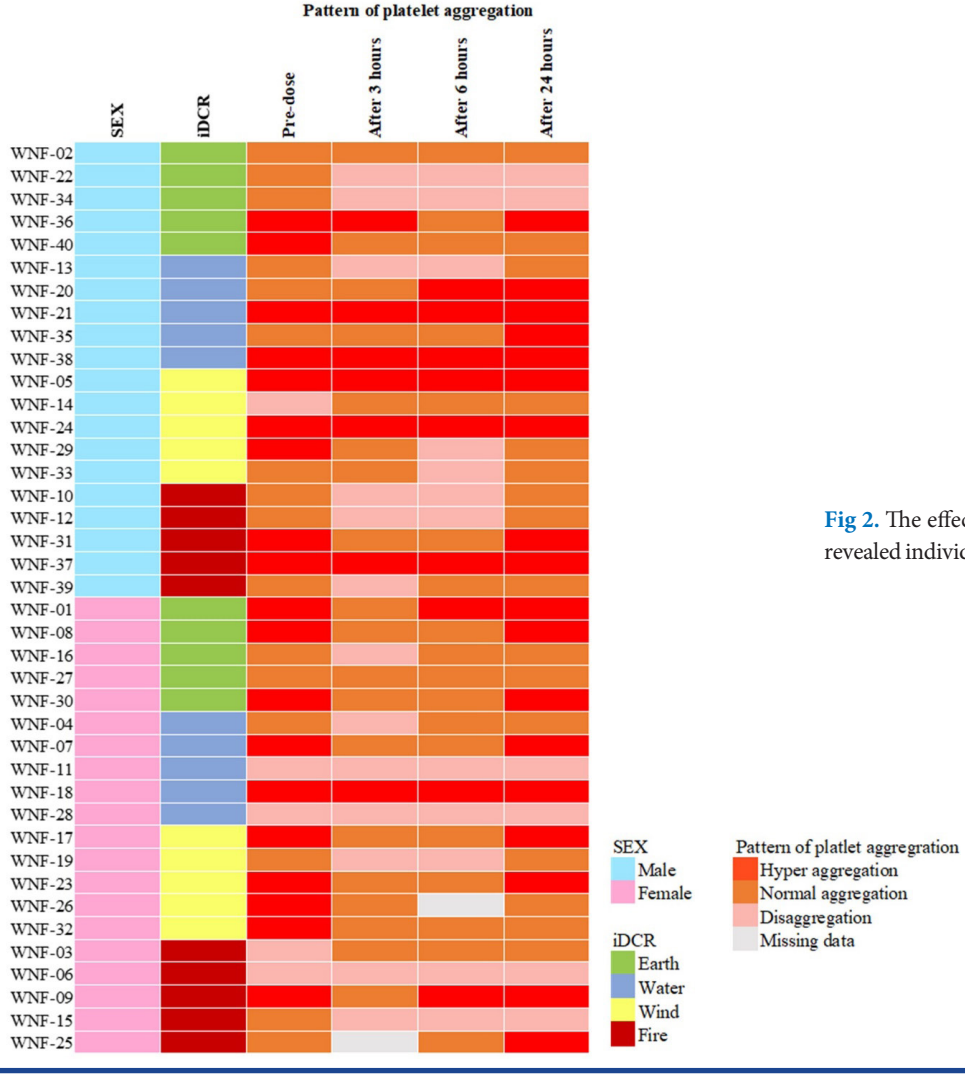


Fig 2. The effect of WNF on platelet aggregation revealed individual patterns after 3, 6 and 24 hours.

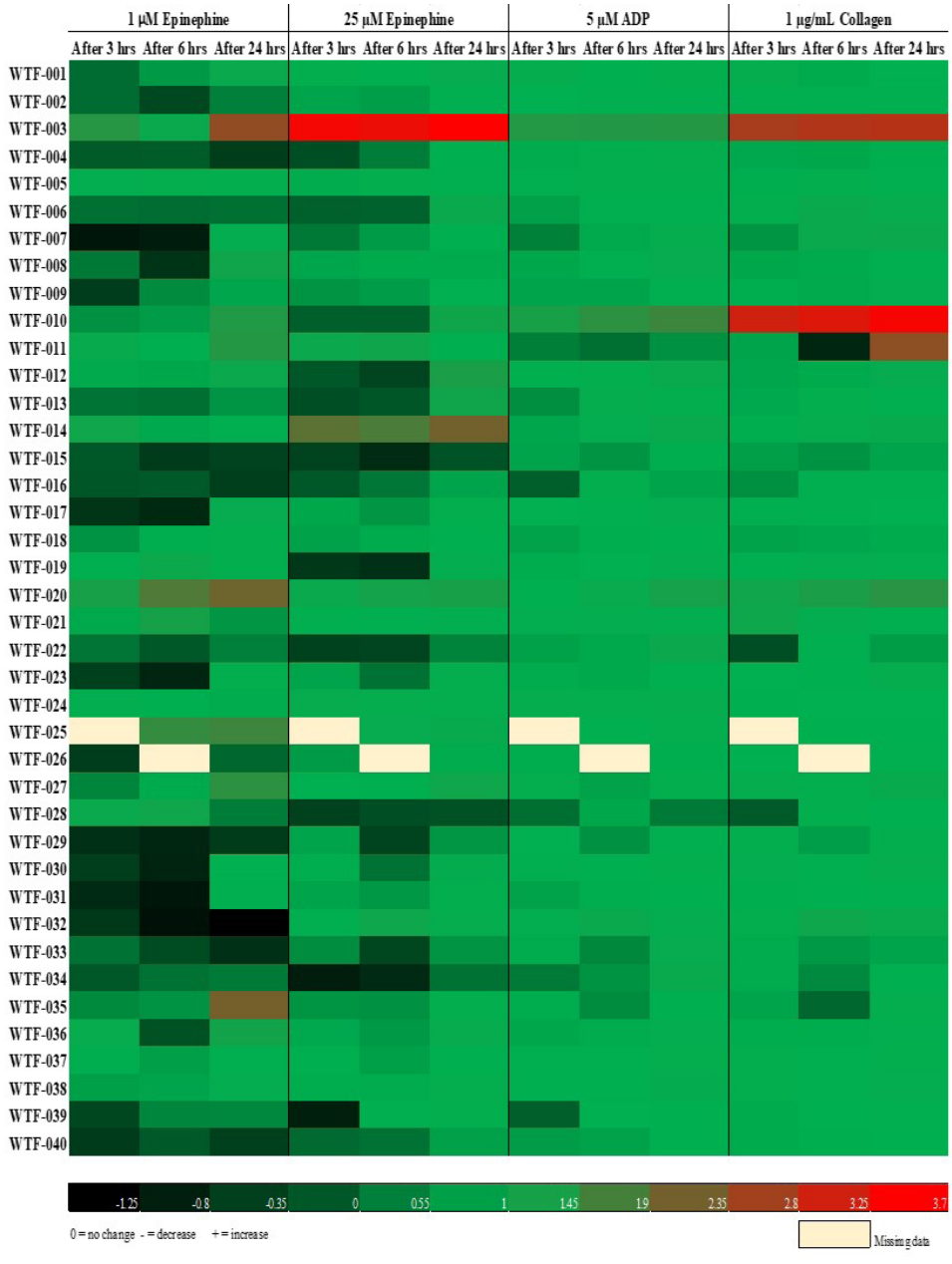


Fig 3. Heatmap of percent platelet aggregation in each subject for each agonist after WNF administration

DISCUSSION

The Thai Herbal Wattana Formula is indicated for pain relief and anti-inflammation like NSAIDs in OA knee patients.[7] A study on the WNF also revealed an anti-inflammatory impact that may be attributed to an enzyme's COX-specific inhibitory activity.[6] It is well-known that reducing thromboxane A2 production by suppressing COX enzymes affects platelet aggregation and raises the risk of bleeding.[8] However, the lack of an anti-platelet aggregation study is a cause of concern about the safety of older people or blood disorders using WNF.

The aggregation pattern observed in the 40 participants of this study before treatment is similar to one observed previously in healthy subjects and is known as hyperaggregation.[13,14] According to Thai traditional medicine theory, which supports these findings, the participants' Earth iCDR is the heaviest, slowest-changing element. Due to these reasons, no disaggregation pattern was observed. Additionally, the subjects' Wind iCDR, which is stimulated more quickly than other iCDR components is intrinsically reflective of motion movements. Hyperaggregation may be present in the Wind element more than others.[1] In our study, the WNF siginifcantly inhibited aggregatation by Epi, ADP and collagen. According to previous studies, many receptors and signaling pathways are involved in the anti-platelet aggregation impact of WNF components. PAF-induced platelet aggregation, 5-HT release by platelets, and an increase in free calcium in platelets can all be inhibited by safflower aqueous extract.[15] Additionally, hydroxysafflor yellow A, safflower yellow A, luteolin and carthamin, the

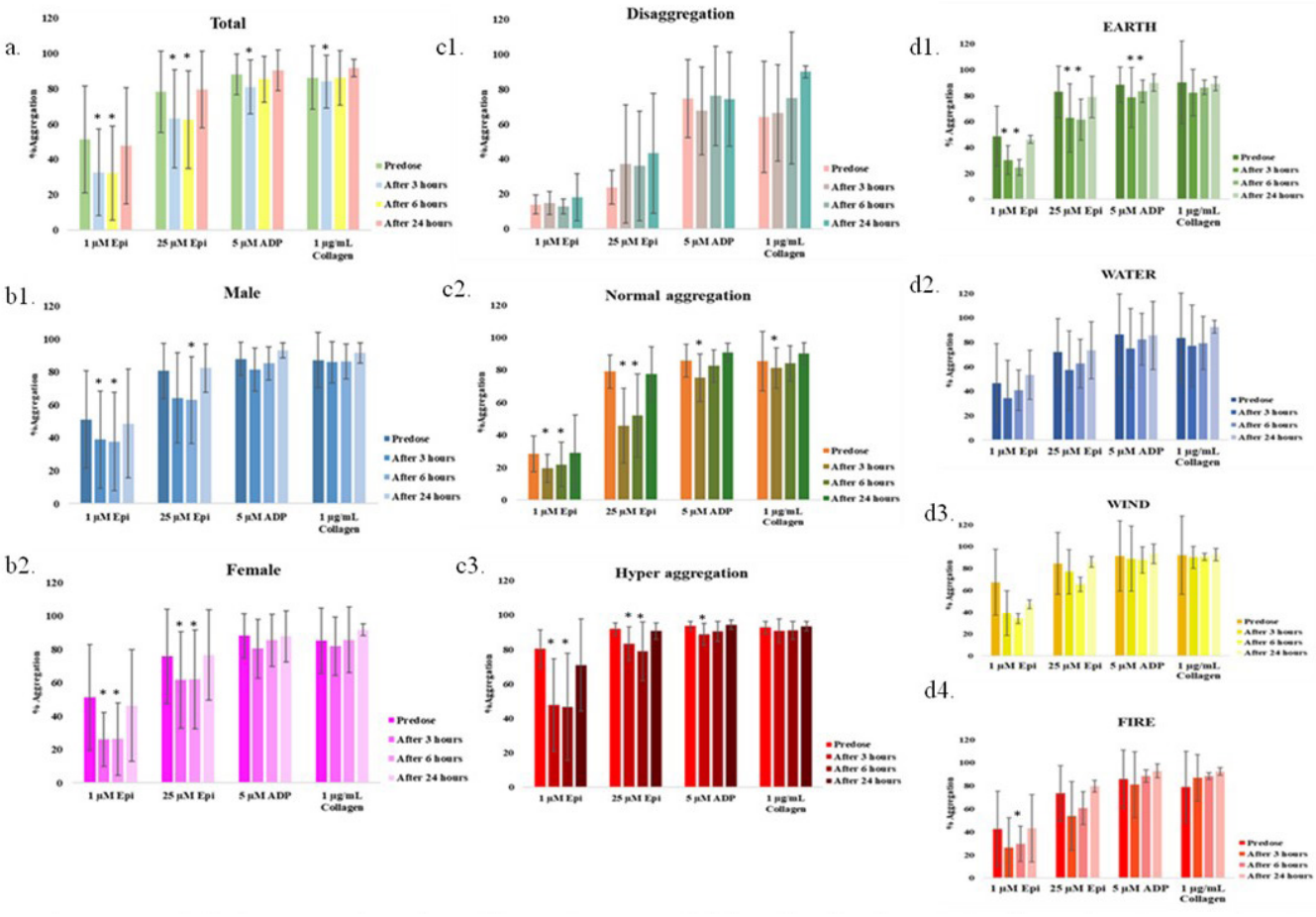


Fig 4. The average of platelet aggregation of 40 subjects after WNF administration (a) sub analysis with sex (b1-2), pattern (c1-3) and iDCR (d1-4). Aggregation of platelet was induced by 1 µM Epi, 25 µM Epi, 5 µM ADP and 1 µg/ml Col. Percent aggregation of platelet after 3, 6 and 24 hours of WNF administration were compare to predose and interpreted as percent of control. Data was shown as mean ± SD. *Post-hoc Wilcoxon test by Friedman test, Significance level was set at *P-value* < 0.05

safflower's active marker, can prevent ADP-controlled aggregation of human platelets.[16,17] (Brazilin, isolated from heartwood of *Caesalpinia sappan* acts as a collagen receptor agonist.[18] An extract of *Cyperus rotundus* in ethanol demonstrated effective inhibition of thrombin, collagen, or AA-induced platelet aggregation.[19] The major active component of *piper nigrum*, piperine, significantly reduced AA liberation by attenuating cPLA2 activity in collagen-stimulated platelets.[20] A dose-dependent reduction of AA-induced human platelet aggregation was shown with *T. chebula* fruit extract.[21] Interpreting the effects of the WNF on platelets has been a challenge due to significant inter-individual variability in aggregation between various agonists. This could be the result of multiple pathways that lead to platelet aggregation and the involvement of numerous platelet receptors in each pathway. Additionally, each subject's specific genetic diversity significantly impacts changing platelet responsiveness and function. In any case, additional research is still required to comprehend the mechanism. We must be aware of platelet aggregation's effects on the WNF in individual patients.

CONCLUSION

This study is the first to examine how the WNF affects platelet aggregation in healthy volunteers with various innate *Dhatu Chao Ruean* (iDCR) groups. In this investigation, there were no drug-related adverse events related to the WNF. The results suggest that 1,000 mg of WNF could impact platelet aggregation (Fig 5). Out of 40 subjects, 60% displayed a downward trend of platelet aggregation patterns (Fig 5a). Similar results were revealed by an analysis based on gender, but the female group had a trend to greater downward platelet pattern than the male group (Fig 5b). Earth, Wind, and Fire iCDR groups under investigation also showed a downward trend, while the Water iCDR group showed no change (Fig 5c). Within 24 hours, the patterns of platelet status and percent platelet aggregation changed. After being stimulated with 1 µM Epi, 25 µM Epi, 5 µM ADP and

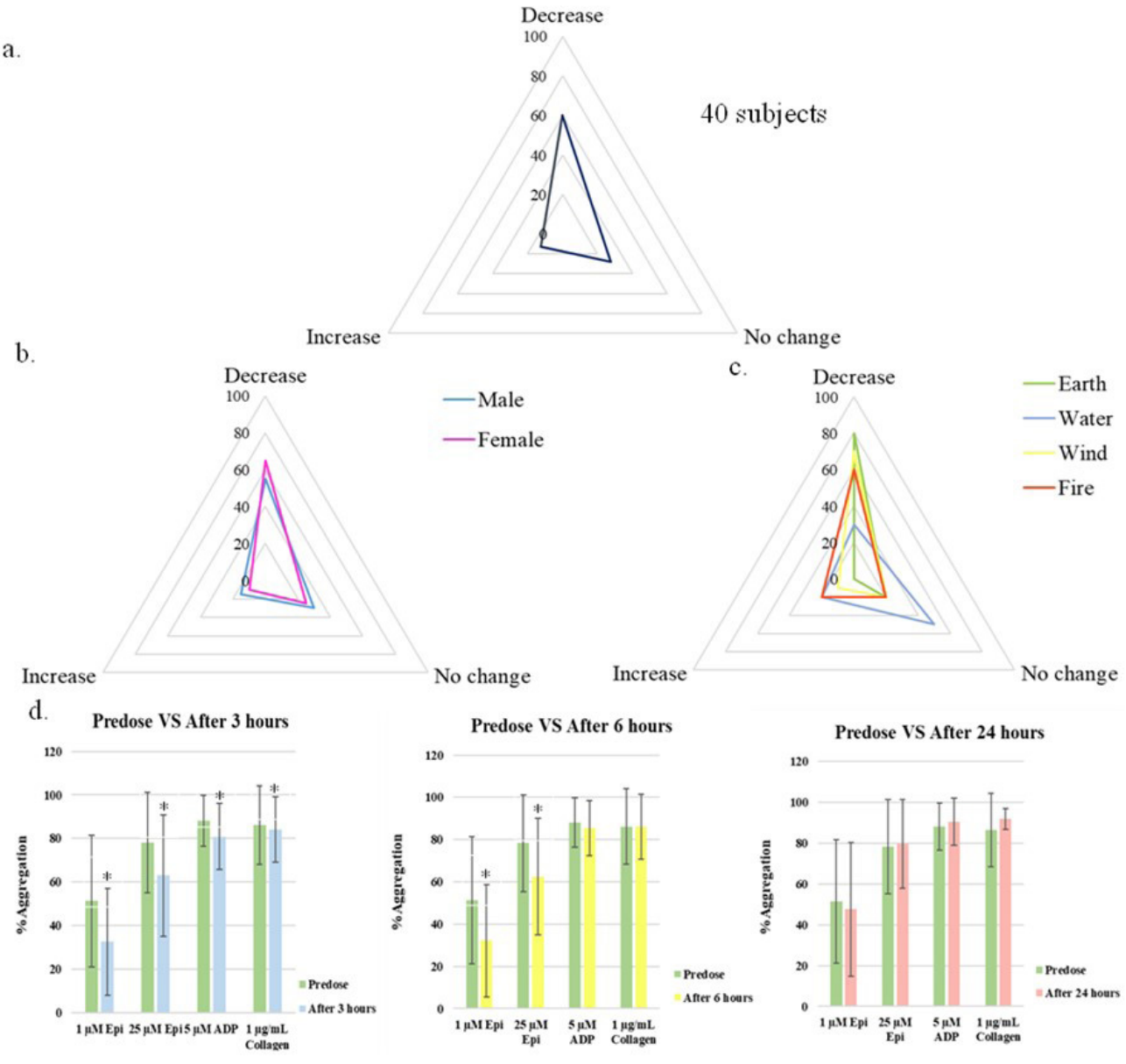


Fig 5. The effect of the WNF on platelet aggregation is defined as the percentage of platelet aggregation pattern changing (a: 40 subjects, b: different sex, c: different iCDR) and the effect of WNF on platelet aggregation agonists of 40 subjects (d), Data is shown as mean ± SD. *Post-hoc Wilcoxon test by Friedman test, Significance level was set at *P-value* < 0.05

1 µg/ml Col at 3 hours, the WNF significantly reduced the percentage of platelet aggregation (Fig 5d). Females with Earth iDCR or Wind iDCR with hyperaggregation patterns should use the WNF with caution. The effect of the WNF on platelet aggregation in an individual may be due to intrinsic influences, including iDCR and genetic variations in drug metabolizing enzymes of each volunteer. This supports calls for the concept of personalized medicine based on platelet reactivity. It should be used with caution in older adults and patients with a history of blood disorders, with special attention on herb-drug interactions, such as aspirin or other NSAIDs.

ACKNOWLEDGEMENTS

The study was financially supported by the Agricultural Research and Development Agency (Public Organization) (ARDA). The authors would like to thank the Manufacturing Unit of Herbal Medicines and Products, the Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University for authenticated plant material and the facilities provided for the study.

REFERENCES

1. Laohapand T and Jaturatamrong U, Thai Traditional Medicine in the Faculty of Medicine Siriraj Hospital, Ayurved Thamrong School, Center of Applied Thai Traditional Medicine, Faculty of

Medicine Siriraj Hospital, Mahidol University. Bangkok: Supavanich Press; 2009.
2. Panich U, Pluemsamran T, Tangsupa-a-nan V, Wattanarangsan J, Phadungrakwittaya R, Akarasereenont P, et al. Protective effect of AVS073, a polyherbal formula, against UVA-induced melanogenesis through a redox mechanism involving glutathione-related antioxidant defense. BMC Complement Altern Med. 2013;13:159.10 page.
3. Duangsa-ard S, Wongkajornsilp A, Akarasereenont P, Huabprasert S, Chongputtharaksa T, Laohapand T. The effects of Ayurved Siriraj Wattana recipe on splenocytes in Wistar rat. Siriraj Med J. 2013;65(3):73-6.
4. Wongkajornsilp A, Numchaisermsuk N, Sa-ngiamsuntorn K, Akarasereenont P, Wamanuttajinda V, Kasetsinsombat K, et al. Effects of the Ayurved Siriraj Wattana recipe on functional and phenotypic characterization of cytokine-induced killer cells and dendritic cells in vitro. BMC Complement Altern Med. 2016;16(489):11 page.
5. Htoo HH, Limsuvan S, Thamsermsang O, Hernandez JF, Checler F, Govitrapong P, et al. The Polyherbal Wattana Formula Displays Anti-Amyloidogenic Properties by Increasing α-Secretase Activities. PLos One. 2017;1-17.
6. Charoenkij P, Palo T, Chotewuttakorn S, Limsuvan S, Laohapand T, Akarasereenont P. The effect of Ayurved Siriraj Wattana Recipe (AVS073) on LPS induced COX-2 expression in human PBMC. Siriraj Med J. 2016;68(2):90-6.
7. Pengkhum T, Chatsiricharoenkul S, Akarasereenont P, Charoencholvanich K. Phase II clinical trial of Ayurved Siriraj Wattana recipe for symptomatic relief in patients with osteoarthritis of the knee. J Med Assoc Thai. 2012;95(3):452-60.
8. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol. 1995 Mar;35(3):209-19.
9. Cattaneo M. Light Transmission Aggregometry and ATP Release for the Diagnostic Assessment of Platelet Function. Semin Thromb Hemost. 2009;35:158–67.
10. Ketsa-Ard K, Poungvarin N, Juengchareon M, Jarerat S, Kittigul L. Clinical study on antithrombotic effects of ticlopidine in ischemic stroke. J Med Assoc Thai. 1991;74(6):331-9.
11. Akarasereenont P, Tripatara P, Chotewuttakorn S, Palo T, Thaworn A. The effects of estrone, estradiol and estriol on platelet aggregation induced by adrenaline and adenosine diphosphate. Platelets. 2006;17(7):441-7.
12. Femia EA, Scavone M, Lecchi A, Cattaneo M. Effect of platelet count on platelet aggregation measured with impedance aggregometry (multiplate analyzer) and with light transmission aggregometry. J Thromb Haemost. 2013;11:2193–6.
13. Yee DL, Bergeron AL, Sun CW, Dong JF, Bray PF. Platelet hyperreactivity generalizes to multiple forms of stimulation. J Thromb Haemost. 2006;4(9):2043-50.
14. Sirikarin T, Palo T, Chotewuttakorn S, Chandranipapongse W, Limsuvan S, Akarasereenont P. The Effects of *Andrographis paniculata* on Platelet Activity in Healthy Thai Volunteers. Evid Based Complement Alternat Med. 2018;2018:2458281.
15. Huang D, Lu Y, Shi L, Zhang J, Shen J, Bao M, et al. Effect of safflower yellow on platelet activating factor mediated platelet activation in patients with coronary heart disease. Bangladesh J Pharmacol. 2012;7:140-4.
16. Lu PH, Kuo CY, Chan CC, Wang LK, Chen ML, Tzeng IS, et al. Safflower Extract Inhibits ADP-Induced Human Platelet Aggregation. Plants (Basel). 2021;10(6):1192.
17. Li HX, Han SY, Wang XW, Ma X, Zhang K, Wang L, et al. Effect of the carthamins yellow from *Carthamus tinctorius* L. on hemorheological disorders of blood stasis in rats. Food Chem Toxicol. 2009;47(8):1797-802.
18. Chang Y, Huang SKH, Lu WJ, Chung CL, Chen WL, Lu SH, et al. Brazilin isolated from *Caesalpinia sappan* L. acts as a novel collagen receptor agonist in human platelets. J Biomed Sci. 2013;20(4):11 page.
19. Seo EJ, Lee DU, Kwakf JH, Lee SM, Kimg YS, Jung YS. Antiplatelet effects of *Cyperus rotundus* and its component (+)-nootkatone. J Ethnopharmacol. 2011;135(1):48-54.
20. Son DJ, Akiba S, Hong JT, Yun YP, Hwang SY, Park YH, et al. Piperine Inhibits the Activities of Platelet Cytosolic Phospholipase A2 and Thromboxane A2 Synthase without Affecting Cyclooxygenase-1 Activity: Different Mechanisms of Action Are Involved in the Inhibition of Platelet Aggregation and Macrophage Inflammatory Response. Nutrients. 2014;6:3336-52.
21. Haq MZU, Shahid SA, Ahmed S, Ahmad S, Qayum M, Khan I. Anti-platelet activity of methanolic extract of *Grewia asiatica* L. leaves and *Terminalla chebula* Retz. fruits. J Med Plants Res. 2012;6(10):2029-32.

Outcomes Comparison of Early versus Late Surfactant Replacement Therapy in Neonates with Respiratory Distress Syndrome

Chutinun Wongkhonkaen, M.D., Pongsatorn Paopongsawan, M.D., Junya Jirapradittha, M.D., Pakaphan Kiatchoosakun, M.D.

Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Thailand.

ABSTRACT

Objective: To compare durations of invasive mechanical ventilator (IMV), other types of ventilator support and neonatal outcomes between neonates who received early versus late surfactant replacement therapy (E-SRT vs. L-SRT).

Materials and Methods: This retrospective study included neonates with gestational age (GA) less than 35 weeks or birth weight (BW) less than 2,000 grams, born between January 1, 2017 to December 31, 2021. Neonates who received SRT before 2 hours of life were defined as E-SRT and neonates who received SRT later were defined as L-SRT. Durations of IMV, other types of ventilator support, neonatal outcomes and length of stays were documented.

Results: Eighty-three neonates had received SRT with 52 (62.7%) had E-SRT and 31 (37.3%) had L-SRT. Neonates in E-SRT group had significantly lower GA and BW than neonates in L-SRT group (median GA 27 vs. 30 weeks; $p = 0.002$ and median BW 885 vs. 1330 grams; $p = 0.003$) and had longer duration of IMV but not significant (median 19.0 vs. 10.5 days; $p = 0.219$). There were no significant differences in durations of other types of ventilator support. After adjusted for sex, GA and BW, there were no significant differences in neonatal outcomes between neonates in each group. Ventilator-associated pneumonia (VAP) and septicemia were independent factors associated with prolonged IMV, ventilator supports and length of stays.

Conclusion: Timing of SRT was not associated with duration of IMV. VAP and septicemia were important factors prolonging ventilator durations and length of stays and should be prevented.

Keywords: surfactant replacement therapy, respiratory distress syndrome, timing of surfactant, neonatal outcomes
(Siriraj Med J 2023; 75: 330-342)

INTRODUCTION

Respiratory distress syndrome (RDS) is an important disease affecting preterm neonates worldwide leading to acute neonatal respiratory failure and deaths.[1] Since the introduction of maternal antenatal corticosteroid injection and surfactant replacement therapy (SRT) for neonates, the mortality and morbidity rates of neonates with RDS have decreased dramatically with 30-40% reduction in neonatal mortality and 35-60% reduction in pneumothorax and air leak syndrome.[2] Improvements in non-invasive ventilation (NIV) support for neonates, for example nasal continuous positive airway pressure (NCPAP) or heated humidified high-flow nasal cannula (HHHFNC), has further decreased the need for intubation, invasive mechanical ventilation (IMV) support and SRT among neonates with mild to moderate RDS.[3]

However, NIV support may have been failed in some neonates with severe RDS and SRT is still necessary. For

Corresponding author: Pongsatorn Paopongsawan
E-mail: pongsatorn@kku.ac.th
Received 3 February 2023 Revised 17 March 2023 Accepted 27 March 2023
ORCID ID:http://orcid.org/0000-0002-9503-4312
https://doi.org/10.33192/smj.v75i5.261175

these neonates, studies showed that early SRT (E-SRT) given within 2 hours of life could reduce the duration of IMV and NIV[4,5] but with increased risks of air leak syndrome.[6] SRT could be given by several techniques such as endotracheal tube with continuous IMV technique (ETT-IMV), intubation-surfactant-extubation technique (INSURE)[7], or less-invasive surfactant administration technique (LISA).[8] However, due to the high cost of surfactant, E-SRT was not given to every neonate and neonates with moderate RDS could deteriorate and eventually needed SRT later beyond 2 hours of life. Late SRT (L-SRT) may lead to prolonged IMV and respiratory complications such as bronchopulmonary dysplasia (BPD) and ventilator-associated pneumonia (VAP).[9]

The primary objective of the study was to compare duration of IMV between neonates with RDS receiving E-SRT and L-SRT. Other objectives included duration of NIV and oxygen therapy, treatment complications, morbidities and mortality among neonates.

MATERIALS AND METHODS

In this retrospective study, we reviewed medical documents of neonates with gestational age (GA) less than 35 weeks or birth weight (BW) less than 2,000 grams, born between January 1, 2017 and December 31, 2021, at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, who were diagnosed with RDS and had received at least one dose of SRT. Neonates with missing or incomplete medical record would be excluded from the study.

Neonates were grouped into E-SRT group, defined as receiving SRT before 2 hours of life, and L-SRT group, defined as receiving SRT after 2 hours of life. Types of surfactants that neonates received were poractant alfa (Curosurf®, Chiesi Farmaceutici, Italy) or beractant (Survanta®, AbbVie, USA). Criteria for SRT included 1) neonates who were at risk for developing RDS (GA less than 35 weeks), 2) neonates with clinical and radiographic evidences of RDS, and 3) neonates who required FiO_2 more than 40% regardless of types of ventilator support.[10,11] Dosage of SRT ranged from 100-200 mg/kg of phospholipid depended on surfactant products with recommended doses were 200 mg/kg for poractant alfa and 100 mg/kg for beractant. After first dose of SRT, if the neonates clinically deteriorated with FiO_2 requirement reached 40% then additional doses of SRT could be given with time interval no less than 12 hours from each dose and no more than 3 doses in total. Dosage of subsequent SRT were 100 mg/kg of phospholipid for both poractant alfa and beractant.

SRT could be given alone or mixed with budesonide with the aim to prevent BPD. Currently, there is no standard guideline recommending the usage of budesonide, therefore, the decision to administered budesonide was at neonatologists' discretion based on risk for developing BPD such as neonates with GA less than 28 weeks and did not receive a completed course of antenatal corticosteroid. Neonates with risk for infection such as neonates with history of maternal chorioamnionitis or sepsis would not be given budesonide.[12,13]

Collected data included demographic data, maternal characteristics, types, doses and numbers of surfactants used for SRT, methods of SRT, duration of IMV and NIV, duration of oxygen therapy, complications during hospitalization such as air leak syndrome, BPD defined as neonates that needed oxygen supplement at 36 weeks postmenstrual age (PMA) according to National Institute of Child Health and Human Development (NICHD) 2018 criteria[14], VAP, retinopathy of prematurity (ROP), septicemia, necrotizing enterocolitis (NEC), hemodynamically significant patent ductus arteriosus (hsPDA), mortality rate and length of hospital stays.

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Percent, ratio, mean ± standard deviation (SD), mean difference, median with interquartile range (IQR) and difference of medians were used to present descriptive data. Correlation analyses were performed by using chi-square test, Fisher's exact test, Student t-test, or Mann-Whitney U-test and presented in odd ratios. A p-value of less than 0.05 was considered to be statistically significant. Multivariate regression analysis was done to minimize confounding factors and identify possible risks associated with outcomes. This study was approved by the Ethics Committee for Human Research at Khon Kaen University (HE651192).

RESULTS

There were 434 neonates with GA less than 35 weeks or BW less than 2,000 grams born during the study period, of which 83 (19.1%) had received SRT. Among neonates that received SRT, 52 (62.7%) had E-SRT and 31 (37.3%) had L-SRT. Neonates who received E-SRT had significantly lower BW [median 885 (IQR 795,1195) vs. 1330 (IQR 895,1580) grams, difference of medians 280 (95%CI 80-485) grams; $p = 0.003$] and GA [median 27 (IQR 25,29) vs. 30 (IQR 27,31) weeks, difference of medians 2 (95%CI 1-3) weeks; $p = 0.002$] than neonates who received L-SRT. More mothers in E-SRT group had multiple medical conditions than mothers in L-SRT group though not statistically significant (30.8% vs. 22.6%; $p = 0.116$). Multiple gestation was the

most common medical condition among mothers in E-SRT group while hypertension was the most common condition among mothers in L-SRT group. Also, twin-twin transfusion syndrome and acardiac twins were found only among mothers in E-SRT group. Mothers in both groups similarly received antenatal corticosteroid and medications. Mothers in E-SRT group tended to have more complications of pregnancy than mothers in L-SRT group but not statistically significant (90.4% vs. 74.2%; $p = 0.093$). Neonatal and maternal characteristics were shown in Table 1.

TABLE 1. Neonatal and maternal characteristics.

	Early SRT N = 52 (%)	Late SRT N = 31 (%)	Difference of medians (95%CI)	*P*-value
Neonatal characteristics				
Sex (Male)	33 (63.4)	19 (61.3)	-	0.843
Body type			-	0.736
SGA	3 (5.8)	2 (6.4)	-	
AGA	48 (92.3)	29 (93.6)	-	
LGA	1 (1.9)	0 (0.0)	-	
Admission status			-	0.054
In-born	49 (94.2)	25 (80.6)	-	
Out-born	3 (5.8)	6 (19.4)	-	
Birth weight (grams)†	885 (795, 1195)	1330 (895,1580)	280 (80-485)	0.003*
Gestational age (weeks)†	27 (25,29)	30 (27,31)	2 (1-3)	0.002*
Maternal characteristics				
Serology status				0.357
Normal	50 (96.1)	28 (90.3)	-	
Abnormal	2 (3.9)	3 (9.7)	-	
HBsAg	2 (3.9)	2 (6.5)	-	
VDRL	0 (0.0)	1 (3.2)	-	
Medical condition§				0.135
Single condition	**17 (32.7)**	**17 (54.8)**		
Multiple conditions	**16 (30.8)**	**7 (22.6)**		
Multiple gestation	13	5	-	
Hypertension	11	12	-	
Elderly primigravida	8	4	-	
Diabetes	4	2	-	
Twin-twin transfusion	4	0	-	
No antenatal care	4	2	-	
Congestive heart failure	4	0	-	
Urinary tract infection	3	2	-	
Acardiac twins	2	0	-	
End-stage renal disease	2	0	-	
Drug abuse	0	2	-	
Thyroid	1	0	-	

TABLE 1. Neonatal and maternal characteristics. (Continued)

	Early SRT N = 52 (%)	Late SRT N = 31 (%)	Difference of medians (95%CI)	*P*-value
Amniotic fluid status				0.847
Normal	41 (78.8)	26 (83.9)	-	
Oligohydramnios	7 (13.5)	3 (9.7)	-	
Polyhydramnios	4 (7.7)	2 (6.4)	-	
Route of delivery				0.853
Vaginal	18 (34.6)	12 (38.7)	-	
Elective caesarean	1 (1.9)	1 (3.2)	-	
Emergency caesarean	33 (63.5)	18 (58.1)	-	
Antenatal corticosteroid				0.823
None	11 (21.1)	7 (22.6)	-	
Partial	14 (27.0)	10 (32.2)	-	
Complete	27 (51.9)	14 (45.2)	-	
Other medication§				0.765
Yes	**37 (71.1)**	**23 (74.2)**	-	
- Antibiotics	23	11	-	
- Magnesium	18	14	-	
- Antihypertensive	6	9	-	
- Tocolytics	9	2	-	
- Insulin	1	0	-	
No	**15 (28.9)**	**8 (25.8)**	-	
Complication of pregnancy§				0.093
Single complication	**13 (25.0)**	**9 (29.0)**	-	
Multiple complications	**34 (65.4)**	**14 (45.2)**	-	
Preterm labor	35	15	-	
Birth asphyxia	32	7	-	
PROM	11	8	-	
Fetal distress	11	4	-	
Placenta previa	6	2	-	
Hydrops fetalis	5	0	-	
Chorioamnionitis	3	2	-	
Birth before arrival	2	3	-	
Abruptio placenta	1	2	-	

Abbreviations: SRT = surfactant replacement therapy, SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age, † = median and interquartile range, * = statistically significant, HBsAg = hepatitis B surface antigen, VDRL = venereal disease research laboratory, § = could have more than one conditions, PROM = premature rupture of membrane

Surfactant and respiratory support characteristics

Neonates in E-SRT group were intubated more than neonates in L-SRT group (92.3% vs. 70.9%; $p = 0.010$), and were mostly intubated immediately at labor room while neonates in L-SRT group were mostly intubated later at neonatal intensive care unit (NICU). Neonates in E-SRT group were supported by IMV more than L-SRT group (86.5% vs. 29.0%; $p < 0.001$) and the most frequently used ventilator mode was conventional mode.

The most common surfactant used in each group was poractant alfa followed by poractant alfa mixed with budesonide. Neonates in E-SRT group received more of poractant alfa mixed with budesonide than neonates in L-SRT group although not significant (25.0% vs. 6.4%; $p = 0.099$). Dosage of surfactant used for SRT was similar between each group (158 ± 31 vs. 152 ± 24 mg/kg; $p = 0.976$). The median of timing of SRT in E-SRT and L-SRT group were 1.4 and 5.0 hours, respectively ($p < 0.001$).

The most common technique for SRT was ETT-IMV technique in both groups but neonates in E-SRT group received more SRT via ETT-IMV technique than neonates in L-SRT group (90.4% vs. 51.6%; $p < 0.001$). Also, more neonates in E-SRT group required multiple doses of SRT than L-SRT group (23.1% vs. 6.5%; $p = 0.044$). Surfactant types, SRT techniques and ventilator characteristics were shown in Table 2.

Duration of ventilator supports

Among 83 neonates, 70 neonates were intubated using IMV support with 48 in E-SRT group and 22 in L-SRT group. Overall median of IMV duration was 14.5 (IQR 3.0,32.0) days. Duration of IMV in E-SRT group was longer than L-SRT group but not statistically significant [median 19.0 (IQR 3.0,35.0) days vs. 10.5 (IQR 2.0,28.0) days; difference of medians 3.0 days (95%CI -1.0 to 14.0); $p = 0.219$]. At the age of 60 days, neonates in L-SRT group had significantly higher IMV-free days [median 49.5 (IQR 32.0-58.0) days] than neonates in E-SRT group [median 25.0 (IQR 0.0-42.5) days; $p < 0.001$].

There were 72 neonates receiving NIV support with 41 in E-SRT group and 31 in L-SRT group. Eleven neonates died during IMV and had never received NIV support. Among neonates who received NIV, duration of NIV support was longer in E-SRT group than L-SRT group though not statistically significant [median 42.5 (IQR 26.5,54.0) days vs. 31.0 (IQR 13.0,51.0) days; $p = 0.239$]. However, neonates in L-SRT group had significantly higher NIV-free days at the age of 60 days than neonates in E-SRT group [median 20.0 (IQR 0.0,41.0) days vs. 0.0 (IQR 0.0,22.0) days; $p = 0.034$].

Duration of oxygen usage had a similar trend with IMV and NIV duration, with neonates in L-SRT had higher oxygen free days at the age of 60 days than E-SRT group [median 16.0 (IQR 0.0,36.0) days vs. 0.0 (IQR 0.0,23.0) days; $p = 0.041$].

There were no significant differences in oxygen usage at 28 days, oxygen usage at 36 weeks PMA and home oxygen usage between neonates of each group. Durations of ventilator supports and oxygen supplements were shown in Table 3.

Other outcomes

There were 13 neonates who died before discharge, all of which were in E-SRT group. Neonates in E-SRT group tended to have higher rates of IVH, air leak syndrome, hsPDA, septicemia, VAP, and NEC than neonates in L-SRT group. However, after adjusted for sex, GA and BW, none of the aforementioned outcomes was significantly different.

Among 70 neonates who survived until the timing of diagnosis, ROP and BPD were higher among neonates in E-SRT group than L-SRT group but after adjustment for sex, GA and BW, the difference became insignificant. BPD severity did not differ significantly among neonates in each group, however, rate of stage 3 ROP was higher among neonates in E-SRT group ($p = 0.015$). Also, 10 neonates (25.6%) in E-SRT group required treatment for ROP while none of neonates in L-SRT group needed treatment ($p = 0.004$).

Length of hospital stays between neonates in E-SRT group (mean 70 ± 44 days) and L-SRT group (mean 72 ± 35 days) was similar between both groups (mean difference 1.7 days, 95%CI (-16.8) to 20.3 days; $p = 0.853$). Other outcomes of neonates were shown in Table 4.

Characteristics of non-surviving neonates

Among 52 neonates in E-SRT group, 13 neonates had died; 12 neonates died within 28 days of life (neonatal death) and 1 died after 28 days (post-neonatal death). Of these 13 neonates, 11 were intubated until death while 2 neonates were extubated but died afterward. There were no significant differences in sex, body type, admission status, BW, GA and doses of SRT between neonates who survived and died. Duration of IMV among neonates who died was significantly shorter than neonates who survived [median 4 (IQR 2,14) days vs. 24 (IQR 6,37) days, difference of medians 16 (95%CI 2-26) days; $p = 0.015$]. Similarly, duration of oxygen supplement was

TABLE 2. Surfactant, SRT techniques and ventilator characteristics.

	Early SRT N = 52 (%)				Late SRT N = 31 (%)				*P*-value
Intubation									0.010*
Intubated	48 (92.3)				22 (70.9)				
Never intubated	4 (7.7)				9 (29.1)				
Timing of intubation									<0.001*
Never intubated	4 (7.7)				9 (29.1)				
Immediately at LR	45 (86.5)				8 (25.8)				
Later at NICU	3 (5.8)				14 (45.1)				
Age of Intubation (hours)†	0 (0,0)				4.75 (0,13)				<0.001*
Ventilation mode before SRT									<0.001*
NIV	7 (13.5)				22 (70.9)				
Conventional	30 (57.7)				9 (29.1)				
HFOV	15 (28.8)				0 (0.0)				
Surfactant type	**P**	**P+Bd**	**B**	**B+Bd**	**P**	**P+Bd**	**B**	**B+Bd**	
First dose	37 (71.1)	13 (25.0)	2 (3.9)	0 (0.0)	28 (90.3)	2 (6.4)	1 (3.2)	0 (0.0)	0.099
Second dose	11 (21.1)	0 (0.0)	0 (0.0)	1 (1.9)	2 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	0.141
Third dose	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
Surfactant dosage (mg/kg)‡									
First dose	158 ± 31				152 ± 24				0.976
Second dose	118 ± 26				131 ± 16				0.542
Third dose	100 ± 0				N/A				N/A
Doses of SRT									0.044*
Single	40 (76.9)				29 (93.5)				
Multiple	12 (23.1)				2 (6.5)				
Timing of first dose SRT (hours)†	1.4 (1,1.8)				5.0 (2.9, 13.5)				<0.001*
SRT technique	**ETT-IMV**	**INSURE**	**LISA**		**ETT-IMV**	**INSURE**	**LISA**		
First dose	47 (90.4)	3 (5.7)	2 (4.2)		16 (51.6)	7 (22.6)	8 (25.8)		<0.001*
Second dose	12 (100.0)	0 (0)	0 (0)		2 (100.0)	0 (0)	0 (0)		N/A
Third dose	2 (100.0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)		N/A

Abbreviations: SRT = surfactant replacement therapy, * = statistically significant, P = poractant alfa, P+Bd = poractant alfa and budesonide, B = beractant, B+Bd = beractant and budesonide, ETT-IMV = endotracheal tube with invasive mechanical ventilation technique, INSURE = intubation-surfactant-extubation technique, LISA = less-invasive surfactant administration technique, † = median and interquartile range, ‡ = mean ± standard deviation, SRT = surfactant replacement therapy, NIV = non-invasive ventilation, HFOV = high-frequency oscillatory ventilation

TABLE 3. Durations of ventilator support and oxygen supplements.

Primary outcomes	**Total N = 70**	**Early SRT N = 48**	**Late SRT N = 22**	**Difference of medians (95% CI)**	***P*-value**
Duration of IMV (days)†	14.5 (3.0,32.0)	19.0 (3.0,35.0)	10.5 (2.0,28.0)	3.0 (-1.0 to 14.0)	0.219
IMV-free days at 60 days (days)†	32.0 (14.0,54.0)	25.0 (0.0,42.5)	49.5 (32.0,58.0)	-21.0 (-30.0 to -8.0)	<0.001*
Secondary outcomes	**Total N = 72**	**Early SRT N = 41**	**Late SRT N = 31**	**Difference of medians (95% CI)**	***P*-value**
Duration of NIV (days)†	37.0 (22.0,53.5)	42.5 (26.5,54.0)	31.0 (13.0,51.0)	7.0 (-5.0 to 19.0)	0.239
NIV-free days at 60 days (days)†	3.0 (0.0,29.5)	0.0 (0.0,22.0)	20.0 (0.0,41.0)	-1.5 (-20.0 to 0.0)	0.034*
	Total N = 83	**Early SRT N = 52**	**Late SRT N = 31**	**Difference of medians (95% CI)**	***P*-value**
Duration of oxygen (days)†	44.0 (12.5,79.5)	44.0 (6.0,82.5)	44.0 (24.0,71.0)	-3.0 (-20.0 to 15.0)	0.655
Oxygen free days at 60 days (days)†	0.0 (0.0,28.5)	0.0 (0.0,23.0)	16.0 (0.0,36.0)	-1.0 (-16.0 to 0.0)	0.041*
	Total N = 71 (%)	**Early SRT N = 40 (%)**	**Late SRT N = 31 (%)**	**Adjusted OR (95%CI)**	***P*-value**
Neonates using oxygen at 28 days (%)†,‡	53 (74.6)	31 (77.5)	22 (70.9)	1.41 (0.48-4.11)	0.586
Neonates using oxygen at 36 weeks (%)†,‡	43 (60.6)	27 (67.5)	16 (51.6)	1.95 (0.74-5.13)	0.223
Neonates required home oxygen (%)†,‡	10 (14.1)	6 (15.0)	4 (12.9)	1.19 (0.31-4.65)	0.541

Abbreviations: 95%CI = 95% confidence interval, † = median and interquartile range, * = statistically significant, OR = odd ratio, ‡ = only surviving to discharge neonates

also shorter among neonates who died [median 4 (IQR 2,14) days vs. 57 (IQR 28,85) days, difference of medians 49 (95%CI 21-70) days; $p < 0.001$]. However, duration of NIV was not statistically different. Common causes of death were lung hypoplasia, septicemia and severe IVH. Details about non-surviving neonates were shown in Table 5.

Factors associated with duration of ventilator support and length of stays

Multivariate regression analysis found that factors independently associated with IMV duration were VAP, and septicemia. Neonates who had VAP would have longer duration of IMV than neonates without VAP with mean increase of 19.8 days (95%CI 11.3-28.3 days; $p < 0.001$). Similarly, neonates with septicemia would have longer IMV duration with a mean increase of 13.4 days (95%CI 4.4-22.4 days; $p = 0.004$).

Factors associated with increased duration of NIV were number of SRT dose, and hsPDA. Duration of NIV increased by 19.9 days (95%CI 2.6-37.3 days; $p = 0.025$) per each SRT dose received while having hsPDA increased NIV duration by 13.1 days (95%CI 1.7-24.5 days; $p = 0.025$). In contrary, higher BW or GA, and having completed course of antenatal steroid was associated with decreased duration of NIV. Per each 100 grams increased in BW

TABLE 4. Other outcomes.

Outcomes	Early SRT N = 52 (%)	Late SRT N = 31 (%)	OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value
Death	13 (25.0)	0 (0.0)	N/A	0.002*	N/A	N/A
Intraventricular hemorrhage	42 (80.7)	24 (77.4)	1.23 (0.41-3.64)	0.715	1.32 (0.36-4.77)	0.674
Grade 1	29 (55.8)	18 (58.1)				
Grade 2	4 (7.7)	3 (9.7)	N/A	0.724	N/A	0.575
Grade 3	3 (5.8)	2 (6.4)				
Grade 4	6 (11.4)	1 (3.2)				
Air leak syndrome	15 (28.8)	7 (22.6)	1.39 (0.49-3.91)	0.532	1.07 (0.34-3.33)	0.908
Hemodynamically significant PDA	26 (50.0)	7 (22.6)	3.43 (1.26-9.34)	0.016*	2.15 (0.72-6.46)	0.173
Septicemia	15 (28.8)	2 (6.4)	5.88 (1.24-27.79)	0.025*	3.08 (0.58-16.33)	0.185
Ventilator-associated pneumonia	30 (57.7)	7 (22.6)	4.67 (1.71-12.78)	0.003*	2.93 (0.97-8.87)	0.058
Necrotizing enterocolitis	10 (19.2)	5 (16.1)	1.24 (0.38-4.03)	0.723	1.33 (0.35-5.03)	0.677
Stage 1	5 (9.6)	5 (16.1)				
Stage 2	3 (5.8)	0 (0.0)	N/A	0.147	N/A	0.274
Stage 3	2 (3.8)	0 (0.0)				
Length of hospital stays (days)‡	70.4 ± 44.5	72.2 ± 34.7	1.7§ (-16.8 to 20.3)	0.853	N/A	N/A
	Early SRT N = 39 (%)	**Late SRT N = 31 (%)**	**OR (95%CI)**	***p*-value**	**Adjusted OR (95%CI)**	***p*-value**
Bronchopulmonary dysplasia†	26 (66.7)	16 (51.7)	1.88 (0.71-4.95)	0.228	1.09 (0.36-3.33)	0.687
Mild	0 (0.0)	3 (9.7)	N/A	0.082	N/A	N/A
Moderate	14 (35.9)	7 (22.6)	1.92 (0.66-5.58)	0.297	1.29 (0.30-5.46)	0.370
Severe	12 (30.8)	6 (19.4)	1.85 (0.60-5.68)	0.281	0.34 (0.05-2.13)	0.309
Retinopathy of prematurity†	20 (51.3)	5 (6.4)	5.46 (1.74-17.24)	0.003*	3.40 (0.91-12.66)	0.068
Stage 1	3 (7.7)	0 (0.0)	N/A	0.249	N/A	N/A
Stage 2	11 (28.2)	5 (16.1)	1.79 (0.54-5.95)	0.391	1.01 (0.26-3.92)	0.985
Stage 3	7 (17.9)	0 (0.0)	N/A	0.015*	N/A	N/A
Neonates received ROP treatment†	10 (25.6)	0 (0.0)	N/A	0.004*	N/A	N/A

Abbreviations: SRT = surfactant replacement therapy, OR = odd ratio, 95%CI = 95% confidence interval, * = statistically significant, ROP = retinopathy of prematurity, ‡ = mean ± SD, § = mean difference, † = Excluded neonates who had died before the timing of diagnosis

TABLE 5. Characteristics of non-surviving neonates.

	Alive N = 39 (%)	Dead N = 13 (%)	Difference of medians (95% CI)	*p*-value
Sex: Male	23 (58.9)	10 (76.9)	-	0.244
Body type				0.801
SGA	2 (5.1)	1 (7.7)	-	
AGA	36 (92.3)	12 (92.3)	-	
LGA	1 (2.6)	0 (0.0)	-	
Admission status				0.303
In-born	36 (92.3)	13 (100.0)	-	
Out-born	3 (7.7)	0 (0.0)	-	
Birth weight (grams)†	890 (820,1205)	830 (690,1082)	90 (-151 to 255)	0.369
Gestational age (weeks)†	27 (25,28)	26 (24,29)	1 (-1 to 2)	0.332
Doses of SRT				0.128
Single	32 (82.1)	8 (61.5)	-	
Multiple	7 (17.9)	5 (38.5)	-	
Duration of IMV (days)†	24 (6,37)	4 (2,14)	16 (2-26)	0.015*
Duration of NIV (days)†	40 (26,54)	28 (11,46)	11 (-29 to 47)	0.512
Duration of Oxygen (days)†	57 (28,85)	4 (2,14)	49 (21-70)	<0.001*
Timing of death				N/A
Early neonatal (≤ 7 d)	-	7 (53.8)	-	
Late neonatal (8-28 d)	-	5 (38.5)	-	
Post neonatal (> 28 d)	-	1 (7.7)	-	
Cause of death				N/A
Lung hypoplasia	-	4	-	
Septicemia	-	3	-	
Severe IVH	-	3	-	
Hydrops fetalis	-	1	-	
HIE	-	1	-	
Pulmonary hemorrhage	-	1	-	

Abbreviations: † = median and interquartile range, * = statistically significant

could reduce NIV duration by 3.2 days (95%CI 1.6-4.8 days; $p < 0.001$). Similarly, each week increased in GA was associated with a 4.1-day (95%CI 1.4-6.6 days; $p = 0.003$) reduction in NIV duration. Having completed antenatal corticosteroid could reduce NIV duration by 6.9 days (95%CI 0.5-13.4 days; $p = 0.035$).

Longer length of stays was associated with number of SRT dose, VAP, septicemia and hsPDA while increased in GA and BW was associated with shorter length of stays. With each week increased in GA associated with 5.4 days (95%CI 2.7-8.0 days; $p < 0.001$) reduction in length of stays. On the contrary, having septicemia, multiple doses of SRT, VAP, or hsPDA would prolong duration of hospitalization. Factors associated with duration of ventilator support and length of stays were shown in Table 6.

TABLE 6. Factors associated with ventilator support and length of stays.

Factors associated with IMV duration	Days change in ventilator support	95%CI	*P*-value
Neonatal Factors			
Birth weight (per each 100 gram)	0.1	(-1.0) – 1.2	0.804
Gestational age (per each week)	0.4	(-1.3) – 2.1	0.623
Body type (SGA)	8.3	(-4.9) – 21.5	0.214
Completed antenatal steroid	-0.1	(-4.5) – 4.3	0.959
Surfactant Factors			
Early SRT	0.6	(-7.8) – 9.0	0.888
Surfactant characteristic (no budesonide)	-3.2	(-13.2) – 6.7	0.516
SRT technique of first dose (INSURE)	0.8	(-6.3) – 7.9	0.826
Number of surfactant (per each dose)	7.1	(-3.9) – 18.3	0.201
Dosage of first surfactant (per each 10 mg/kg)	0.1	(-1.1) – 1.3	0.835
Postnatal Complications			
Ventilator associated pneumonia	19.8	11.3 – 28.3	<0.001*
Septicemia	13.4	4.4 – 22.4	0.004*
Necrotizing enterocolitis	-3.5	(-12.7) – 5.6	0.433
Air leak syndrome	0.5	(-7.3) – 8.3	0.896
Hemodynamic significant PDA	1.9	(-5.3) – 9.2	0.590
Factors associated with NIV duration	**Days change in ventilator support**	**95%CI**	***P*-value**
Neonatal Factors			
Birth weight (per each 100 gram)	-3.2	(-4.8) – (-1.6)	<0.001*
Gestational age (per each week)	-4.1	(-6.6) – (-1.4)	0.003*
Body type (SGA)	4.1	(-14.6) – 22.8	0.663
Completed antenatal steroid	-6.9	(-13.4) – (-0.5)	0.035*
Surfactant Factors			
Early SRT	8.3	(-3.1) – 19.7	0.151
Surfactant characteristic (no budesonide)	-2.6	(-16.9) – 11.6	0.711
SRT technique of first dose (INSURE)	2.6	(-4.6) – 9.9	0.473
Number of surfactant (per each dose)	19.9	2.6 – 37.3	0.025*
Dosage of first surfactant (per each 10 mg/kg)	-1.3	(-3.1) – (-0.4)	0.150
Postnatal Complications			
Ventilator associated pneumonia	3.9	(-8.4) – 16.2	0.527
Septicemia	4.9	(-9.3) – 19.1	0.497
Necrotizing enterocolitis	0.8	(-11.2) – 12.8	0.894
Air leak syndrome	-8.2	(-20.8) – 4.4	0.198
Hemodynamic significant PDA	13.1	1.7 – 24.5	0.025*

TABLE 6. Factors associated with ventilator support and length of stays. (Continued)

Factors associated with length of stays	Days change in ventilator support	95%CI	*P*-value
Neonatal Factors			
Birth weight (per each 100 gram)	-3.5	-5.2 – (-1.8)	<0.001*
Gestational age (per each week)	-5.4	-8.0 – (-2.7)	<0.001*
Body type (SGA)	13.2	-7.1 – 33.5	0.199
Completed antenatal steroid	-3.7	-10.8 – 3.2	0.284
Surfactant Factors			
Early SRT	11.7	-0.6 – 24.0	0.063
Surfactant characteristic (no budesonide)	4.8	-10.6 – 20.3	0.534
SRT technique of first dose (INSURE)	-1.9	-9.8 – 5.9	0.626
Number of surfactant (per each dose)	27.8	8.9 – 46.6	0.011*
Dosage of first surfactant (per each 10 mg/kg)	0.4	-1.6 – 2.3	0.702
Postnatal Complications			
Ventilator associated pneumonia	16.9	3.5 – 30.3	0.020*
Septicemia	21.4	5.9 – 36.9	0.008*
Necrotizing enterocolitis	-4.7	-17.7 – 8.3	0.470
Air leak syndrome	-13.0	-26.4 – 0.4	0.056
Hemodynamic significant PDA	12.5	0.2 – 24.9	0.047*

Abbreviations: IMV = invasive mechanical ventilator, 95%CI = 95% confidence interval, * = statistically significant, SRT = surfactant replacement therapy, NIV = non-invasive mechanical ventilator, PDA = patent ductus arteriosus

DISCUSSION

Several studies showed that E-SRT could benefit neonates with RDS more than L-SRT in shortening the duration of IMV and NIV.[4,5] A 2012 Cochrane review also concluded that E-SRT could reduce risk for air leak syndrome, BPD and mortality rate.[15] However, this study demonstrated that neonates who received E-SRT had longer duration of IMV than neonates receiving L-SRT although not statistically significant. Similarly, duration of NIV, duration of oxygen usage, oxygen usage at 28 days and oxygen usage at 36 weeks PMA were also longer among neonates in E-SRT group but also not statistically significant. The reason for these conflicting outcomes could be explained by the lower GA and BW and higher rates of hsPDA, septicemia and VAP among neonates in E-SRT group which could be associated with more severe RDS with critically ill conditions prompting immediate intubation and SRT while neonates in L-SRT group could be more medically stable and received SRT later when RDS had progressed. Clinical severity of neonates in E-SRT group could be noted with more neonates received multiple doses of SRT than neonates in L-SRT group. Likewise, this also reflected in the significantly lower number of neonates in E-SRT group with IMV-free, NIV-free, and oxygen-free days at age of 60 days than L-SRT group.

This study found that factors independently associated with longer duration of respiratory support were having VAP, and septicemia. VAP is a common complication among preterm neonates causing inflammation and injury to the lungs while septicemia causes systemic inflammatory response syndrome leading to inflammatory lung injury. Additionally, neonates with VAP and septicemia are likely to be medically unstable requiring prolonged IMV support which could directly injure the lungs by volutrauma and barotrauma leading to BPD.[16,17] Multiple doses of SRT was shown to help reducing mortality and respiratory supports among neonates with severe RDS.[18] In this study, most of neonates who received multiple doses of SRT were in E-SRT group who had lower GA and BW and could possibly have more severe RDS leading to the requirement of multiple doses of SRT.

These neonates could have other pathogenic mechanisms, such as infection, causing surfactant inactivation and, therefore, requiring subsequent SRT.[19] This study also found that neonates in E-SRT group had higher rate of VAP and septicemia which could better explain the longer duration of IMV support rather than by having multiple doses of SRT.

In terms of NIV, multiple factors were associated with longer duration of NIV support such as number of SRT dose and hsPDA similar to previous studies that demonstrated hsPDA could contribute to longer duration of IMV, NIV and oxygen supplements.[20,21] Higher number of SRT dose was associated with more severe RDS which could also lead to longer duration of IMV, NIV, length of stays. Although length of stays did not differ significantly between each group, factors that could prolonged hospitalization were VAP, septicemia, and hsPDA according to this study.

After adjusted for sex, GA and BW, there was no significant differences about IVH, air leak syndrome, hsPDA, septicemia, VAP, NEC, and BPD between neonates in E-SRT and L-SRT groups which mean that timing of SRT was not associated with adverse outcomes. Neonates in E-SRT group also had significantly more IMV support before SRT than L-SRT group. It is known that IMV is associated with lung injury due to volutrauma and barotrauma leading to BPD. At our institution, pressure-controlled with volume guarantee (VG) for conventional IMV and HFOV with VG were used in all neonates who were intubated to minimized fluctuation of tidal volume, and thus, minimizing volutrauma effect from IMV. This could explain the BPD rate among neonates in both group which did not differ significantly. However, ROP rate was higher among neonates in E-SRT group which could be caused by the longer duration of IMV, NIV and oxygen supplement.

Another finding from this study was the mortality rate which was significantly higher among neonates in E-SRT group. However, causes of death were not related to RDS i.e., lung hypoplasia, severe IVH and septicemia, which were mainly associated with prematurity and was not treatable with SRT. There were no significant differences in characteristics of neonates in E-SRT group who survived or died in terms of sex, GA and BW.

This study demonstrated that VAP and septicemia were important risk factors that could prolong duration of IMV while timing of SRT did not show to be associated with. Additionally, VAP and septicemia were also associated with longer length of stays. Strict protocol to prevent VAP and septicemia should be implemented to help shorten the need for ventilator support and hospital stays. Additionally, this study found that timing of SRT did not associate with prolonged duration of ventilator support or other adverse outcomes. Therefore, in resource-limited settings it would be logical to wait and selectively provide SRT to neonates who are in need of the treatment to maximize SRT effectiveness and to avoid unnecessary SRT with less concern for adverse outcomes. Treating hsPDA may also reduce duration of NIV and length of stays.

Limitations

Several limitations were noted in this study. The number of neonates receiving SRT was relatively small and the design of the study was retrospective, therefore, the results might be affected by confounding factors. There were no standard criteria for SRT or extubation causing treatment variation among neonates. Surfactant types and doses were also varied among neonates. Recommended dose for poractant alfa was 200 mg/kg and for beractant was 100 mg/kg but due to cost constrain, majority of neonates had received lower dose than the recommendation. A prospective randomized control trial study with larger population and standard criteria for SRT, dosage of surfactant and extubation criteria could provide more accurate results.

CONCLUSION

Neonates who received E-SRT had longer duration of IMV than neonates who received L-SRT but not statistically significant. Also, there were no significant differences in other neonatal outcomes between each group. Adverse outcomes were likely to be related to GA and BW rather than timing of SRT. VAP and septicemia were major factors associated with prolonged ventilator support and adverse neonatal outcomes, thus, emphasis on preventing VAP and septicemia could be beneficial for neonates.

ACKNOWLEDGEMENTS

We would like to acknowledge Mr.Gurdeep Singh for editing the manuscript via Publication Clinic KKU, Thailand.

Conflicts of interest statement

Authors had no conflict of interest to declare.

REFERENCES

1. Ainsworth SB. Pathophysiology of Neonatal Respiratory Distress Syndrome. Treat Respir Med. 2005;4(6):423-37.
2. Jobe AH. 158 - Pathophysiology of Respiratory Distress Syndrome. In: Polin RA, Abman SH, Rowitch DH, Benitz WE, Fox WW,

editors. Fetal and Neonatal Physiology (Fifth Edition): Elsevier; 2017.p.1604-19.e2.
3. Kirsten GF, Kirsten CL, Henning PA, Smith J, Holgate SL, Bekker A, et al. The Outcome of ELBW Infants Treated With NCPAP and InSurE in a Resource-Limited Institution. Pediatrics. 2012;129(4):e952-e9.
4. Kandraju H, Murki S, Subramanian S, Gaddam P, Deorari A, Kumar P. Early routine versus late selective surfactant in preterm neonates with respiratory distress syndrome on nasal continuous positive airway pressure: a randomized controlled trial. Neonatology. 2013;103(2):148-54.
5. Kim SM, Park YJ, Chung SH, Choi YS, Kim CH, Bae CW. Early prophylactic versus late selective use of surfactant for respiratory distress syndrome in very preterm infants: a collaborative study of 53 multi-center trials in Korea. J Korean Med Sci. 2014;29(8):1126-31.
6. Rebello CM, Nacif LF, Deutsch AD, Paes AT. Timing of initial surfactant treatment in very low birth weight newborns. Einstein (Sao Paulo). 2010;8(3):320-4.
7. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrøm K, et al. Surfactant therapy and nasal continuous positive airway pressure for newborns with respiratory distress syndrome. Danish-Swedish Multicenter Study Group. N Engl J Med. 1994;331(16):1051-5.
8. Kribs A, Roll C, Göpel W, Wieg C, Groneck P, Laux R, et al. Nonintubated Surfactant Application vs Conventional Therapy in Extremely Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr. 2015;169(8):723-30.
9. Bancalari E, del Moral T. Bronchopulmonary Dysplasia and Surfactant. Neonatology. 2001;80(Suppl. 1):7-13.
10. Polin RA, Carlo WA. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014;133(1):156-63.
11. Ng EH, Shah V. Guidelines for surfactant replacement therapy in neonates. Paediatr Child Health. 2021;26(1):35-49.
12. Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, et al. Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. Pediatrics. 2008;121(5):e1310-8.
13. Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS, et al. Intratracheal Administration of Budesonide/Surfactant to Prevent Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2016;193(1):86-95.
14. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. J Pediatr. 2018;197:300-8.
15. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012;11(11):CD001456.
16. Cernada M, Brugada M, Golombek S, Vento M. Ventilator-Associated Pneumonia in Neonatal Patients: An Update. Neonatology. 2014;105(2):98-107.
17. Balany J, Bhandari V. Understanding the Impact of Infection, Inflammation, and Their Persistence in the Pathogenesis of Bronchopulmonary Dysplasia. Front Med (Lausanne). 2015;2:90.
18. Soll R, Ozek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2009;(1):CD000141.
19. Tsakalidis C, Giougki E, Karagianni P, Dokos C, Rallis D, Nikolaidis N. Is there a necessity for multiple doses of surfactant for respiratory distress syndrome of premature infants? Turk J Pediatr. 2012;54(4):368-75.
20. Willis KA, Weems MF. Hemodynamically significant patent ductus arteriosus and the development of bronchopulmonary dysplasia. Congenit Heart Dis. 2019;14(1):27-32.
21. Potsiurko S, Dobryanskyy D, Sekretar L. Patent ductus arteriosus, systemic NT-proBNP concentrations and development of bronchopulmonary dysplasia in very preterm infants: retrospective data analysis from a randomized controlled trial. BMC Pediatrics. 2021;21(1):286.

Transvaginal Urethrolysis as a Treatment Option for Women with Recurrent Cystitis

Sunporn Boonwong, M.D.*, Atichet Sawangchareon, M.D., Patkawat Ramart, M.D.***

**Division of Urology, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, 10700, Thailand, **Division of Urology, Department of Surgery, Taksin Hospital, Medical Service Department, Bangkok Metropolitan Administration, Bangkok, 10600, Thailand.*

ABSTRACT

Objective: To demonstrate the outcome of transvaginal urethrolysis as a treatment option for women with recurrent cystitis, which could be caused from voiding problems. In the case of a failure of non-invasive treatment, the surgical procedure to decrease outlet resistance may have a role.

Materials and Methods: Between January 2016 and December 2020, women with recurrent cystitis who underwent urethrolysis at Siriraj Hospital were retrospectively reviewed. Only women who were followed-up for more than 6 months were analyzed. Cure was defined by no clinical symptoms of cystitis, no pyuria on urine analysis, and/or negative urine culture during the follow-up period.

Results: In total, 52 women underwent transvaginal urethrolysis. The overall cure rate was observed 53.9% (28 cases) at a median follow-up time of 11.9 (6–59) months. Eighteen of the 44 cases (40.9%) who underwent a video urodynamics study showed bladder outlet obstruction, defined as a Solomon–Greenwell bladder outlet obstruction index of more than 5. None of the characteristics or urodynamics parameters showed statistically significant differences between the cure and failure groups. Postoperative urinary incontinence was reported in 14 cases (26.9%) but showed no statistical difference between the cure and failure group (p = 0.748).

Conclusion: Bladder outlet obstruction is a common cause of recurrent cystitis. Transvaginal urethrolysis may have a role as treatment for women with recurrent cystitis from voiding dysfunction who have failed non- and less-invasive treatments. Here, the overall cure rate was 53.8%. A factor associated with the cure rate could not be demonstrated in this study.

Keywords: Recurrent cystitis; voiding dysfunction; bladder outlet obstruction; detrusor underactivity; urethrolysis
(Siriraj Med J 2023; 75: 343-349)

INTRODUCTION

Cystitis is an inflammation of the urinary bladder and presents with dysuria in conjunction with urinary frequency, urgency, hematuria, worsening urinary incontinence, or suprapubic pain[1], and is usually associated with infection. The incidence of cystitis is significantly higher in women as a result of lower urinary tract anatomy. A study into the self-reported incidence of urinary tract infection (UTI) showed that 10.8% of women aged 18 years old or older have reported at least one presumed UTI during the past 12 months and estimated that 60.4% of all women experience at least one episode of UTI in a lifetime.[2] A study of community-acquired *Escherichia coli* cystitis reported that 49.2% of female patients had at least one episode of recurrent urinary tract infection (UTI) during 12-month follow-up and most of them

Corresponding author: Patkawat Ramart
E-mail: patkawat.ram@mahidol.ac.th
Received 15 February 2023 Revised 10 March 2023 Accepted 11 March 2023
ORCID ID:http://orcid.org/0000-0002-3394-9349
https://doi.org/10.33192/smj.v75i5.261230

were recurrent cystitis.[3] After the first episode of cystitis in young women, the 6-month risk of second UTI was reported to be 26.6%.[4] Moreover, genitourinary tract infection was found to be the second most common infection in a geriatric population.[5]

Complicated UTI, including recurrent infection, and urinary tract infection in an immunocompromised host, and/or with multi-drug resistant bacteria and in patients with a suspected anatomical or functional abnormality of the urinary tract, should be investigated.[1] Therefore, recurrent cystitis is considered an unusual problem, particularly from bacterial infection. The widely accepted definition of recurrent cystitis is described as 3 or more episodes of cystitis confirmed by a positive urine culture during a previous 12-month period or 2 or more episodes of infection during a 6-month period.[1]

Bladder outlet obstruction (BOO) is another cause of recurrent cystitis, so the concept of reducing outlet resistance to treat women with recurrent cystitis was proposed and studied in the past.[6-8] Treatment options include biofeedback[9], alpha-adrenergic antagonist[9], urethral dilation, internal urethrotomy[6,7], and urethrolysis.[8] Specifically, urethrolysis is an outlet reducing procedure that is used to treat female urethral syndrome[8] and bladder outlet obstruction after anti-incontinence procedures.[10,11] The procedure can be performed by a transvaginal, suprameatal, or retropubic approach.

The majority of studies have demonstrated that urethrolysis is an effective treatment for bladder outlet obstruction after anti-incontinence procedures and the success rate is between 58%–87%.[11-14] So far, to the best of our knowledge, there has been only one study on urethrolysis as a treatment in women with recurrent cystitis[8], but the surgical technique reported was different from in other studies. Therefore, this study aimed to demonstrate the outcome and role of transvaginal urethrolysis considering the same surgical techniques as other studies[11-13], more specifically for the case of lower urinary tract abnormality, which is a cause of recurrent cystitis. The second aim was to identify the predictive factors that might affect the outcome of urethrolysis.

MATERIALS AND METHODS

After the study was approved by the institutional review board, the medical records of all female patients who underwent urethrolysis between January 2016 and December 2020 at Siriraj Hospital were retrospectively reviewed. Only patients who had a history of recurrent cystitis and who were followed up at least 6 months after urethrolysis were enrolled and analyzed. Most cases had failed non- and less-invasive treatment, including alpha-adrenergic antagonist and urethral dilation, before it was decided to perform urethrolysis.

Patients who had a history of pelvic radiation, neurologic diseases with a significant abnormal neurologic examination, abnormal urinary tract findings on imaging studies, pelvic organ prolapse more than stage I on vaginal examination, and a history of past urethrolysis were excluded. Information from the medical records, including age, voiding symptoms, parity, history of vaginal surgery, diabetes mellitus, findings on vaginal examination, video urodynamics (VUDS) report, and outcome during the follow-up period were collected.

Recurrent cystitis was defined by 3 or more occurrences of clinical symptoms, including dysuria, frequency, and urgency, as well as demonstrated pyuria (White blood cells > 5 per high power field) on urine analysis (UA) and a positive urine culture for bacteria in the past year. All the cases must have failed to respond to proper antibiotics and subsequent medications, including alpha-adrenergic antagonists, bethanechol chloride, or vaginal estrogen, for at least 3 months.

To identify a cause of recurrent cystitis, careful history taking, vaginal examination, and/or video urodynamics study (VUDS) were performed. Vaginal examination indicated a loss of urethral mobility, and fixed and over-angulated urethra in all cases. If the clinical history indicated that BOO was strongly related to a past vaginal surgery, and/or vaginal examination revealed a mesh extrusion, VUDS was omitted. VUDS was performed in a sitting position on a radiolucent commode chair. The bladder outlet obstruction index for females (BOOIf), known as the Solomon–Greenwell formula, was used as a diagnostic criterion.[15] If BOOIf was more than 5, the patient was diagnosed as BOO.

During pressure-flow studies (PFS), if a patient was unable to void with a urethral catheter in place, the catheter would be removed, and then the patient would attempt to void with the rectal catheter in place to measure abdominal pressure, and fluoroscopy was utilized to demonstrate the urethral anatomy. Abnormal urethral findings on the fluoroscopic examination, including distortion or disproportion, were reported (Fig 1). In cases of unsuccessfully performed PFS both with and without the urethral catheter, free uroflowmetry and post-void residual urine tests were performed and measured in a private room, and these patients were diagnosed as non-specific voiding dysfunction (NVD). All the NVD showed a loss of urethral mobility and over-angulated urethra, as well as maximal urinary flow rate (Qmax), which was less than 20 ml/sec.

To demonstrate the outcome of urethrolysis in

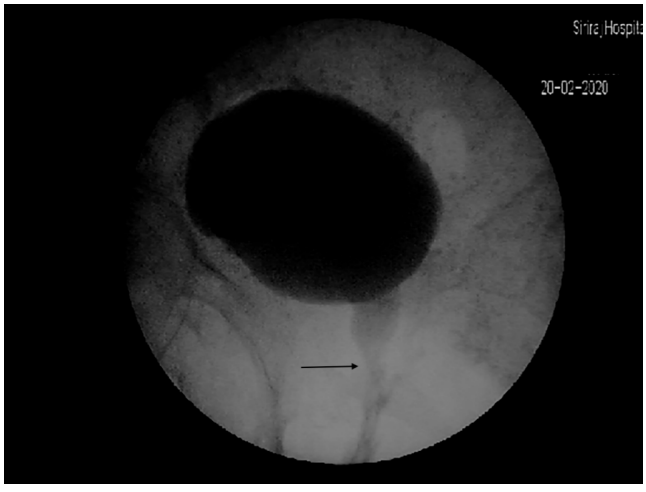


Fig 1. Fluoroscopic picture in a woman with recurrent cystitis demonstrated disproportion of the urethra (arrow) during a pressure-flow study.

the different types, they were categorized as clinical voiding dysfunction (CVD) and urodynamic bladder outlet obstruction (UBO). Clinical voiding dysfunction (CVD) included bladder outlet obstruction related to a past vaginal surgery, vaginal mesh extrusion, abnormal urethral findings on fluoroscopic examination, BOOIf ≤ 5 in the pressure-flow study or non-specific voiding dysfunction (NVD), while urodynamic bladder outlet obstruction (UBO) was only indicated in a case with a successfully performed pressure-flow study and BOOIf of more than 5.

For the outcome of urethrolysis, in order to make clear on the definition of cure, it was defined by no clinical symptoms and no pyuria on urine analysis during the follow-up period. Because asymptomatic bacteriuria might sometimes develop clinically significant cystitis which patients did not receive an appropriate investigation and took antibiotic by their own. In contrast, failure was defined as recurrent clinical symptoms of cystitis and demonstrated pyuria on urine analysis or a positive urine culture during the follow-up period.

Surgical technique

For transvaginal urethrolysis, a patient was positioned in the exaggerated dorsal lithotomy, and the operation was performed under general anesthesia. After the urethral catheter was indwelled and the bladder was emptied, the vagina was examined. Urethral mobility was evaluated by pulling the catheter. Bilateral incisions were made at the anterior vaginal wall, along the paraurethral area. The vaginal wall was dissected until the pubocervical fascia was identified. The fascia was punctured and disintegrated by curved-Mayo scissors and then the prevesical space was entered. In order to avoid bladder perforation, the bladder must be emptied before puncture and the curved-Mayo scissors must be pointed laterally, close to the pubic rami. Paraurethral tissue was bluntly dissected by the index finger while the paraurethral area and prevesical space were also freed up. In the case of synthetic mesh implantation, nearly the entire mesh was removed. The urethral mobility was re-evaluated by pulling the urethral catheter and by observing an increasingly downward movement of the urethra compared to preoperative evaluation. Bleeding was checked and secured. Vaginal incisions were properly re-approximated with non-absorbable sutures without intentional overbite stitches to avoid further scarring, potentially leading to a urethral obstruction. Vaginal packing with betadine-soaked gauze was kept in place for 24 hours. At 24-hour postoperative, the vaginal packing and urethral catheter were removed and the patient was discharged.

Statistical analysis

Descriptive statistics regarding age, diabetes mellitus, and past vaginal surgery were reported using the quantity as a number and percentage. Each of the video urodynamics parameters, including maximal urinary flow rate (Qmax), detrusor pressure at a maximal flow rate (PdetQmax), voided volume (VV), and post-void residual (PVR), were reported as the median with the minimum and maximum value according to the normal distribution. To analyze the factors implicating the urethrolysis outcome, qualitative factors, including the voiding symptoms, diabetes mellitus (DM), and past vaginal surgery, were compared by using the Chi-square test and Fisher's exact test. While the quantitative data, including age, Qmax, PdetQmax, and other urodynamics parameters, were compared by the unpaired t-test and Mann–Whitney U-test and reported as the mean or median between these two groups. All the data were analyzed using the program SPSS Inc., released in 2009, PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. These analyses used a 2-tailed test and considered statistically significant when $p < 0.05$.

RESULTS

A total of 127 cases who underwent urethrolysis during 5 years in our institute were reviewed and 7 cases were excluded because of a history of pelvic radiation. Only 52 cases met the inclusion criteria. The mean age was 68.8 ± 12.5 years old and 18 cases (34.6%) complained of voiding symptoms. Diabetes mellitus (DM) was found for 16 cases (30.8%) and the median parity was 3 (0–10). Twenty-four cases (46.2%) had a history of past vaginal surgery, including pelvic organ prolapse

procedures (9 cases), anti-incontinence procedures (8 cases), and combined prolapse organ prolapse with anti-incontinence procedures (5 cases). In these groups, 5 cases had bladder outlet obstruction strongly related to vaginal surgery and 3 cases had vaginal mesh extrusion, so they underwent transvaginal urethrolysis without preoperative video urodynamics study (VUDS). The remaining 44 cases had VUDS performed, including 30 cases (68.2%) with a successful pressure-flow study (PFS) and 14 cases (31.8%) with an unsuccessful PFS, which were categorized as non-specific voiding dysfunction (NVD). In the successful PFS, BOO, which was named as urodynamic bladder outlet obstruction (UBO), and non-bladder outlet obstruction were diagnosed in 18 and 12 cases, respectively. In addition, 28 of the 44 cases (63.3%) who had VUDS performed showed an abnormal urethra on fluoroscopic examination. To easily apply clinical practice, 34 cases were categorized as clinical voiding dysfunction (CVD), and 18 cases were also categorized as urodynamic bladder outlet obstruction (UBO) (Table 1).

Overall, the cure rate was observed as 53.8% (28 cases) and the median follow-up time was 11.9 (6–59) months. The cure rates between CVD and UBO were 55.9% and 50.9%, respectively, and there was no statistically significant difference between the two groups ($p = 0.91$). The predictive factors associated with the cure rate were analyzed but no characteristics showed a statistically significant difference (Table 2). In a subgroup analysis of UBO, there was no significant urodynamic parameters associated with the cure rate (Table 3).

There was no intraoperative bladder or urethral injury. One case required postoperative blood transfusion without any further intervention and one case had vaginal infection, which was successfully treated with oral antibiotics. During follow-up, 14 cases (26.9%) reported urinary incontinence (UI), among whom 8 had only mild symptoms, using only 1 protective pad per day, while 5 cases had severe urinary incontinence. Among the severe urinary incontinence cases, 3 were requested and scheduled for anti-incontinence procedures. The urinary incontinence rate was not statistically significant difference between the cure and failure group ($p = 0.748$). Interestingly, 8 of the 14 cases did not have recurrent cystitis during the follow-up period. Five cases (9.6%) that reported overactive bladder after urethrolysis required medical treatment. Four cases of the failure group underwent repeated urethrolysis because their clinical cystitis was improved during the initial 6 months of the postoperative period and voiding dysfunction was confirmed. Two cases still had recurrent cystitis postoperatively and the remaining complained of urinary incontinence and voiding symptoms without recurrent cystitis.

DISCUSSION

Recurrent cystitis in women is considered a complicated urinary tract infection (UTI) and an unusual problem. The AUA/CUA/SUFU guideline suggests complicated UTI should be investigated to identify a possible anatomical and functional abnormality.[1] Recurrent cystitis is another presentation of voiding problems, especially bladder outlet obstruction (BOO) after anti-incontinence procedures[12,16], even though, the majority of cases present with storage symptoms or combined storage and voiding symptoms rather than voiding symptoms alone.[8,10-12]

When focusing on the treatment of recurrent cystitis from voiding problems, some cases have mixed functional and anatomical problems. Therefore, all the cases in this study had been initially treated with an alpha-adrenergic antagonist with an aim to theoretically reduce outlet resistance, but they still had recurrent episodes of cystitis. For anatomical BOO without pelvic organ prolapse, the treatment options are urethral dilation, urethrotomy, urethrolysis, and urethroplasty.[17]

In the past studies, the improvement rate was 80%–100% of women with recurrent cystitis who were treated with urethral dilation using a sound dilator up to 40–45 Fr., but it needed repeat dilation.[18-19] In the present study, the majority of cases had been treated with urethral dilation with Hegar dilators, but they were not improved, and then they accepted the risk from urethrolysis after counseling. Moreover, 28 cases had abnormal urethral findings on fluoroscopic examination, which confirmed that the urethral narrowing or distortion was from outside of the lumen, named "periurethral fibrosis". Because of this reason, urethrotomy was not considered in this study, even though urethrotomy followed by urethral dilation up to 40–46 Fr. has shown excellent results in 31%–52% of cases.[6,20]

Most studies demonstrated that urethrolysis was an effective treatment for BOO after an anti-incontinence procedure and the success rate was 58%–87%.[11-14] There was only one study of urethrolysis used for treating 40 women with recurrent frequency and dysuria demonstrated who failed medical treatment and urethral dilation, and showed that 18 of the 40 women (45.0%) reported good results at a mean follow-up time of 10.7 (range 4–36) months. Only one woman who had recurrent frequency and dysuria with recurrent UTI reported poor results that were unsatisfactory, but urethrolysis was performed using a different technique, described as releasing the posterior support along the urethra. Two cases had stress

TABLE 1. Demographic data of all the cases.

Characteristics	Results (n = 52)
Age (years), mean±SD	68.6±12.5
Voiding symptoms, n (%)	18 (34.6)
Diabetes mellitus, n (%)	16 (30.8)
Parity, median (range)	3 (0 – 10)
Past vaginal surgery, n (%)	24 (46.2)
Pelvic organ prolapse procedures	9
Anti-incontinence procedures	8
Combined pelvic organ prolapse and anti-incontinence procedures	5
Clinical voiding dysfunction (CVD), n (%)	34 (65.4)
BOO† related to vaginal surgery without performing VUDS‡	5
Vaginal mesh extrusion without performing VUDS‡	3
NVD§	10
NVD§ with abnormal urethra	4
BOOIf¶ ≤ 5 with abnormal urethra	10
BOOIf¶ ≤ 5 without abnormal urethra	2
Urodynamic bladder outlet obstruction (UBO)††, n (%)	18 (34.6)
Qmax‡‡ (ml/sec), median (min, max)	6.9 (0.7, 11.0)
PdetQmax§§ (cmH2O), median (min, max)	33.0 (16.6, 68.3)
Voided volume (ml), median (min, max)	145 (110)
Postvoid residual urine (ml), median (IQR)	46.5 (0, 358)
BOOIf¶ score, median (min, max)	16.6 (6.0, 51.1)
Abnormal urethra on fluoroscopic examination	14
Follow-up time (months), mean (range)	11.9 (6 – 59)
Urinary incontinence after urethrolysis, n (%)	14 (26.9)

† BOO or bladder outlet obstruction.
‡ VUDS or video urodynamics study.
§ NVD or non-specific voiding dysfunction was defined as a loss of urethral mobility and overangulated urethra on vaginal examination and a maximal urinary flow rate (Qmax) < 20 ml/sec on free uroflowmetry and an unsuccessful pressure-flow study with and without a urethral catheter.
¶ BOOIf or bladder outlet obstruction index for female defined by Solomon–Greenwell.
†† UBO or urodynamic bladder outlet obstruction was indicated in successful PFS and BOOIf > 5.
‡‡ Qmax or maximal urinary flow rate.
§§ PdetQmax or detrusor pressure at the maximal urinary flow rate.

urinary incontinence after urethrolysis.[8] In our study, the overall cure rate, defined by no clinical symptoms and no pyuria on urinalysis during the follow-up period, was 53.8%.

Some studies mentioned that urethrolysis may be reasonable for clinical BOO without urodynamic proof by using a history of vaginal surgery, fixed or hypersuspended urethra on physical examination, or trabeculation on cystoscopy.[12,13] The outcomes were similar between clearly defined urodynamic BOO and the inability to generate detrusor contraction on the UDS.[12] This study also demonstrated that both CVD and UBO

TABLE 2. Characteristics associated with the cure rate.

Characteristics	Total (n = 52)	Treatment outcome		*P*-value
		Cure (n = 28)	Failure (n = 24)	
Age (years), mean±SD	68.6±12.5	70.0±12.2	68.3±13.1	0.839
Voiding symptoms, n (%)	18 (34.6)	12 (42.9)	6 (25.0)	0.291
Diabetes mellitus, n (%)	16 (30.8)	7 (25.0)	9 (37.5)	0.501
Past vaginal surgery, n (%)	24 (46.2)	11 (39.3)	13 (54.2)	0.427
Group				0.910
Clinical bladder outlet obstruction, n (%)	34 (65.4)	19 (67.9)	15 (62.5)	
Urodynamic bladder outlet obstruction, n (%)	18 (34.6)	9 (32.1)	9 (37.5)	
Follow-up time (months), mean (range)	11.9 (6–59)	10.7 (6–59)	17.9 (6–52)	0.192
Urinary incontinence after urethrolysis, n (%)	14 (26.9)	8 (28.6)	6 (25.0)	0.748

TABLE 3. Subgroup analysis of the pressure-flow study parameters in urodynamic bladder outlet obstruction (UBO).

Pressure-flow study parameters	Total (n = 18)	Treatment outcome		*P*-value
		Cure (n = 9)	Failure (n = 9)	
Qmax† (ml/sec), median (min–max)	6.9 (0.7–11.0)	8.7 (0.7–11.0)	6.5 (3.2–8.3)	0.354
PdetQmax‡ (cmH2O), median (min–max)	33.0 (16.6–68.3)	37.5 (18.1–54.1)	28.4 (16.6–68.3)	0.453
Voided volume (ml), median (min–max)	145 (4–356)	164 (4–356)	113 (47–318)	0.566
Postvoid residual urine (ml), median (IQR)	46.5 (110)	20 (82.5)	89 (143.5)	0.265
BOOIf§ score, median (min–max)	16.6 (6.0–51.1)	16.6 (10.0–40.3)	16.5 (6.0–51.1)	0.566
Abnormal urethra, n (%)	14 (77.8)	7 (77.8)	7 (77.8)	1.000

† Qmax or maximal urinary flow rate.
‡ PdetQmax or detrusor pressure at the maximal urinary flow rate.
§ BOOIf or bladder outlet obstruction index for females defined by Solomon–Greenwell.

had the same cure rate. It is a matter of fact that the female lower urinary tract anatomy and function is unreliable, and so it is difficult to initiate the most appropriate criteria for bladder outlet obstruction upon urodynamics study as in males.[21] So, clinical information, including the patient's history and precise vaginal examination, may be an important key. Unfortunately, the present study could not demonstrate any factor associated with the cure rate.

Previous studies have reported various postoperative urinary incontinence rates, ranging from 0% to 38.9%[11-13,22], depending on the population and surgical technique. The postoperative urinary incontinence rate in our study was 26.9%. Postoperative overactive bladder (OAB) is another problem that impacts the quality of life and individual satisfaction.[12,23] About 50% of cases had OAB symptoms after urethrolysis, and preoperative overactive bladder and/or detrusor overactivity (DO) are indicators of poor postoperative satisfaction.[23] Our study showed that 9.6% of cases had OAB symptoms that required medical treatment. Interestingly, postoperative OAB in our study was low because if our patients had both

OAB symptoms and recurrent cystitis, they were not diagnosed as OAB. Moreover, the repeat urethrolysis rate was widely different from that in past studies because of the different indications and diagnoses. In our study, only 4 cases were classified as failed urethrolysis at more than 6 months postoperatively; however, they had some symptoms improvement. After re-evaluation, they agreed to repeat urethrolysis.

The strengths of this study include that we studied in more specific conditions voiding dysfunction causing recurrent cystitis, and the surgical procedure was performed by a single surgeon with the same surgical technique, and also that no previous urethrolysis was performed in the cohort population. The limitations were the retrospective design of this study, which meant there were some missing data and only a small number of enrolled cases.

In conclusion, after the failure of non- and less-invasive treatments, urethrolysis may be a treatment option for women with recurrent cystitis from voiding problems. The overall cure rate was 53.8% in this study. Either clinical or urodynamic bladder outlet obstruction can be used as an indication for urethrolysis and here showed a comparable cure rate. No factor associated with the cure rate was demonstrated.

REFERENCES

1. Anger J, Lee U, Ackerman AL, Chou R, Chughtai B, Clemens JQ, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol 2019;202(2):282-9.
2. Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol 2000;10(8):509-15.
3. Ikaheimo R, Siitonen A, Heiskanen T, Karkkainen U, Kuosmanen P, Lipponen P, et al., Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. Clin Infect Dis 1996;22(1):91-9.
4. Foxman B. Recurring urinary tract infection: incidence and risk factors. Am J Public Health 1990;80(3):331-3.
5. Ruben FL, Dearwater SR, Norden CW, Kuller LH, Gartner K, Shalley A, et al., Clinical infections in the noninstitutionalized geriatric age group: methods utilized and incidence of infections. The Pittsburgh Good Health Study. Am J Epidemiol 1995;141(2):145-57.
6. Farrar DJ, Green NA, Ashken MH. An evaluation of Otis urethrotomy in female patients with recurrent urinary tract infections. Br J Urol 1973;45(6):610-5.
7. Keitzer WA, Allen JS. Operative treatment of chronic cystitis by urethrotomy: 10 years of experience. J Urol 1970;103(4):429-31.
8. Smith PJ, Powell PH, George NJ, Kirk D. Urethrolysis in the management of females with recurrent frequency and dysuria. Br J Urol 1981;53(6):634-6.
9. Minardi D, Pellegrinelli F, Conti A, Fontana D, Mattia M, Milanese G, et al. alpha1-Blockers for the treatment of recurrent urinary tract infections in women with dysfunctional voiding: a prospective randomized study. Int J Urol 2015;22(1):115-21.
10. Nitti VW, Raz S. Obstruction following anti-incontinence procedures: diagnosis and treatment with transvaginal urethrolysis. J Urol 1994;152(1):93-8.
11. McCrery R, Appell R. Transvaginal urethrolysis for obstruction after antiincontinence surgery. Int Urogynecol J Pelvic Floor Dysfunct 2007;18(6):627-33.
12. Foster HE, McGuire EJ. Management of urethral obstruction with transvaginal urethrolysis. J Urol 1993;150(5 Pt 1):1448-51.
13. Carr LK, Webster GD. Voiding dysfunction following incontinence surgery: diagnosis and treatment with retropubic or vaginal urethrolysis. J Urol 1997;157(3):821-3.
14. Goldman HB, Rackley RR, Appell RA. The efficacy of urethrolysis without re-suspension for iatrogenic urethral obstruction. J Urol 1999;161(1):196-8; discussion 198-9.
15. Solomon E, Yasmin H, Duffy M, Rashid T, Akinluyi E, Greenwell TJ. Developing and validating a new nomogram for diagnosing bladder outlet obstruction in women. Neurourol Urodyn 2018;37(1):368-78.
16. Woodman PJ, Ruiz HL. Retropubic urethrolysis without resuspension for the management of posturethropexy urinary retention and voiding dysfunction. Mil Med 2004;169(2):117-20.
17. Meier K, and Padmanabhan P. Female bladder outlet obstruction: an update on diagnosis and management. Curr Opin Urol 2016;26(4):334-41.
18. Essenhigh DM, Ardran GM, Cope V. A study of the bladder outlet in lower urinary tract infections in women. Br J Urol 1968;40(3):268-77.
19. McCannel DA, Haile W. Urethral narrowing and its treatment: a possible solution for the problems of recurrent urinary infection and the "irritable bladder". Int Urol Nephrol 1982;14(4):407-14.
20. Immergut MA, Gilbert EC. The clinical response of women to internal urethrotomy. J Urol 1973;109(1):90-1.
21. Pang KH, Campi R, Arlandis S, Bo K, Chapple CR, Costantini E, et al., Diagnostic Tests for Female Bladder Outlet Obstruction: A Systematic Review from the European Association of Urology Non-neurogenic Female LUTS Guidelines Panel. Eur Urol Focus 2022;8(4):1015-30.
22. Giannis G, Bousouni E, Mueller MD, Imboden S, Mohr S, Raio L, et al. Can urethrolysis resolve outlet obstruction related symptoms after Burch colposuspension for stress urinary incontinence? Eur J Obstet Gynecol Reprod Biol 2015;195:103-7.
23. Starkman JS, Duffy JW 3rd, Wolter CE, Kaufman MR, Scarpero HM, Dmochowski RR. The evolution of obstruction induced overactive bladder symptoms following urethrolysis for female bladder outlet obstruction. J Urol 2008;179(3):1018-23.

The Relationship between Kolb Learning Style and Academic Performances in Orthopedic Residents

Cherdsak Iramaneerat, M.D., Ph.D.*,, Surin Thanapipatsiri, M.D.***, Thasaneeya Ratanaroutai Nopparatjamjomras, Ph.D.**, Thos Harnroongroj, M.D., M.Sc.*****

**Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, **Siriraj Health Science Education Excellence Center, Faculty of Medicine Siriraj Hospital, ***Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: The assimilating and converging Kolb learning style were reported to have positive correlation with critical thinking ability in Orthopedic resident. However, the relationship between Kolb learning styles and academic performance remained controversy. The objective of this study is to report the relationship between Kolb learning style and academic performance in Orthopedic residents.

Materials and Methods: The causal comparative cross-sectional study on 48 Orthopedic residents of academic year 2020 was conducted. The demographic characteristics of the participants were reviewed. The scores from the multiple choices question (MCQ) in-training examination, the objective structured clinical examination (OSCE) and the global performance rating scale were collected to represent academic performances of each Miller's pyramid of assessment level. The Kolb learning style inventory were allocated. The statistical analysis was performed and $p < 0.05$ was considered statistically significant difference.

Results: The response rate was 100%. There was no statistically significant difference of MCQ in-training examination, OSCE and global performance rating scale among each learning style as p=0.789, 0.493 and 0.407, respectively. The assimilating and converging styles were the 2 learning styles which had the academic performance scores above the average scores in all assessments.

Conclusion: This study could not demonstrate the significant difference of academic performances among Kolb learning style in Orthopedic residents. However, the assimilating and converging style had the consistent scores above average scores in all domains. The Orthopedic learning experience should focus on the development of reflective observation, abstract conceptualization and active experimentation to facilitate effective improvement in academic performance of the residents.

Keywords: Kolb learning styles; Orthopedic residents; academic performance (Siriraj Med J 2023; 75: 350-355)

INTRODUCTION

Orthopedic resident training requires the development of knowledge, skill and attitude in the limited 4-year time frame.[1] Effective experiential learning principle has been proved as an important learning process to enhance the competency development and improve critical thinking skill in Orthopedic resident.[2] The commonly used experiential learning in Orthopedic training is "Kolb learning cycle" which is compose of 4 sequential learning processes as concrete experience, reflective observation, abstract conceptualization and active experimentation (Fig 1).[2-5]

Corresponding author: Thos Harnroongroj
E-mail: harnroongrojt@gmail.com
Received 9 February 2023 Revised 8 March 2023 Accepted 12 March 2023
ORCID ID:http://orcid.org/0000-0003-3330-6869
https://doi.org/10.33192/smj.v75i5.261255

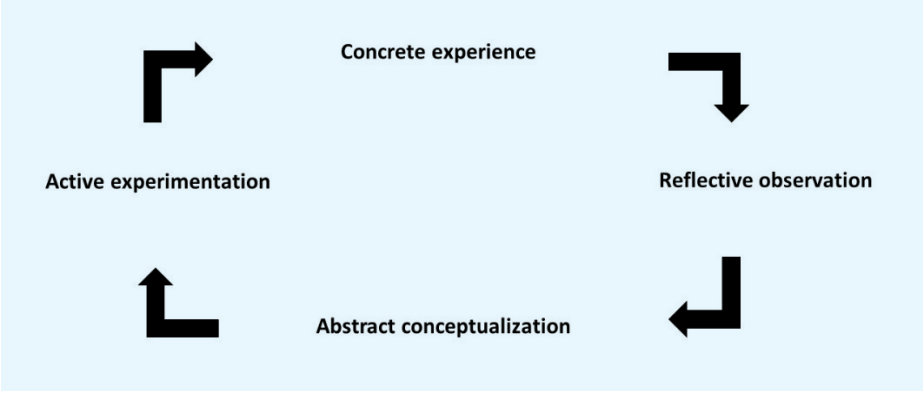


Fig 1. The Kolb experiential learning cycle which was composed of 4 sequential learning steps as concrete experience, reflective observation, abstract conceptualization and active experimentation.

According to the "Kolb learning cycle", the learners could be divided into 4 different "Kolb learning styles" depended on the 2 commonly used learning processes as diverging (concrete experience-reflective observation), assimilating (reflective observation-abstract conceptualization), converging (abstract conceptualization-active experimentation), and accommodating (active experimentation-concrete experience).[6] Previous studies found that the 2 commonest Kolb learning styles in Orthopedic residents were mixed between converging (25.0% - 53.5%), assimilating (9.9% - 37.5 %) and accommodating (18.3% - 22.9%).[1,2] And, converging and assimilating was associated with good critical thinking ability as these 2 learning styles used abstract conceptualization as an important process of deep learning strategy.[2] Despite those mentioned studies, none had demonstrated the significant relationship between the Kolb learning styles and academic performance in Orthopedic resident.

The objective of this study is to find out the relationship between Kolb learning style and academic performance in Orthopedic resident. The hypothesis in this study is converging and assimilating style which has positive relationship with critical thinking ability[2] will have positive relationship with the good academic performance.

MATERIALS AND METHODS

The design of this study was causal comparative cross-sectional study. The study was conducted under the approval of the institutional review board (COA no. Si 010/2021). The Orthopedic residents during academic year 2020 of single institute were included. And, the resident who did not desire to reveal the demographic or educational data as well as unwilled to do the questionnaire was excluded. Finally, there were 48 participants enrolled in this study without excluded sample.

The demographic profile of the participants were reviewed which included sex, age, the graduated medical school and the grade point average of graduated medicine degree. The 5-level Likert scale type native language Kolb learning style inventory version 3.1 which was consisted of 48 learning habit phrases representing 4 different Kolb learning processes (concrete experience, reflective observation, abstract conceptualization and active experimentation) were allocated to participants to evaluate the Kolb learning style individually.[6] The consideration of Kolb learning style was categorized using cartesian graph by calculating of the score of concrete experience minus abstract conceptualization and reflective observation minus active experimentation (Fig 2). The content validity and internal consistency reliability of this questionnaire was acceptable with the Cronbach alpha co-efficient of 0.93.[6,7] The questionnaires were collected and analyzed by one well-trained author at the mid-academic year.

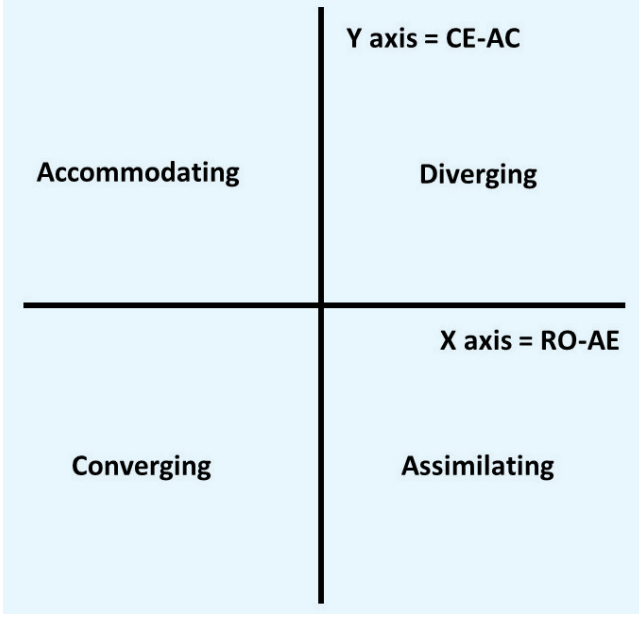


Fig 2. The Kolb learning style categorization was based on the calculation using cartesian graph. The vertical line (y axis) was the absolute score of concrete experience minus to abstract conceptualization (CE - AC). The horizontal line (x axis) was the absolute score of reflective observation minus active experimentation (RO - AE). The final plot on the graph was the individual learning style.

The academic performance assessments in this study included variety of levels according to Miller's pyramid of assessment. For the level of "knows" and "knows how", the academic performance was represented by the multiple choices question (MCQ) in-training examination. The test was composed of 100 MCQs included all Orthopedic subspecialties and basic science knowledge. The score was ranged from 0 to 100. For the level of "shows how", the objective structural clinical examination (OSCE) score was reviewed. The test included 9 stations (1 station per 1 sub-specialty) and the score was ranged from 0 to 100 on each test. So, the total score of OSCE was 900. And, for the level of "does", the global performance rating scale of the rotation along the whole academic year included 12 rotations (1 rotation per month) was examined. The score was ranged from 0 to 28. The scoring system was a 5-level Likert scale included 7 domains as moral-ethics, knowledge, psychomotor, intelligence, interpersonal, communication and responsibility skills. The MCQ in-training examination and OSCE were held at the 11-month of the academic year. All participants in every resident year did the same tests. While, the score of the global performance rating scale was reviewed at the first month of new academic year after all residents finished their all 12 rotations. The score reviews were performed altogether by two authors.

Statistical analysis

The statistical analysis was done using IBM SPSS Statistics for Windows 21.0 (IBM Corp, Armonk, NY). The categorical data was presented as number, percentage and ratio. The Shapiro-Wilk test was used to evaluate the normality of the interval data. Mean and standard deviation (SD) was presented for normal distributed data. And, median and interquartile range (IQR) was presented for non-normal distributed data. The comparison of interval data was done using Analysis of the Variance (ANOVA) and Kruskal-Wallis H test depended on the data distribution. The statistically significant difference was considered as $p < 0.05$.

RESULTS

The response rate of the questionnaires was 100 %. The mean (SD) age of the participants was 30.4 (1.36) years old. There were 44 men (91.7 %) and 4 women (8.3 %). The mean (SD) GPA of medicine degree was 3.27 (0.33). The Kolb learning styles in Orthopedic residents included 18 assimilating (37.5 %), 12 converging (25.0 %), 11 accommodating (22.9 %) and 7 diverging (14.6 %). There was no statistically significant difference of learning styles among each resident year, $p = 0.810$. (Table 1)

The comparative analysis of the academic performance scores demonstrated no statistically significant difference of MCQ in-training examination, OSCE and global performance rating scores among each Kolb learning style as p=0.789, 0.493 and 0.409, respectively. However, it was shown that assimilating and converging styles had the mean academic scores above the total average scores for all 3 assessments. While, the diverging styles had the mean score above the average score only in global performance rating score. The accommodating style had the mean score below the average score for all examinations (Table 2, 3 and 4).

TABLE 1. The distribution of Kolb learning styles in Orthopedic residents.

Resident training year	Diverging	Assimilating	Converging	Assimilating
Fourth (12)	3 (25.0%)	5 (41.7%)	2 (16.7%)	2 (16.7%)
Third (12)	2 (16.7%)	5 (41.7%)	2 (16.7%)	3 (25.0%)
Second (12)	0 (0.0 %)	4 (33.3%)	4 (33.3%)	4 (33.3%)
First (12)	2 (16.7%)	4 (33.3%)	4 (33.3%)	2 (16.7%)
Total (48)	7 (14.6%)	18 (37.5 %)	12 (25.0%)	11 (22.9%)

* chi-square demonstrated no statistically significant difference of learning style in each training year as p=0.810.

TABLE 2. The relationship of Kolb learning styles and the multiple choices question (MCQ) in-training examination scores (n = 48).

Kolb learning styles	MCQ in-training examination scores Mean (SD)
Diverging (7)	56.3 (5.38)
Assimilating (18)	58.6 (9.38)
Converging (12)	57.4 (12.3)
Accommodating (11)	54.8 (9.54)
Total (48)	57.1 (9.61)

* One way ANOVA demonstrated no statistically significant difference of scores among each learning style as p=0.789.

TABLE 3. The relationship of Kolb learning styles and the objective structural clinical examination (OSCE) scores (n = 48).

Kolb learning styles	OSCE scores Mean (SD)
Diverging (7)	604.4 (62.2)
Assimilating (18)	639.6 (72.7)
Converging (12)	650.6 (79.2)
Accommodating (11)	612.8 (79.2)
Total (48)	631.1 (76.7)

* One way ANOVA demonstrated no statistically significant difference of scores among each learning style as p=0.493.

TABLE 4. The relationship of Kolb learning styles and the global performance rating scores (n = 48).

Kolb learning styles	Global performance rating scores Mean (SD)
Diverging (7)	24.7 (0.84)
Assimilating (18)	23.9 (1.81)
Converging (12)	24.0 (1.39)
Accommodating (11)	23.4 (2.05)
Total (48)	23.8 (1.67)

* One way ANOVA demonstrated no statistically significant difference of scores among each learning style as p=0.407.

DISCUSSION

According to the result of this study, there was no statistically significant difference of academic performance scores regarding to Kolb learning styles. As a result, the hypothesis of this study was rejected. However, there was an interesting finding that the assimilating and converging style had the mean academic performance scores above the average scores for all assessments.

The assimilating and converging style shared the similar concept of experiential learning as the using of "abstract conceptualization" for the gathering experiences.[1,2,7] The learning characteristics of these 2 learning styles could be defined as "deep learning strategy".[8,9] Deep learning strategy involved the effective learning processes as using intrinsic motivation, apparent understanding of the meaning of what was learnt, connecting the new to prior knowledge (constructivism) and critically evaluating of knowledge.[8] And, this learning strategy had been reported to be associated with good academic achievement.[8-10] Apart from "abstract conceptualization, these 2 learning styles also used "reflective observation" and "active experimentation" for the learning.

In the educational context application, the learning processes regarding to these 2 learning styles as reflective observation, abstract conceptualization and active experimentation should be promoted. The Kolb learning style in individual learner could be adapted regarding to the maturity and learning experience.[11] Effective reflective observation and abstract conceptualization could be utilized by encouraging a "reflection" process for all available Orthopedic learning experiences. A reflection is "a complex and deliberate process of thinking about and interpreting experience in order to learn from it". This learning tool could enhance deep integrated and lifelong learning to the learner.[12,13] A reflection could be divided into 3 different levels of complexity as descriptive, practical and critical reflection. A critical reflection was emphasized as the most beneficial type.[12,14] The important factors which could promote the effective reflection of the learners were suitable available time and environment.[12-14] The instructor should plan the strategy which could provide available time for the Orthopedic residents to do reflection. This included the effective time management that was preserved for doing this learning process or using the assisting learning tools which allowed the learners to do the reflection at the suitable time such as e-learning or e-portfolio especially in the high service workload situation.[14,15]

Supporting the active experimentation in Orthopedic learning experience could be managed in various ways. The introduction of simulation for development of the skill domain played an important role. The Orthopedic residents would be able to enhance their experiential learning gradually. The simulation allowed the residents to repeat their skill practice with safety environment.[16,17] Julthongpipat et al. studied the development of simulation model for transradial catheterization practice in 18 fellows. The results demonstrated that the fellows satisfied with the simulation model and this training method provided the benefit as increasing familiarity and confidence to their practice.[18] Many studies in the orthopedic field supported the benefit of using simulation in orthopedic learning experience. Angelo et al. reported the traditional learning combined with supportive simulation training and progressive assessment provided statistically significant better learning outcome compared with the traditional learning alone (p=0.011) for the arthroscopic shoulder joint surgery practicing in 44 orthopaedic residents.[19] Yari SS et al reported the statistically significant improvement of performance score (p=0.003 and 0.035) using virtual simulator for the teaching of knee and shoulder arthroscopy in 18 Orthopaedic residents.[16]

Apart from the simulation, formative real-time and authentic assessment could also support active experimentation experiences in orthopedic residents. One effective assessment tool which could be done for this purpose was an "entrustable professional activities" (EPAs). EPAs had become one of favorable assessment tool in the Orthopedic field.[20] Dwyer T et al. demonstrated that using EPAs combined with simulation training as a reliable assessment tool to assess the residents' cognitive and psychomotor competencies for the management of patient undergoing surgery for ankle fracture, intertrochanteric fracture and total knee arthroplasty.[21] The strength of EPAs was about the ability to do the assessment formatively which allowed the residents to gradually develop themselves along with the target each upgoing year.[22,23]

This study provided the new in-depth analysis in term of the relationship between Kolb learning styles and academic performance in every level of Miller's pyramid of assessment. Even though, this research could not demonstrate the statistically significant positive-negative relationship between learning style and academic performance. However, the finding that the assimilating and converging learners had academic performance scores above the average scores in all domains could bring the attention to the instructors to facilitate Orthopedic learning experiences involving in effective reflective observation, abstract conceptualization and active experimentation. The limitations of this study included the sample size from the single training center which posed the problem of external validity and the small sample size which led to

statistical underpower in some aspects. We recommended research as a multi-center study involving more numbers of samples which might bring more significant finding in the future.

CONCLUSION

This study could not demonstrate the significant difference of academic performance among each Kolb learning style in Orthopedic residents. However, the assimilating and converging style had the consistent scores of all academic performance domains above the average scores. In term of application, the Orthopedic learning experience should emphasize on the development of reflective observation, abstract conceptualization and active experimentation to facilitate effective Orthopedic competency development and improving academic performance.

REFERENCES

1. Richard RD, Deegan BF, Klena JC. The Learning Styles of Orthopedic Residents, Faculty and Applicants at an Academic Program. J Surg Educ. 2014;71(1):110-8.
2. Harnroongroj T, Thanapipatsiri S, Nopparatjamjomras TN, Iramaneerat C. The Relationship Between Learning Styles, Academic Achievement, and Critical Thinking Skills Among Orthopedic Residents. Proceeding of Graduate Research Forum. 2022
3. Sand JN, Elison-Bowers P, Wing II TJ, Kendrick L. Experiential Learning and Clinical Education. Psychology. 2014;18(4):1-7.
4. Kolb DA. Experiential learning: Experience as the source of learning and development. Englewood Cliffs. New Jersey. Prentice-Hall; 1984.
5. McCarthy M. Experiential Learning Theory: From Theory to Practice. Journal of Business & Economics Research. 2016;14(3): 91-100.
6. Lerdlop W. Learning Styles of Students in the Faculty of Science and Technology. Suan Sunandha Rajabhat University, Bangkok. Bangkok: Suan Sunandha Rajabhat University; 2011.
7. Kolb AY, Kolb DA. The Kolb Learning Style Inventory Version 3.1 2005 Technical Specifications. Experiential Based Learning Systems [Internet]. 2005 [Cited 2022 November 30]. Available from: http://www.learningfromexperience.com/.
8. Hayat AA, Shateri K, Amini M, Shokrpour N. Relationships between academic self-efficacy, learning-related emotions, and metacognitive learning strategies with academic performance in medical students: a structural equation model. BMC Med Educ. 2020;20:76.
9. Piumatti G, Guttormsen S, Zurbuchen B, Abbiati M, Gerbase MW, Baroffio A. Trajectories of learning approaches during a full medical curriculum: impact on clinical learning outcomes. BMC Med Educ. 2021;21:370.
10. Kusurka RA, Croiset G, Galindo-Garre F, Ten Cate O. Motivational profiles of medical students: Association with study effort, academic performance and exhaustion. BMC Med Educ. 2013; 13:87.
11. Quillin RC, Cortez AR, Pritts TA, Hanseman DJ, Edwards MJ, Davis BR. Surgical resident learning styles have changed with work hours. J Surg Res. 2016;200:39-45.
12. Mamede S, van Gog T, Moura AS, de Faria RM, Peixoto JM, Rikers RM, Schmidt HG. Reflection as a strategy to foster medical students' acquisition of diagnostic competence. Med Educ. 2012;46(5): 464-72.
13. Hatton N, Smith D. Reflection in teacher education: Towards definition and implementation. Teaching and Teacher Education. 1995;11(1):33-49.
14. Robertson K. Reflection in professional practice and education. Aust Fam Physician. 2005;34(9):781-3.
15. Branch WT, Paranjape A. Feedback and reflection: teaching methods for clinical settings. Acad Med. 2002;77:1185-8.
16. Yari SS, Jandhyala CK, Sharareh B, Athiviraham A, Shybut TB. Efficacy of a virtual arthroscopic simulator for Orthopaedic surgery residents by year in training. Orthop J Sports Med. 2018;6(11):2325967118810176.
17. Aim F, Lonjon G, Hannouche D, Nizard R. Effectiveness of virtual reality training in Orthopaedic surgery. Arthroscopy. 2016;32(1):224-32.
18. Julthongpipat K, Dumavibhat C, Towashiraporn K, Patpituck P. Development of Simulation Model for Transradial Catheterization Practice for Physicians. Siriraj Med J. 2022;74(9):570-4.
19. Angelo RL, Ryu RKN, Pedowitz RA, Beach W, Burns J, Dodds J, et al. A proficiency-based progression training curriculum coupled with a model simulator results in the acquisition of a superior arthroscopic Bankart skill set. Arthroscopy. 2015; 31(10):1854-71.
20. Wadey DM, Dev P, Buckley R, Walker D, Hedden D. Competencies for Canadian Orthopaedics surgery core curriculum. J Bone Joint Surg Br. 2009;91(12):1618-22.
21. Dwyer T, Wadey V, Archibald D, Kraemer W, Shantz JS, Townley J, et al. Cognitive and psychomotor entrustable professional activities: Can simulators help assess competency in trainees. Clin Orthop Relat Res. 2016;474:926-34.
22. Van Loon KA, Driessen EW, Teunissen PW, Scheele F. Experiences with EPAs, potential benefits and pitfalls. Medical Teacher. 2014;36(8):698-702.
23. Pinilla S, Lenouvel E, Cantisani A, Kloppel S, Strik W, Huwendiek S, et al. Working with entrustable professional activities in clinical education in undergraduate medical education: a scoping review. BMC Med Educ. 2021;21:172.

Routine Fogarty Catheter Occlusion of Fistula in Esophageal Atresia with Tracheoesophageal Fistula Surgery: A Retrospective Study

Darunee Sripadungkul, M.D.*,, Noriko Miyazawa, M.D., Ph.D.*, Eri Shinto, M.D.***, Yuko Kanke, M.D.****, Haruto Fujita, M.D.*****

**Department of Anesthesiology, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan, **Department of Anesthesiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand., ***Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan., ****Department of Anesthesiology, Tochigi Medical Center, Tochigi, Japan, *****Department of Anesthesiology, Keio University School of Medicine, Tokyo, Japan.*

ABSTRACT

Objective: We aimed to analyze the outcomes of patients who underwent surgical repair of congenital esophageal atresia (EA) with a distal tracheoesophageal fistula (EA/TEF) or a Gross type C with successful routine Fogarty catheter occlusion of TEF.

Materials and Methods: We retrospectively reviewed the medical records of patients who underwent surgical repair of Gross type C with successful routine Fogarty catheter occlusion of fistula between April 2010 and November 2016.

Results: Nineteen patients were enrolled and included for analysis. Mean gestational age was 38.7 (1.9) weeks with 2 (10.5%) neonates born prematurely. Mean birthweight was 2569.3 (425.3) g. Five (26.3%) patients required mechanical ventilation (MV) before surgical repair of TEF. Median post-operative required MV after TEF surgery was 4 (3-6) days. The most common of post-operative complications were wound dehiscence (10.5%) and pneumothorax (10.5%). Long-term complications were gastroesophageal reflux disease (36.8%) and tracheomalacia (31.6%).

Conclusion: The success rate of routine TEF occlusion with a Fogarty catheter was 86.4%. Routine Fogarty catheter occlusion of TEF can be used safely with experienced personnel, low incidence of aspiration and satisfied ventilation. There was no serious complication associated with placement of Fogarty catheter or catheter dislodgement, and it did not occur during any of the procedures.

Keywords: Congenital esophageal atresia (EA); Fogarty catheter; outcomes; tracheoesophageal fistula (TEF) (Siriraj Med J 2023; 75: 356-361)

INTRODUCTION

Congenital esophageal atresia (EA) is a rare congenital anomaly by complete interruption of the esophagus with a prevalence of 1.7 per 10,000 live births.[1] Congenital EA with a distal tracheoesophageal fistula (EA/TEF), or Gross type C, is the most common type, comprising 85% of EA cases.[2] This congenital anomaly is often associated with the anomalies described by the acronym VACTERL (vertebral anomalies, imperforated anus, congenital heart disease (CHD), tracheoesophageal anomalies, renal anomalies and limb anomalies). Surgical repair and anesthetic management are challenging because of the difficulty in management of airway and ventilation, control of adverse hemodynamic from associated anomalies of cardiovascular system and the thoracotomy procedure.[2-4]

Corresponding author: Darunee Sripadungkul
Email: daruneesripa@gmail.com
Received 5 January 2023 Revised 19 March 2023 Accepted 19 March 2023
ORCID ID:http://orcid.org/0000-0003-2228-2224
https://doi.org/10.33192/smj.v75i5.260704

The ideal management of most patients with EA/TEF might be the ligation of the fistula and primary esophageal repair performed in a single operation. Nevertheless, patients with persistent aspiration and recurrent pneumonia from the existing fistula induce poor medical conditions, disabling the neonates to withstand corrective surgery performed under general anesthesia. Use of a Fogarty catheter to occlude the fistula, by using rigid or flexible bronchoscopy, can be used to improved lung function and their medical condition.[2,5]

The classic technique for airway and ventilation management for TEF repair is to maintain spontaneous ventilation and pass the endotracheal tube (ET) tip distal to fistula.[6] Despite this technique, ineffective ventilation may occur because of inadvertent placement of the ET in the fistula, unintentional ventilation of the fistula, or massive gastric distention.[7] When TEF is very near or at the carina, this technique becomes impossible and unreliable.[8] Alternative technique is to controlled ventilation with muscle relaxant and placement a Fogarty catheter in the fistula under rigid or flexible bronchoscopy for separation of the airway and gastrointestinal (GI) tract. Previous studies have described the use of Fogarty balloon occlusion in unstable patients or in H-type fistulas that may be difficult to identify, and re-operative procedures.[5,9,10] The benefits of routine use of Fogarty catheters in the repair of TEF were reduction of aspiration, improved ventilation, safely and expeditiously.[11]

We aimed to analyze the outcomes of patients who underwent surgical repair of Gross type C EA/TEF with successful routine Fogarty catheter occlusion of tracheoesophageal fistula in a single institution.

MATERIALS AND METHODS

Study design

After approval of the institutional review board (H28b-135), we retrospectively reviewed the medical records of patients who underwent surgical repair of Gross type C EA/TEF between April 2010 and November 2016 at Tokyo Metropolitan Children's Medical Center. Inclusion criteria included patients who underwent surgical repair of Gross type C EA/TEF with successful routine Fogarty catheter occlusion of fistula. We exclude the patient who underwent surgical repair of Gross type C EA/TEF with unsuccessful routine Fogarty catheter occlusion of fistula. The data collected and analyzed consist of three sections. The first section evaluated patient characteristics, including gender, gestational age (GA), birth weight (BW), Apgar score, day of life (DOL) at surgery, body weight at surgery, and associated anomalies. The second section evaluated surgical management, including initial surgery and other surgical procedures performed on the same admission, and the distance between the upper and lower esophageal ends (esophageal gab). The third section evaluated anesthetic management, including pre-operative events (i.e., desaturation (SpO_2 < 90%)[12], tracheal intubation or tracheostomy pre-operatively, inotropic support), intra-operative events (i.e., desaturation, difficult ventilation, and inotropic support), intra-operative outcomes (surgical time, anesthetic time, fluid management, urine output and blood loss) and post-operative outcomes (duration of received mechanical ventilation (MV), prolonged post-operative MV after TEF repair (≥ 7 days)[13], post-operative complications and long-term complications).

All Gross type C EA/TEF repairs were performed in the lateral decubitus position via thoracotomy. No endoscopic repairs were performed in any of the cases. All patients from the neonatal intensive care unit (NICU) had an intravenous line before surgery. The patients were gently ventilated with a bag and mask before tracheal intubation. We examined all patients with flexible bronchoscopy (Olympus BF-N20 Fiber Bronchoscope, outer diameter 2.2 mm) through the ETT lumen to assess the location and size of the TEF, after which we extubated and inserted a Fogarty catheter (Fogarty arterial embolectomy catheter, 3 Fr, balloon diameter 5 mm, Edwards Lifesciences, Irvine CA, USA). During laryngoscopy, a Fogarty catheter was inserted until the tip reached the mid-trachea, followed by reintubation with an uncuffed endotracheal tube. The tip of the Fogarty catheter was pre-bent to face backward during insertion. Immediate, flexible bronchoscopy was performed again to guide a Fogarty catheter into the TEF until the balloon disappeared and inflated with 1 mL of air. We performed TEF occlusion with a Fogarty catheter in all patients. In addition to standard American Society of Anesthesiologists (ASA) monitoring, patients had invasive pressure monitoring or had percutaneous inserted central catheter (PICC) line was placed pre-operatively during the EA/TEF repair. During anesthetic maintenance, general anesthesia was maintained by remifentanil 0.1-0.3 μg/kg/min, fentanyl 1 μg/kg/dose, midazolam 0.1 mg/kg/dose, rocuronium 0.2-0.3 mg/kg/dose, and a low end-expired concentration of sevoflurane.

After the surgery, all patients retained an endotracheal tube or tracheostomy and were on MV during their transfer to the NICU. Post-operative analgesia was provided primarily with an opioid (fentanyl or morphine hydrochloride), dexmedetomidine, and acetaminophen. Post-operative sedation was provided with midazolam.

Statistical analysis

Data analysis was performed using STATA 10.1. We

used descriptive statistics to describe patient characteristics, surgical management and anesthetic management (intra-operative and post-operative outcomes). Categorical data was presented as number and percentage. Continuous data was analyzed using the Shapiro-Wilk test for normality test and presented as mean (standard deviation) and median (interquartile range).

We calculated the proportion using the number of participants with non-missing data. The estimated required sample size was 18 patients as calculated using the formula for an infinite population proportion with a proportion (p) of 0.754 and calculated error (d) of 0.20. The total population consisted of 19 patients. The study was analyzed and presented with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

RESULTS

A total of 22 patients were identified as having undergone surgical repair of Gross type C EA/TEF. We excluded 3 patients who underwent unsuccessful routine Fogarty catheter occlusion of fistula. Nineteen patients were enrolled and included for analysis.

Three patients (13.6%) who failed routine Fogarty catheter occlusion of fistula; however, the medical records were not recorded cause of failure to perform this procedure. Two patients had multiple severe associated anomalies (i.e., preterm, low birth weight (LBW), congenital tracheal stenosis (CTS), CHD score ≥ 3 on the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1),[14,15] pre-operatively desaturation, cardiac arrest which had cardiopulmonary resuscitation (CPR) and on inotropic support, and had distance between the upper and lower esophagus ends ≥ 10 mm. Meanwhile, one patient had CHD (RACHS-1 score < 3), and vocal cord paralysis.

Patient characteristics

Twelve (63.2%) patients were male. Mean GA was 38.7 (1.9) weeks with 2 (10.5%) neonates born prematurely. Mean BW was 2569.3 (425.3) g with 9 (47.4%) neonates having a LBW (BW less than 2500 g). Median Apgar score at 1 and 5 minutes were 8 (8-9) and 9 (8-9). The patients with type C EA/TEF underwent surgery repair on median day of life (DOL) 1 (1-1) and mean body weight at surgery was 2453.1 (375.3) g. Total associated anomalies were found in 11 (57.9%) patients. Congenital heart diseases (CHD) were the most frequently occurring comorbidities (n=11 patients; 57.9%). Nine patients with CHD scored < 3 on RACHS-1 and two patients had a RACHS-1 score ≥ 3. The associated anomalies with VACTREL were found in 4 (21.1%) patients. The associated anomalies with others (i.e., CTS, cleft lip and cleft palate, aspiration pneumonitis, and chromosomal abnormalities (Trisomy 21)) were found in 3 (15.8%) patients.

Surgical management

In the primary TEF repairs were found in 18 patients, 16 patients underwent TEF repair, and 1 underwent TEF repair with colostomy due to associated imperforate anus. Meanwhile, 1 patient underwent TEF repair with gastrostomy and colostomy due to associated cloacal malformation. The other surgical procedures performed on the same admission included early revision of their TEF repair (staged TEF repair) in 1 (5.3%) patient, gastrostomy and colostomy due to imperforate anus in 1, while 3 required cardiac surgery before their initial discharge home. In addition, the distance between the upper and lower esophagus ends had a distance ≥ 10 mm were found in 5 (26.3%) patients.

Anesthetic management

In pre-operative events, four patients (21.1%) had desaturation, four patients (21.1%) required intubation due to aspiration pneumonia, CHD, LBW, or prematurity, one patient (5.3%) had tracheostomy due to CTS, and two patients (10.5%) required inotropic support before surgery. Intra-operatively, twelve patients (63.2%) had desaturation, three patients (15.8%) difficult ventilation, and five patients (26.3%) required inotropic support during operation.

We routinely performed Fogarty catheter occlusion of tracheoesophageal fistula in all patients with successfully in 19 of 22 patients (86.4%). Table 1 shows anesthetic management (intra-operative and post-operative outcomes) to evaluate surgical time, anesthetic time, fluid management, urine output, blood loss, duration of received MV, prolonged post-operative MV, post-operative complications, and long-term complications. Five (26.3%) patients required MV before surgical repair of TEF. Median pre-operative required MV in five patients was 1 (0-2) day. Median post-operative required MV after TEF surgery was 4 (3-6) days. Three patients (15.8%) required prolonged post-operative MV that had pre-operative MV. All patients had invasive pressure monitoring during the EA/TEF repair. A percutaneous inserted central catheter (PICC) line was placed pre-operatively in four (21.1%) patients.

DISCUSSION

We included 19 patients in the study who underwent surgical repair of Gross type C EA/TEF with successful routine Fogarty catheter occlusion of fistula. All patients

TABLE 1. Anesthetic management (intra-operative and post-operative outcomes) (n=19)

Anesthetic management	Outcomes
Intra-operative outcomes	
Surgical time (min; mean (SD))	126.2 (34.5)
Anesthetic time (min; mean (SD))	217 (43.3)
Fluid management (ml/kg/h; mean (SD))	21.5 (7.2)
Urine output (ml/kg/h; median (IQR))	0.5 (0-2.3)
Blood loss (ml/kg; median (IQR))	1.2 (0.5-2.5)
Post-operative outcomes	
Duration of received mechanical ventilation (day; median (IQR))	4 (3-6)
Prolonged post-operative mechanical ventilation (≥ 7 days) (n (%))	3 (15.8%)
Post-operative complications (n (%))	
Wound dehiscence	2 (10.5%)
Pneumothorax	2 (10.5%)
Anastomotic leakage	1 (5.3%)
Anastomotic stricture	1 (5.3%)
Sepsis	1 (5.3%)
Chylothorax	1 (5.3%)
Atelectasis	1 (5.3%)
Long-term complications (n (%))	
Gastroesophageal reflux disease (GERD)	7 (36.8%)
Tracheomalacia	6 (31.6%)

Abbreviations: SD, standard deviation; IQR, interquartile range; n, number; %, percentages

were operated on by the same pediatric surgical team with virtually the same anesthesia methods. Anesthetic management of Gross type C EA/TEF generally depends on patient comorbidity, location and size of TEF, anesthetist preference, and local hospital practice. Three patients (15.8%) required prolonged post-operative MV (≥ 7 days). The most common post-operative complications after TEF surgery were wound dehiscence (10.5%), and pneumothorax (10.5%). Long-term complications after TEF surgery were GERD (36.8%) and tracheomalacia (31.6%).

Pre-operative mechanical ventilation occurred in five of 19 patients (26.3%) in this study, similar to a report from previous study where 15 of 53 patients (28.3%) were intubated and mechanically ventilated before surgery.[16] By comparison, another study showed that 20 of 106 patients (18.9%) were intubated before the theater.[4]

Congenital heart disease was the most frequent comorbidity in our study, occurring in 11 patients (57.9%), similar to the report from previous study wherein eight of 15 patients had CHD (53.3%).[3] However, congenital heart disease may underestimate during the pre-operative period because of pre-operative transthoracic echocardiography in children reported the concordance was 77.7%. Therefore, we should concern of unexpected cardiac events during the peri-operative period.[17] In this study, there were two preterm patients (10.5%) and LBW in 9 patients (47.4%). The previous study also reported that there were preterm patients in three (20%), LBW in five (33.3%), and very low birth weight (VLBW) in one (6.7%) of 15 patients.[3]

Previous study reported their practice included routine bronchoscopy, muscle paralysis, ventilation before intubation, and all large TEFs occluded with a Fogarty catheter same as at our hospital.[18] The advantages of flexible bronchoscopy include assessment of the exact location and size of the TEF, placement of a catheter to aid in surgical identification of the TEF, and assessment of tracheomalacia or vascular rings.[6] Complications of flexible bronchoscopy in very small patients have been

well described, including oxygen desaturation, coughing, epistaxis, laryngospasm, bronchospasm, and life-threatening complications (i.e., tension pneumothorax).[19]

Previous studies have described the use of Fogarty balloon occlusion in unstable patients or in H-type fistulas, and re-operative procedures.[5,9,10] The benefits of routine use of Fogarty catheters in the repair of TEF were reduction of aspiration, improved ventilation, safely and expeditiously.[8,11,20] After the TEF was blocked with the balloon of the catheter, the patient could be mechanically ventilated with positive pressure even if the surgical procedure was prolonged. In our study, the success rate of routine TEF occlusion with a Fogarty catheter was 86.4% (19 of 22 patients) which our patients had more than the previous study that had only 5 patients (100%) of successful routine TEF occlusion with a Fogarty catheter.[11] There was no serious complication associated with placement of Fogarty catheter or catheter dislodgement, and it did not occur during any of the procedures.

In our study, three patient (15.8%) required post-operative prolonged MV. One patient did not have CHD, but was preterm, LBW, and required inotropic support. One patient was associated with CHD (RACHS-1 score < 3), LBW, CTS, required tracheostomy pre-operatively, and required staged operation. In addition, the remaining one patient was associated with CHD (RACHS-1 score ≥ 3), and required intubation pre-operatively. Previous studies suggested that peri-operative risk factors for prolonged MV following cardiac surgery in pediatric patients were pre-operative MV, younger age, LBW, RACHS-1 score ≥ 3, acute kidney injury, respiratory infection, a higher dose of inotropes, and pulmonary hypertension.[13,21]

The most common post-operative complications in this study were wound dehiscence in 2 (10.5%) and pneumothorax in 2 (10.5%) patients, while other complications were anastomotic leakage in 1 (5.3%) and anastomotic stricture in 1 (5.3%) patient. Different from the previous study that found anastomotic stricture in 43-71.9%, anastomotic leakage in 11.5-18%, and recurrent distal TEF (type C) in 5-9%.[22,23] Meanwhile, long-term complications in this study were found gastroesophageal reflux disease (GERD) in 7 (36.8%) and tracheomalacia in 6 (31.6%) patients, while in the previous study were found GERD in 73 (79.3%) and tracheomalacia in 29 (31.5%) patients.[22]

The results contribute a clearer understanding of routine Fogarty catheter occlusion of fistula in patients who underwent surgical repair of Gross type C EA/TEF that it may be suitable for patients who had the mean BW was 2569.3 (425.3) g. There was no serious complication associated with placement of Fogarty catheter or catheter dislodgement, and it did not occur during any of the procedures.

The study has limitations: *(a)* it was based on a single center, local practice pattern, *(b)* it had a retrospective design, which could have a selection bias, missing clinical data and limit the cause of failed routine TEF occlusion with a Fogarty catheter, and (c) although our study sample size more than previous studies, but it might constrain its generalizability. However, we need larger sample size to make a firm conclusion. Further study is recommended to assess prospective data from large numbers of patients among a cross-section of institutions.

CONCLUSION

The success rate of routine TEF occlusion with a Fogarty catheter was 86.4%. Routine Fogarty catheter occlusion of TEF can be used safely with experienced personnel, low incidence of aspiration and satisfied ventilation. With the increase in the number of cases, there was no serious complication associated with placement of Fogarty catheter or catheter dislodgement, and it did not occur during any of the procedures.

ACKNOWLEDGMENTS

We thank (a) the anesthesiologists at Tokyo Metropolitan Children's Medical Center for their help and assistance (b) Miss Piyanan Suparattanagool, Clinical Epidemiology Unit, for assistance with the biostatistics and (c) Professor Polpun Boonmak, Faculty of Medicine, Khon Kaen University, Thailand, for his valuable suggestion and encouragement.

Conflict of Interest Statement

All authors have no conflict of interest.

REFERENCES

1. Khan S, Matta SR. Congenital anomalies: Esophageal atresia and tracheoesophageal fistula. In: Kliegman RM, Geme JS, Blum NJ, Shah SS, Tasker RC, Wilson KM, eds. Nelson textbook of pediatrics. 21th ed. Philadelphia, PA: Elsevier; 2019. p.1929-31.
2. Uzumcugil F. Anesthetic management of tracheo-esophageal fistula. Curr Chall Thorac Surg. 2022;4:27. doi:10.21037/ccts-20-183
3. Yang CF, Soong WJ, Jeng MJ, Chen SJ, Lee YS, Tsao PC, et al. Esophageal atresia with tracheoesophageal fistula: ten years of experience in an institute. J Chin Med Assoc. 2006;69(7):317-21. doi:10.1016/S1726-4901(09)70265-5
4. Knottenbelt G, Costi D, Stephens P, Beringer R, Davidson A. An audit of anesthetic management and complications of tracheo-esophageal fistula and esophageal atresia repair. Paediatr Anaesth. 2012;22(3):268-74. doi:10.1111/j.1460-9592.2011.03738.x

5. Chang JW, Choo O, Shin YS, Hong J, Kim C. Temporary closure of congenital tracheoesophageal fistula with Fogarty catheter. Laryngoscope. 2013;123(12):3219-22. doi:10.1002/lary.24164
6. Ho AM, Dion JM, Wong JC. Airway and Ventilatory Management Options in Congenital Tracheoesophageal Fistula Repair. J Cardiothorac Vasc Anesth. 2016;30(2):515-20. doi:10.1053/j.jvca.2015.04.005
7. Alabbad SI, Shaw K, Puligandla PS, Carranza R, Bernard C, Laberge JM. The pitfalls of endotracheal intubation beyond the fistula in babies with type C esophageal atresia. Semin Pediatr Surg. 2009;18(2):116-8. doi:10.1053/j.sempedsurg.2009.02.011
8. Ho AM, Wong JC, Chui PT, Karmakar MK. Case report: Use of two balloon-tipped catheters during thoracoscopic repair of a type C tracheoesophageal fistula in a neonate. Can J Anaesth. 2007;54(3):223-6. doi:10.1007/BF03022644
9. Ratan SK, Rattan KN, Ratan J, Bhatia V, Sodhi PK, Bhatia M. Temporary transgastric fistula occlusion as salvage procedure in neonates with esophageal atresia with wide distal fistula and moderate to severe pneumonia. Pediatr Surg Int. 2005;21(7):527-31. doi:10.1007/s00383-005-1407-8
10. Richenbacher WE, Ballantine TV. Esophageal atresia, distal tracheoesophageal fistula, and an air shunt that compromised mechanical ventilation. J Pediatr Surg. 1990;25(12):1216-8. doi:10.1016/0022-3468(90)90507-6
11. Pepper VK, Boomer LA, Thung AK, Grischkan JM, Diefenbach KA. Routine Bronchoscopy and Fogarty Catheter Occlusion of Tracheoesophageal Fistulas. J Laparoendosc Adv Surg Tech A. 2017;27(1):97-100. doi:10.1089/lap.2015.0607
12. Stollar F, Glangetas A, Luterbacher F, Gervaix A, Barazzone-Argiroffo C, Galetto-Lacour A. Frequency, Timing, Risk Factors, and Outcomes of Desaturation in Infants With Acute Bronchiolitis and Initially Normal Oxygen Saturation. JAMA Netw Open. 2020;3(12):e2030905. doi:10.1001/jamanetworkopen.2020.30905
13. Polito A, Patorno E, Costello JM, Salvin JW, Emani SM, Rajagopal S, et al. Perioperative factors associated with prolonged mechanical ventilation after complex congenital heart surgery. Pediatr Crit Care Med. 2011;12(3):e122-6. doi:10.1097/PCC.0b013e3181e912bd
14. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2002;123(1):110-8. doi:10.1067/mtc.2002.119064
15. Jenkins KJ, Gauvreau K. Center-specific differences in mortality: Preliminary analyses using the Risk Adjustment in Congenital Heart Surgery (RACHS-1) method. J Thorac Cardiovasc Surg. 2002;124(1):97-104. doi:10.1067/mtc.2002.122311
16. Diaz LK, Akpek EA, Dinavahi R, Andropoulos DB. Tracheoesophageal fistula and associated congenital heart disease: implications for anesthetic management and survival. Paediatr Anaesth. 2005;15(10):862-9. doi:10.1111/j.1460-9592.2005.01582.x
17. Sanphasitvong V, Jim LY, Tantiwongkosri K. Impact of Accuracy of Preoperative Transthoracic Echocardiography on Complex Congenital Heart Surgery in Pediatrics. Siriraj Med J. 2019;71(6):480-5. https://doi.org/10.33192/Smj.2019.71
18. Andropoulos DB, Rowe RW, Betts JM. Anaesthetic and surgical airway management during tracheo-oesophageal fistula repair. Paediatr Anaesth. 1998;8(4):313-9. doi:10.1046/j.1460-9592.1998.00734.x
19. Atzori P, Iacobelli BD, Bottero S, Spirydakis J, Laviani R, Trucchi A, et al. Preoperative tracheobronchoscopy in newborns with esophageal atresia: does it matter? J Pediatr Surg. 2006;41(6):1054-57. doi:10.1016/j.jpedsurg.2006.01.074
20. Reeves ST, Burt N, Smith CD. Is it time to reevaluate the airway management of tracheoesophageal fistula? Anesth Analg. 1995;81(4):866-9. doi:10.1097/00000539-199510000-00036
21. Tabib A, Abrishami SE, Mahdavi M, Mortezaeian H, Totonchi Z. Predictors of Prolonged Mechanical Ventilation in Pediatric Patients After Cardiac Surgery for Congenital Heart Disease. Res Cardiovasc Med. 2016;5(3):e30391. doi:10.5812/cardiovascmed.30391
22. Friedmacher F, Kroneis B, Huber-Zeyringer A, Schober P, Till H, Sauer H, et al. Postoperative Complications and Functional Outcome after Esophageal Atresia Repair: Results from Longitudinal Single-Center Follow-Up. J Gastrointest Surg. 2017;21(6):927-35. doi:10.1007/s11605-017-3423-0
23. Lal DR, Gadepalli SK, Downard CD, Ostlie DJ, Minneci PC, Swedler RM, et al. Challenging surgical dogma in the management of proximal esophageal atresia with distal tracheoesophageal fistula: Outcomes from the Midwest Pediatric Surgery Consortium. J Pediatr Surg. 2018;53(7):1267-72. doi:10.1016/j.jpedsurg.2017.05.024

The Feasibility and Outcomes of Retrograde Intrarenal Surgery to Treat Staghorn Renal Calculi

Sunai Leewansangtong, M.D., Karn Liangkobkit, M.D., Chaiyong Nualyong, M.D., Sittiporn Srinualnad, M.D., Bansithi Chaiyaprasithi, M.D., Tawatchai Taweemonkongsap, M.D., Kittipong Phinthusophon, M.D., Siros Jitpraphai, M.D., Patkawat Ramart, M.D., Varat Woranisarakul, M.D., Chalairat Suk-ouichai, M.D., Thawatchai Mankongsrisuk, M.D., Thitipat Hansomwong, M.D., Kantima Jongjitaree, M.D., Ekkarin Chotikawanich, M.D.

Division of Urology, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

ABSTRACT

Objective: To study the safety and efficacy of retrograde intrarenal surgery (RIRS) in patients with staghorn stones.

Materials and Methods: This retrospective observational study was carried out between May 2016 and October 2020, which is when we performed RIRS in staghorn stone patients. Medical records of all patients with this condition in the database of Siriraj Hospital were reviewed. A total of 35 patients were eligible for this study. Descriptive statistics were used to assess the safety and efficacy of RIRS in patients with staghorn stones.

Results: In total, 31.43% of patients were stone-free after the first round of RIRS and 59.55% achieved stone-free status after the second procedure. The stone-free rate did not increase after a second round of RIRS. The median size of all staghorn stones was 3.1 cm. Unfortunately, we found two sepsis patients in this study. We also found eight events of minor complications, including fever and minimal ureteric injury in 54 sessions of RIRS we performed. However, no major injuries or bleeding requiring blood transfusion was identified.

Conclusion: Percutaneous nephrolithotomy (PCNL) is still considered the first-line therapy for kidney stones over two centimeters with a favorable stone-free rate. But, in some patients with limitations such as uncorrectable coagulopathies, impaired renal function, single kidney, and morbid obesity, RIRS is a good choice to reduce the likelihood of serious complications and have an acceptable stone-free rate. However, a prospective study should be performed to confirm these findings.

Keywords: Retrograde intrarenal surgery; staghorn stones; percutaneous nephrolithotomy; complication; stone-free rate (Siriraj Med J 2023; 75: 362-368)

INTRODUCTION

Urolithiasis is a major public health problem in Northeastern and Northern Thailand. It can cause flank pain, nausea, pain when urinating, bloody urine, and urinary tract infection. In a study from 2020, urolithiasis was found mostly in middle-aged and the elderly between 50-69.[1] The highest incidence of urolithiasis in Thailand is in the Northeast of the country, accounting for 16.9% of all cases.[2]

Although there is no clear definition, staghorn stones commonly refer to stones with more than one branching of the collecting system that may divide completely or partially depending on the level of occupancy.[3,4] Staghorn stones are often associated with infection or metabolic abnormalities, and can lead to obstruction, kidney loss, sepsis, and death if left untreated.[5,6]

According to AUA and EAU guidelines, since percutaneous nephrolithotomy (PCNL) provides a higher

Corresponding author: Ekkarin Chotikawanich
E-mail: ekkarinc@yahoo.com
Received 27 February 2023 Revised 14 March 2023 Accepted 23 March 2023
ORCID ID:http://orcid.org/0000-0003-3914-2770
https://doi.org/10.33192/smj.v75i5.261510

stone-free rate than Shockwave Lithotripsy (SWL) or Ureteroscopy (URS), PCNL is considered as first-line therapy for symptomatic patients who have a stone burden >20 mm.[7,8]

Open surgery or laparoscopic/robotic-assisted procedures are alternative modalities with a good stone-free rate.[3] However, some patients are not suited for this treatment or may prefer less invasive procedures. Hence, we attempted to find other modalities that could provide a stone-free rate (SFR) similar to PCNL, with a lower incidence of complications and reduced hospitalizations.

We found many studies with retrograde intrarenal surgery (RIRS) in larger stones (>20 mm), with higher stone-free rates and fewer complications than PCNL due to well-developed instruments, such as the flexibility or size of the endoscope, accessory equipment, and techniques.[9] Therefore, we aimed to study the safety and efficacy of the retrograde endoscopic technique in patients with staghorn stones treated at our hospital.

MATERIALS AND METHODS

This was a retrospective observational study. At our institute, we performed retrograde intrarenal surgery in staghorn stone patients in May 2016. After the study was approved by the Ethics Committee (COA no. Si 153/2022), medical records of all patients with staghorn stones treated by RIRS in the database of our tertiary referral university hospital from May 2016 to October 2020 was reviewed. We excluded a complete staghorn stone, patients under 18 or those who had received other modalities in their first attempt such as PCNL, SWL, and open surgery, and those who denied treatment, had incomplete data, and patients who failed to follow-up. In total, we had 35 patients who underwent RIRS as their first lithotripsy attempt and were eligible for this study. Patients who possessed staghorn stones in both kidneys were considered as two subjects with a stone in each kidney. However, patients who had a non-staghorn stone on the contralateral side were counted as one subject.

The size of the stones, maximum, and mean of the Hounsfield Units (HU) were measured using the same "DICOM viewer" program and the same observer in all patients. In X-ray results, we used the widest diameter. In computerized tomography (CT) results, we used the largest diameter from both coronal and axial views.

The operative notes and techniques were reviewed, including ureteral access sheath size and fluoroscopy time. Estimated blood loss and operative time was collected by reviewing the anesthesiologist's record, and the complications, both immediate and delayed were recorded by reviewing IPD charts, operative notes, and OPD records up to a maximum of 6 months after the latest procedure. The glomerular filtration rate (GFR) was obtained in the same visit or at least two weeks before every operation.

Currently, intraoperative and postoperative complications are commonly classified according to modified Satava and modified Clavien classification systems.[10-16] In our research, post-operative problems were categorized into four groups: fever, sepsis, others, and no complications summarized by the modified Clavien classification system. We defined sepsis according to the positive hemoculture result. To classify peri-operative complications, we employed the modified Satava classification system. However, we still specified specific complications along with classification grading to obtain a clear perspective.

There were three urologists involved in our project. After general anesthesia, cystoscopy, sheath 22Fr, and 30-degree lens were used in all cases. Hydrophilic tip wire was passed inside to the renal pelvis under a fluorograph. A double-lumen catheter was replaced over the guidewire, and the super-stiff guidewire was inserted into the hole of the catheter. Ureteral access sheath, 11/13Fr or 12/14Fr, replaced the catheter over the stiff wire. Afterwards, a flexible video ureteroscope URF-V – Olympus was inserted. Renal stones were identified and disintegrated with Ho-YAG laser setting 1J 20Hz. A retrograde pyelogram was performed, and a DJ stent inserted.

After the operation, stone analysis was carried out using the Fourier transform infrared spectroscopy (FTIR) technique at our institute after authorization by nephrologists. The maximum compound from stone analysis was used to represent the etiology of the stone of the patient.

Stone-free was defined as no residual stone or a stone fragment less than 2 mm on a standard radiograph, CT scan, or sonography (depending on the type of stone) at a maximum of six-month follow-up after the latest procedure. The remaining stones were categorized into a lower pole and a non-lower pole.

The data was divided into four parts as follows: patient data including gender, age, race, underlying disease, medication, glomerular filtration rate, hydronephrosis, and previous treatment history. Surgical data included operative time, blood loss during surgery, size of access sheath used, perioperative complications, and fluoroscopy time. Post-surgery data included number of procedures performed, post-operative complications, glomerular filtration rate, and post-treatment stone-free rate. Last but not least, stone data included size, type, location,

opacity, Hounsfield Units, and stone analysis.

Descriptive statistics were used to characterize populations. Qualitative variables such as gender was presented as frequency and percentage. Quantitative variables such as age, size, and Hounsfield Units, which are non-normal distributions of continuous data, were represented by the median and min-max or IQR values. The frequency of stone-free rates and complications were reported as number and percentage. Unfortunately, the number of patients was limited, so we were unable to analyze the statistic module.

RESULTS

A total of 36 participants in the study were divided into 12 men, and 23 women, with a median age of 63 (IQR 56-73). The underlying medical conditions were as follows: hypertension, 25 people (71.43%), hyperlipidemia, 19 people (54.29%), diabetes, 15 people (42.86%), chronic kidney disease, nine people (25.71%), any type of cancer, two people (5.71%), and no underlying disease, four people (11.43%), respectively.

The median size of all staghorn stones was 3.1 cm, with a range from 1.5-7.16 cm, and 10 people had it on the right and 25 on the left side. The median of maximum Hounsfield Units was 1226 HU (IQR 813-1661) and the median of the mean of Hounsfield Units was 950 HU (IQR 584-1332). Twelve subjects (34.29%) had radiopaque stones and 21 (60%) had radiolucent stones, and the remainder were unspecified (5.71%). In total, 13 people had hydronephrosis (37.14%). The demographic data is shown in Table 1.

In this study, we divided stones into three main types: calcium, non-calcium stones, and uric stones. The most common type were calcium-based stones, accounting for 18 (51.4%), followed by nine uric stones (25.7%), five non-calcium stones (14.3%), and three uncategorized stones (8.6%).

The peri-operative and post-operative outcomes are shown in Table 2. The stone-free rate was 31.43%, and 59.55% after the first and second procedures, respectively. The stone-free rate did not increase after the second procedure.

For the operation, we used ureteral access sheaths size 11/13Fr or 12/14Fr in almost all cases. The median operative time was 80 minutes for the first procedure, 60 minutes for the second, 35 minutes for the third, and 90 minutes for the fourth procedure, with an estimated blood loss of less than 30 ml in each session, except for patients who switched to PCNL.

A total of 10 patients were pre-stented for RIRS due to a narrowed or swollen ureter, and inability to access the stones. Nine underwent pre-stenting before the first

TABLE 1. Demographic data.

Sex male (n,%)	12	34.3%
Sex female (n,%)	23	65.7%
Age (Median, IQR)	63	56.0-73.0
DM (n,%)	15	42.9%
HT (n,%)	25	71.4%
DLP (n,%)	19	54.3%
CA (n,%)	2	5.7%
CKD (n,%)	9	25.7%
no U/D (n,%)	4	11.4%
Lt. staghorn	25	71.4%
Rt. Staghorn	10	28.6%
CT size (Median, Min-Max)	3.1	1.5-7.16
HU max (Median, IQR)	1226.0	813.0-1661.0
HU mean (Median, IQR)	950.0	584.0-1332.0
Hydronephrosis (n,%)	13	37.1%

TABLE 2. Perioperative outcomes.

		1st Operation		2nd Operation		3rd Operation		4th Operation	
		Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent
RIRS	Patients (N)	35	100.0%	15	100.0%	3	100.0%	1	100.0%
	Cumulative SFR	11	31.4%	9	59.6%	0	59.6%	0	59.6%
	Operative time (Median, IQR)	80	60.0-120.0	60	35.0-85.0	35	20.0-35.0	90	90.0-90.0
	Overall complication	8	22.9%	3	20.0%	0	0.0%	0	0.0%
	Fever	3	8.6%	3	20.0%	0	0.0%	0	0.0%
	Sepsis	2	5.7%	0	0.0%	0	0.0%	0	0.0%
	Injury	2	5.7%	0	0.0%	0	0.0%	0	0.0%
	Other complication	1	2.9%	0	0.0%	0	0.0%	0	0.0%
	No complication	28	80.0%	12	80.0%	3	100.0%	1	100.0%

RIRS session and one patient before the second RIRS session. Intra-operative problems of this step were seen in two subjects with a ureteral injury, which falls under Grade 1 of the modified Satava classification system. Meanwhile, the patient had a low-grade fever during post-operative problems. All cases resolved after stenting and routine post operative care.

We had a total of 35 patients who underwent RIRS as the first step. Grade 1 and 3A complications of the modified Clavien classification were noted in four and two patients respectively. Two patients had a fever, two were septic, one had acute urinary retention, and one had both ureteral injury and fever. The remaining 28 patients had no complications. One patient also had pure ureteral injury, not including the other patient mentioned before, accounting for Grade 1 of the modified Satava classification system. All patients recovered after conservative treatment. The stone-free success rate of the first procedure was 31.43% (11 patients). The remaining stones were found in the lower pole accounting for 95.83% (23 patients) and in the non-lower pole location for 29.17% (7 patients). In some cases, there was more than one location of the remaining stone.

During the second procedure, six patients stopped operative management, with three switching to medical treatment, and two failing to follow-up. The remaining stones were all lower pole stones characterized by four calcium base stones, one uric, and one unknown type. The size was about 0.8-2.5 cm. The remaining 18 patients in this group were divided into two subgroups, including three patients who underwent PCNL and 15 who underwent RIRS. In the RIRS group, we found three patients that had a fever (Grade 1 of modified Clavien), however, the other 12 had no complications. The stone-free rate was 60.00% (9 out of 15 patients) for this procedure and the cumulative stone-free rate for the RIRS group was 59.55%. Since some patients had more than one site of remaining stones, they were in both the lower pole and non-lower pole group for three patients (50%) and three patients (50%) in the lower pole group. In terms of complications, we found two patients with fever, while the other patient had a serious bleeding complication and required transfusion, which falls under Grade 1 and 2 of the modified Clavien classification. Also, PCNL did not improve the stone-free rate in the second procedure. Remaining stones from PCNL were found in the lower pole of all three patients, accounting for 100%.

In the third and fourth procedures, we had only five patients in both groups, and we didn't notice any complications and the stone-free rate did not increase significantly. We found only one patient who was stone-free from PCNL in the third procedure. It was difficult to use statistical methods and percentage reports in these groups because the population was too small.

In summary, a total of four patients underwent PCNL due to stone burden. The number of patients in this group was too small to conclude and justify the stone-free rate and surgical complications for PCNL. However, in these cases, three patients had an estimated blood loss of 250, 300, and 600 ml, respectively, but only one person required a transfusion. The estimated blood loss in the PCNL group tended to be higher than RIRS. The operative time was more than 120 minutes in most cases, which is higher than the average of RIRS as mentioned above.

DISCUSSION

Percutaneous kidney stone surgery is considered by both the American Urological Association (AUA) and European Association of Urology (EAU) as first-line therapy for kidney stones over two centimeters in size and branching calculi, with a single-stage rate of 83%-95% stone-free.[7,8] The indication for PCNL includes many factors such as stone size, stone location, patient, and stone composition, all of which affect the surgeon's decision. Stones larger than 2 cm, staghorn stones, and lower pole stones more than 1 cm are not suitable for SWL. Meanwhile, obese patients or patients with distal obstruction preventing the passage of stone fragments are suitable for PCNL. The stone composition and hardness are also factors to be concerned about. For example, the PCNL method is preferred to treat cystine stones.[3,7,8]

Although we already have past data on stone-free rates, data on complications was lacking. In the past, there was no definitive criteria for PCNL complications. The decision was made by the surgeon who reported on complications, and mostly focused on intraoperative periods making it difficult to compare the actual complications of PNCL. Data on PCNL complications from multiple studies revealed that a lack of standardized reporting led to a large disparity in outcomes of grading complications, which explains the wide incidence range of 20% to 83%.[17-23] Fortunately, nowadays, the severity of PCNL complications is classified using the modified Clavien classification system, which allows for more standardized storage of the complications.[10,11,16] Consequently, the data collection process revealed that complications under this system decreased from the previous incidence, however, serious complications remained.

The contraindications for PCNL include pregnancy, bleeding disorders, and uncontrolled urinary tract infections. PCNL can cause many complications such as bleeding, infection, pneumothorax, hydrothorax, hemothorax, urinothorax, persistent nephrocutaneous fistula, rupture of the pelvicalyceal system, small bowel perforation, liver injury, splenic injury, and colonic perforation. A mini-review by the Clinical Research of the Endourological Society (CROES) on the topic of "Complications associated with percutaneous nephrolithotomy" reported an overall complication rate of 21.5%. This was the result from an international multi-center study of 5,803 patients conducted across 96 centers in Europe, Asia, North America, South America, and Australia. They found that the complication rate reported by the modified Clavien system was as follows: no complications (79.5%), I (11.1%), II (5.3%), IIIa (2.3%), IIIb (1.3%), IVa (0.3%), IVb (0.2%), and V (0.03%) respectively.[17] The most common minor complication was transient fever, which is consistent with the results of our study. Major PCNL complications were grades III, IV, and V of the modified Clavien system and involved renal pelvis perforation, serious bleeding, severe infection, or adjacent organ injury as mentioned above.

While PCNL demonstrated a strong therapeutic effect, it is also riskier due to its invasiveness nature and some limitations.[3,18,23] For instance, it has higher complication rates, increased risk of bleeding, and can lead to perioperative blood loss which may require transfusion, embolization, or in rare instances, nephrectomy leading to a lengthy hospital stay compared to RIRS. Moreover, the prone position is often preferred in PCNL procedures, but it requires significantly more effort by an anesthesiologist during operation. As the acceptable risk in each patient may be different, PCNL may not be feasible for every situation, so minimally invasive procedures such as RIRS is much more appealing in fragile patients.

In recent times, RIRS has received more attention and has been used in staghorn stone patients in a variety of research. RIRS yields a lower stone-free rate initially but is comparable to PCNL after several staged RIRS sessions. RIRS also has fewer complications and severity. Many studies showed a decent efficacy with an 83%-93% stone-free rate after three procedures and it is able to cover a large group of patients, including the high-risk as an alternative option to standard treatment.[9,24-29]

In our study, we present a single-center tertiary care series of RIRS for any staghorn stones. The treatment and follow-up data were obtained retrospectively. The stone-free rates in our institutions were only 31% during the first procedure, but this increased to 59.6% after the second procedure, respectively. Since the procedure was performed in patients contraindicated for PCNL and those with complicated cases in the tertiary care center, in combination with other factors such as the small sample size, the surgeon's experience, and case selection methods, the stone-free rate may differ from

other studies. Additionally, thirteen patients who were in the non-stone-free group stopped the procedure and switched to medical treatment divided into six, five, and two patients from the first, second, and third procedures sequentially.

RIRS complications seem to be high when we calculate in percent due to a small sample size. However, in this study, there were no serious complications like those found in PCNL, such as injury to adjacent organs or bleeding that required transfusion. This study had 2 patients (6%) of grade IIIa complication which was septicemia, this figure was higher than an usual complication for RIRS which septic complication was 0.9%.[30] This because of a small sample size as well as staghorn stone is at high risk of infection according to it is mostly infected stone and the surgery requires prolong operative time regards the stone size. PCNL is still considered as the first-line therapy for kidney stones over two centimeters with a favorable stone-free rate. But, in some patients with limitations such as uncorrectable coagulopathies, impaired renal function, single kidney, morbid obesity, severe obstructive pulmonary disease, postural contracture, or those who require treatment preserving renal parenchyma, RIRS is a good choice to reduce the likelihood of complications and have an acceptable stone-free rate in multistage RIRS.

A limitation of this study was that it was a single-center, non-randomized study with a small sample size, and post-operative imaging using plain x-ray may miss small residual stones. Also, the experience of surgeons in tertiary care services may differ. Due to these reasons, the obvious limitation is the reproducibility of the results. Nevertheless, a larger sample size undergoing RIRS with preferable outcomes and usefulness of our described technique will be reviewed.

CONCLUSION

Percutaneous nephrolithotomy (PCNL) is still considered the first-line therapy for kidney stones over two centimeters with a favorable stone-free rate. But, in some patients with limitations such as uncorrectable coagulopathies, impaired renal function, single kidney, and morbid obesity, RIRS is a good choice to reduce the likelihood of serious complications and have an acceptable stone-free rate. However, a prospective study should be performed to confirm these findings.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Ms. Julaporn Pooliam and Ms. Jitsiri Chaiyatho for assistance with statistical analysis.

Potential Conflicts of Interest

There are no conflicts of interest to report. There are no sources of funding to disclose.

REFERENCES

1. Arunkajohnsak N, Taweemonkongsap T, Leewansangtong S, Srinualnad S, Jongjitaree K, Chotikawanich E. The correlation between demographic factors and upper urinary tract stone composition in the Thai population. Heliyon. 2020;6(8):e04649.
2. Yanagawa M, Kawamura J, Onishi T, Soga N, Kameda K, Sriboonlue P, et al. Incidence of urolithiasis in northeast Thailand. Int J Urol. 1997;4(6):537-40.
3. Preminger GM, Assimos DG, Lingeman JE, Nakada SY, Pearle MS, Wolf JS, Jr., et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. J Urol. 2005;173(6):1991-2000.
4. Diri A, Diri B. Management of staghorn renal stones. Ren Fail. 2018;40(1):357-62.
5. Blandy JP, Singh M. The case for a more aggressive approach to staghorn stones. J Urol. 1976;115(5):505-6.
6. Koga S, Arakaki Y, Matsuoka M, Ohyama C. Staghorn calculi--long-term results of management. Br J Urol. 1991;68(2):122-4.
7. Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69(3):475-82.
8. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART II. J Urol. 2016;196(4):1161-9.
9. Barone B, Crocetto F, Vitale R, Di Domenico D, Caputo V, Romano F, et al. Retrograde intra renal surgery versus percutaneous nephrolithotomy for renal stones >2 cm. A systematic review and meta-analysis. Minerva Urol Nefrol. 2020;72(4):441-50.
10. de la Rosette JJ, Opondo D, Daels FP, Giusti G, Serrano A, Kandasami SV, et al. Categorisation of complications and validation of the Clavien score for percutaneous nephrolithotomy. Eur Urol. 2012;62(2):246-55.
11. Shin TS, Cho HJ, Hong SH, Lee JY, Kim SW, Hwang TK. Complications of Percutaneous Nephrolithotomy Classified by the Modified Clavien Grading System: A Single Center's Experience over 16 Years. Korean J Urol. 2011;52(11):769-75.
12. Ozden C, Oztekin CV, Pasali S, Senel S, Demirel D, Bulut S, et al. Analysis of clinical factors associated with intraoperative and postoperative complications of retrograde intrarenal surgery. J Pak Med Assoc. 2021;71(6):1666-70.
13. Tepeler A, Resorlu B, Sahin T, Sarikaya S, Bayindir M, Oguz U, et al. Categorization of intraoperative ureteroscopy complications using modified Satava classification system. World J Urol. 2014;32(1):131-6.
14. Oguz U, Resorlu B, Ozyuvali E, Bozkurt OF, Senocak C, Unsal A. Categorizing intraoperative complications of retrograde intrarenal surgery. Urol Int. 2014;92(2):164-8.
15. Koras O, Bozkurt IH, Karakoyunlu AN, Celik S, Sefik E, Yarımoglu S, et al. Retrospective Analysis of the Factors Affecting Intraoperative and Immediate Postoperative Complications of Retrograde Intrarenal Surgery Classified by the Clavien and Satava Grading Systems. J Endourol. 2021;35(12):1764-72.
16. Tefekli A, Ali Karadag M, Tepeler K, Sari E, Berberoglu Y, Baykal M, et al. Classification of percutaneous nephrolithotomy

complications using the modified clavien grading system: looking for a standard. Eur Urol. 2008;53(1):184-90.
17. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, et al. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: indications, complications, and outcomes in 5803 patients. J Endourol. 2011; 25(1):11-7.
18. Rudnick DM, Stoller ML. Complications of percutaneous nephrostolithotomy. Can J Urol. 1999;6(5):872-5.
19. el-Nahas AR, Eraky I, Shokeir AA, Shoma AM, el-Assmy AM, el-Tabey NA, et al. Factors affecting stone-free rate and complications of percutaneous nephrolithotomy for treatment of staghorn stone. Urology. 2012;79(6):1236-41.
20. Mousavi-Bahar SH, Mehrabi S, Moslemi MK. Percutaneous nephrolithotomy complications in 671 consecutive patients: a single-center experience. Urol J. 2011;8(4):271-6.
21. Segura JW, Patterson DE, LeRoy AJ, Williams HJ, Jr., Barrett DM, Benson RC, Jr., et al. Percutaneous removal of kidney stones: review of 1,000 cases. J Urol. 1985;134(6):1077-81.
22. Rassweiler JJ, Renner C, Eisenberger F. The management of complex renal stones. BJU Int. 2000;86(8):919-28.
23. Taylor E, Miller J, Chi T, Stoller ML. Complications associated with percutaneous nephrolithotomy. Transl Androl Urol. 2012; 1(4):223-8.
24. Al-Qahtani SM, Gil-Deiz-de-Medina S, Traxer O. Predictors of clinical outcomes of flexible ureterorenoscopy with holmium laser for renal stone greater than 2 cm. Adv Urol. 2012;2012:543537.
25. Pevzner M, Stisser BC, Luskin J, Yeamans JC, Cheng-Lucey M, Pahira JJ. Alternative management of complex renal stones. Int Urol Nephrol. 2011;43(3):631-8.
26. Martí José Luis P, Ituren Amparo G, González Lorena V. RESULTADOS ACTUALES DE LA CRIR Y COMPARACIÓN CON NLPC. Archivos Españoles de Urología. 2017;70(1):147-54.
27. Breda A, Ogunyemi O, Leppert JT, Lam JS, Schulam PG. Flexible ureteroscopy and laser lithotripsy for single intrarenal stones 2 cm or greater--is this the new frontier? J Urol. 2008;179(3): 981-4.
28. Cohen J, Cohen S, Grasso M. Ureteropyeloscopic treatment of large, complex intrarenal and proximal ureteral calculi. BJU Int. 2013;111(3 Pt B):E127-31.
29. Nualyong C, Sathidmangkang S, Woranisarakul V, Taweemonkongsap T, Chotikawanich E. Comparison of the outcomes for retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL) in the treatment of renal stones more than 2 centimeters. Insight Urology. 2019;40(1):9-14.
30. Hansomwong T, Nualyong C, Taweemonkongsap T, Amornvesukit T, Phinthusophon K, Jitpraphai S, et al. Perioperative Outcomes of Retrograde Intrarenal Surgery (RIRS) Treatment of Renal Calculi in Siriraj Hospital. J Med Assoc Thai. 2017; 100: 144-149

Validity and Reliability of the Thai version of the Family Dermatology Life Quality Index

Kanokvalai Kulthanan, M.D., Papapit Tuchinda, M.D., Leena Chularojanamontri, M.D., Chuda Rujitharanawong, M.D., Waratchaya Panjapakkul, M.D.

Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: This study aimed to investigate the validity and reliability of the Thai version of FDLQI.

Materials and Methods: Patients and their accompanying family members attending the Dermatology Outpatient Clinic at Siriraj Hospital were asked to complete the Dermatology Life Quality Index (DLQI), FDLQI, and the global question of their QoL (GQoL). The severity of the disease was assessed by physicians, the patients and the family members of the patients.

Results: One hundred family members accompanying 92 patients with dermatological diseases (63% with inflammatory skin diseases and 37% with non-inflammatory skin diseases) were included. The mean age of the family members was 43.5±12.1 years and 70% were women. They had been mostly employed (74%) and graduated from universities (65%). Validity was demonstrated by a positive correlation between FDLQI and GQoL scores (r_s=0.695, P<0.001), and between FDLQI and severity of the patient's disease (r_s=0.578, P<0.001) as evaluated by family members. The FDLQI showed high internal consistency (Cronbach's alpha=0.84) and test-retest reliability (ICC= 0.85).

Conclusion: The construct validity, internal consistency, and test-retest reliability of the Thai FDLQI demonstrated acceptable validity and reliability. The Thai version of FDLQI can be used to assess the QoL of family members of patients with any dermatological diseases.

Keyword: Validity; reliability; Family Dermatology Life Quality Index; FDLQI (Siriraj Med J 2023; 75: 369-376)

INTRODUCTION

Dermatological diseases such as urticaria, atopic dermatitis, psoriasis, epidermolysis bullosa, acne, and hair disorders can have a tremendous impact on mental health of patients, sometimes even more than other physical diseases.[1-4] This impact may not only affect patients, but also cause a negative impact on their close individuals, especially their close family members and partners.[2,5] Many instruments were developed aimed at capturing and measuring quality of life (QoL) of family members of patients with dermatological diseases in order to improve holistic care to a patient as much as possible. Moreover, this dimension has grown much of interest during the last two decades. The Family Dermatology Life Quality Index (FDLQI) is one of the questionnaires designed to measure the QoL of family members of patients affected by dermatologic diseases.[6] It was originally developed in English[7] and was translated and validated for use in many countries, for example, Japan[8], Iran[9], Ukraine[10], etc. This study aimed to investigate the validity and reliability of the Thai version of FDLQI.

MATERIALS AND METHODS

The protocol of this study was approved by the Siriraj Institutional Review Board (COA no. Si 905/2021). Patients and their accompanying family members or

Corresponding author: Leena Chularojanamontri
E-mail: leenajim@gmail.com
Received 6 January 2023 Revised 18 March 2023 Accepted 19 March 2023
ORCID ID:http://orcid.org/0000-0001-6625-6445
https://doi.org/10.33192/smj.v75i5.260735

partners attending the Dermatology Outpatient Clinic at Siriraj Hospital were asked if they were willing to participate in the study. Informed consent was obtained if the patient agreed to participate. The inclusion criteria for the family members or partners of the patients were: (i) 18 years or older, (ii) the first-degree relative who lived in the same household, and (iii) the ability to read and understand Thai language. Family members or partners of patients who had other severe concomitant diseases other than dermatological disease were excluded.

Questionnaires

FDLQI: is a questionnaire that was developed by Basra et al. to measure the QoL of family members or partners of patients with dermatological diseases in 10 aspects over the past month. Ten aspects comprise (i) emotional, (ii) physical well-being, (iii) relationships, (iv) reactions of people, (v) social life, (vi) leisure activities, (vii) burden of care, (viii) extra housework, (ix) job / study and (x) additional expenditure. Each aspect will be evaluated by each question, which will be rated by the score 0 = 'not at all / not relevant', 1 = 'a little', 2 = 'quite a lot' and 3 = 'very much'. Therefore, the score ranges from 0 to 30, indicating 'no' and 'maximum' impacts on quality of life, respectively.[6]

Dermatology Life Quality Index (DLQI): is a questionnaire that was developed by Finlay A.Y. and Khan G.K.[11] It measures the QoL of patients with dermatological diseases over one week. Six aspects of the 10 questions include (i) symptoms and feelings, (ii) daily activities, (iii) social or leisure activities, (iv) work or study, (v) personal relationships, and (vi) effect of treatment. The total DLQI score ranges from 0 to 30 (0 to 3 points for each question), and the higher the score reflects a greater impact on the patient's QoL. This questionnaire has also received the formal permission of the developers to translate into Thai and has already been validated and widely used in Thailand.[12]

Global question: is a simple question used to assess the severity and quality of life of the disease over the past month on a numerical rating scale, with 0 and 10 indicating 'no' and 'worst', respectively.

Translation process of the FDLQI

After receiving permission for the translation into Thai language from the FDLQI developers, our translation process was performed according to their instructions. The translation of the original English language into Thai was carried out by two independent translators who were bilingual. Then, these two Thai versions were read and discussed by four Thai dermatologists (KK, LC, PT, CR) resulting in minor changes to make a conceptual equivalence to the original questionnaire. Afterwards, this version was independently translated back into English by two bilingual English-language experts, who were unaware of the original version. Finally, the same four Thai dermatologists read and discussed both translations in order to find a consensus version. After the backtranslation for FDLQI was approved by one of the developers, a cognitive debriefing was performed in family members of five patients comprised: 1) a 30-year-old woman accompanying her husband with pityrosporum folliculitis for two months, 2) a 54-year-old woman accompanying her daughter with chronic eczema of the left foot for one month, 3) a 28-year-old male accompanying her father with androgenic alopecia for five years, 4) a 58-year-old woman accompanying her mother with xerotic eczema for 18 months and 5) a 60-year-old male accompanying his daughter with post inflammatory hyperpigmentation from acne for 4 months. All agreed that the form of the questions was clear and easily understandable, leading to no change for the final Thai version of the FDLQI.

Participants

A total of 100 family members accompanying 92 patients with dermatological diseases were included. On the visit date, patients were asked to rate their QoL using DLQI and a global QoL question for patients (GQoLP). Their family members were also asked to complete their QoL by the FDLQI and a global QoL question for family members (GQoLF). The physicians, patients themselves, and their family members completed a global question regarding the severity of the patient's disease. After finishing all processes within 10-15 minutes, patients' family members were asked their convenient time for a telephone interview to complete another FDLQI sheet the next day for reliability of the test.

Psychometric Evaluations

Validity: was investigated by comparing the test to other tests that measure the relevant construct. The correlation between patient evaluation scores (DLQI, GQoLP and a global question for patient's disease severity) and the assessment scores of family members (the Thai version of FDLQI, GQoLF, a global question for patient's disease severity) were investigated using Spearman's rank correlation. A correlation coefficient of approximately 0.3, 0.5, and 0.7 was interpreted as a weak, moderate, and strong correlation, respectively.[13] We expected the highest correlation between the Thai version of the FDLQI and GQoLF.

Reliability: Reliability was investigated by Cronbach's alpha and the intraclass correlation coefficient (ICC). The Cronbach value of < 0.5, 0.5- 0.6, 0.6-0.7, 0.7-0.8, 0.8–0.9, >0.9 was interpreted as unacceptable, poor, questionable, acceptable, good and excellent, respectively.[14] An ICC of 0.5 to 0.7, and >0.7 was considered to indicate moderate to good and excellent reproducibility, respectively.[15] All statistical analyses were performed with PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A p-value (P) < 0.05 was considered statistical significance.

RESULTS

Of 100 family members with a mean age of 43.5 ± 12.1 years, 70% were women (Table 1). Thirty-one participants were parents of patients. They had been mostly employed (74%) and graduated from universities (65%). On the other hand, 54 (58.7%) of the 92 patients were men and the mean age was 42.8 ± 21.0 years. The median duration of their dermatological diseases was 12 months. Fifty-eight patients (63.0%) were diagnosed with inflammatory diseases, while the remaining (34/92; 37.0%) had non-inflammatory diseases. Eczema (13/92; 14.1%) and androgenic alopecia (11/92; 12.0%) were primary diseases of each group, respectively.

The total scores of the FDLQI ranged from 0 to 24. Fig 1 shows the percentage of each response to each item. The responses to most items (except burden of care and extra expenditure) were not at all/not relevant, and 'a little'. The burden of care was the most frequently reported problem of family members. The minimum, maximum, and median scores of each questionnaire are shown in Table 2. The median total score of DLQI and FDLQI was equal. Comparison of total scores between inflammatory and non-inflammatory diseases, the median total score of DLQI score of patients with inflammatory diseases (score = 6) was significantly higher than that of patients with non-inflammatory diseases (score = 3) ($P < 0.03$). However, the median total score of FDLQI (score = 4) with inflammatory disease was lower than that of patients with noninflammatory diseases (score = 5.5) but there was no statistical significance ($P = 0.840$) (data not shown).

Table 3 shows the correlations between FDLQI and other instruments. As expected, there was a high correlation between FDLQI and GQoLF ($r_s = 0.695$, $P < 0.001$). The correlation between FDLQI and the severity of the disease of the patients as assessed by family members was moderate ($r_s = 0.578$, $P < 0.001$). No and weak correlations were found between FDLQI, DLQI, GQoLP, and the severity of the diseases of the patients as assessed by the patients themselves and the physicians. The reliability of internal consistency according to the Cronbach alpha scale was 0.84 and this was not significantly improved by deleting individual items (0.81– 0.84) (Table 4). Regarding the reliability of the test-retest, there were 79 family members who responded to the FDLQI retest. The intraclass correlation value for the total FDLQI score was 0.85 which indicated good reproducibility. The difference scores of the test and retest ranged from 0 to 7 with a mean score of 1.16 (SD = 2.4).

DISCUSSION

The burden of skin disease is defined into three dimensions: "now", "long-term" and "family members".[16] The first two affect patients, while the third dimension causes a burden to partners and family members. As the patient is the center, the first two dimensions have been extensively explored, whereas there are relatively limited data for the third dimension. A systematic review of dermatology-specific instruments to evaluate the impact of dermatological conditions on family and caregivers found that there were nine instruments. Eight of them are specific instruments for dermatologic diseases (4 for atopic dermatitis, 2 for psoriasis, 1 for epidermolysis bullosa acquisita, 1 for ichthyosis). Only one of them is the generic questions for dermatologic diseases, the FDLQI.[17] The FDLQI has been used in family members of patients with epidermolysis bullosa[3], atopic dermatitis[10,18], psoriasis[19,20], vitiligo[21,22], leg ulcers[23], and pemphigus.[24] One advantage of FDLQI is that it can be used to compare the QoL of family members under different skin conditions.

In this study, the total FDLQI score ranged from 0 to 24, with a score of 0 reported in 2% of the family members. This demonstrated that there may be no floor or ceiling effect in the Thai version of FDLQI. However, to our knowledge, there are no standard criteria for floor and ceiling effects. McHorney et al.[25] proposed that both effects should be less than 15% and this was supported by other studies[26,27], while other studies proposed that number should be 25%.[28,29] The median total score of DLQI and FDLQI in our study was 4.5 out of the maximum score of 30, which was quite low. These corresponded to those of the United Kingdom[6] and Japan.[8] The reason may be that all the studies were carried out in the outpatient clinic where most patients tend to have mild to moderate disease severity. Additionally, the median duration of the disease of the patients in this study was 12 months. Sajedianfard et al. reported that longer disease duration and more recurrences could decrease the FDLQI score.[24]

The construct validity of the FDLQI was shown by a strong and moderate positive correlation with GQoLF and the severity of the disease of the patients rated by

TABLE 1. Demographic data of patients and their family members

Demographic data	N (%)
Family Members (N=100)	
Sex	
Female	70 (70.0)
Male	30 (30.0)
Mean age ± SD (years)	43.5 ± 12.1
Relation with the patient	
Parent	31 (31.0)
Spouse/partner	27 (27.0)
Sibling	14 (14.0)
Son/daughter	28 (28.0)
Marital status	
Single	31 (31.0)
Married	65 (65.0)
Divorced/widowed/separated	4 (4.0)
Occupation	
Employed	74 (74.0)
Retired	5 (5.0)
Housewife	11 (11.0)
Student	6 (6.0)
Unemployed	4 (4.0)
Educational status	
Primary school	8 (8.0)
Secondary school	28 (28.0)
Vocational	9 (9.0)
University	65 (65.0)
Patients (N=92)*	
Sex	
Female	38 (41.3)
Male	54 (58.7)
Mean age ± SD (years)	42.8 ± 21.0
Median duration of disease (P25, P75) (months)	12 (2.3, 36.0)
Diseases	
Inflammatory	58 (63.0)
Eczema	13 (14.1)
Urticaria	8 (8.7)
Acne	6 (6.5)
Psoriasis	5 (5.4)
Abscess	3 (3.3)
Seborrheic dermatitis	3 (3.3)
Granuloma	3 (2.2)
Pityrosporum folliculitis	2 (2.2)
Insect bite reaction	2 (2.2)
Others[a]	13 (14.1)
Non-inflammatory	34 (37.0)
Androgenic alopecia	11 (12.0)
Alopecia areata	8 (8.7)
Vitiligo	3 (3.3)
Post inflammatory hyperpigmentation	2 (2.2)
Others[b]	10 (10.9)

*One patient could be accompanied by more than one of their family members

[a]atopic dermatitis, candidiasis, chelitis, chronic paronychia, discoid lupus erythematosus, insect bite reaction, kaposi hemagioendothelioma, lichen simplex chronicus, lupus profundus, pyoderma gangrenosum, rosacea, sporotrichosis, *systemic lupus erythematosus*, urticarial vasculitis

[b]aqugenic pruritus, basal cell carcinoma, chronic arsenism, dermatofibroma, filler complication, hyperhydrosis, keloid, melasma, onychomychosis, pearly penile papules

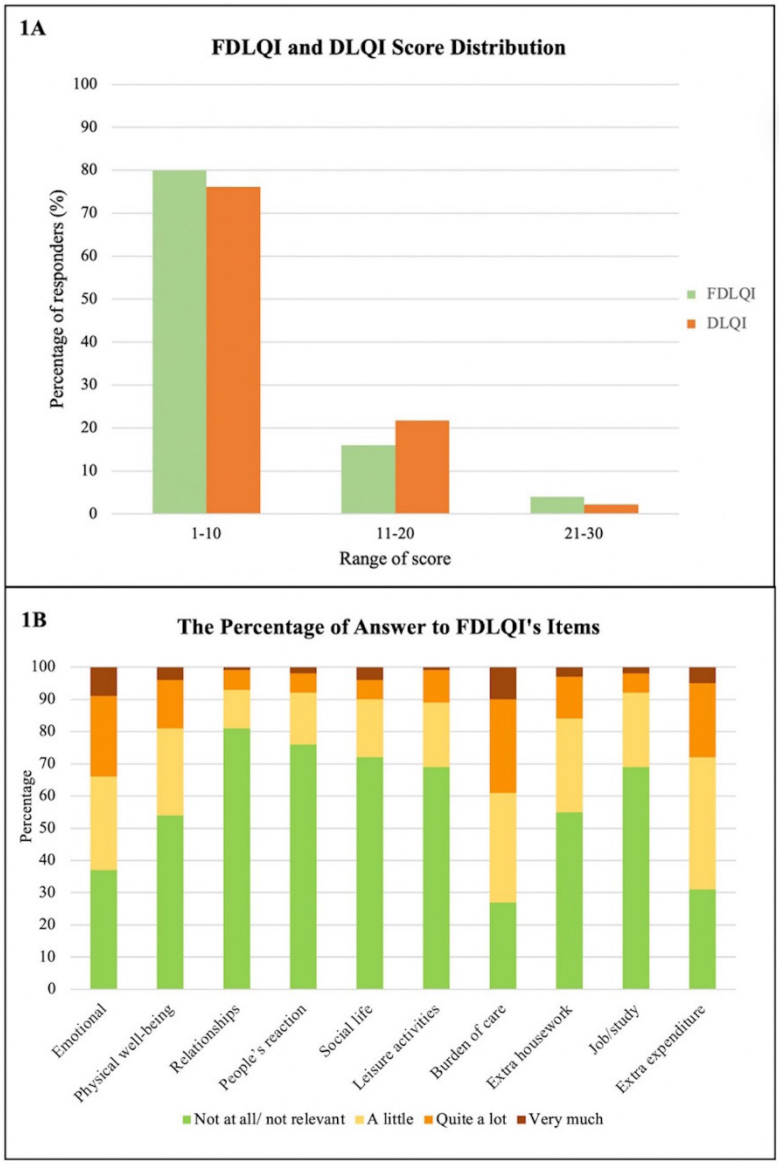


Fig 1. Scores and responses distribution. A, FDLQI and DLQI Score Distribution. B, The percentage of each response to each FDLQI's item
Abbreviations: DLQI: Dermatology Life Quality Index; FDLQI: Family Dermatology Life Quality Index

TABLE 2. Score of each questionnaire

Scores	Median total score (P25, P75)	Minimum score	Maximum score
Patient assessment			
DLQI (range 0-30)	4.5 (2.0, 10.0)	0	26
GQoLP (range 0-10)	3.0 (1.0, 5.0)	0	10
Global question of patient's disease severity (range 0-10)	4.0 (2.0, 5.0)	0	10
Family Members' assessment			
FDLQI (range 0-30)	4.5 (3.0, 10.0)	0	24
GQoLF (range 0-10)	2.0 (0.8, 5.0)	0	10
Global question of patient's disease severity (range 0-10)	4.0 (2.0, 5.0)	0	10
Physicians' assessment			
Global question of patient's disease severity (range 0-10)	3.0 (2.0, 5.0)	0	9

Abbreviations: DLQI; Dermatology Life Quality Index, FDLQI; Family Dermatology Life Quality Index, GqoLF; global QoL question for family members, GqoLP; global QoL question for patients, P; percentile

TABLE 3. Validity of Family Dermatology Life Quality Index (FDLQI) to other questionnaires

Scores	FDLQI r_s	*P*-value
Patient's assessment		
DLQI	0.143	0.174
GQoLP	0.284	0.006*
Global question of patient's disease severity	0.231	0.027*
Family member's assessment		
GQoLF	0.695	<0.001*
Global question of patient's disease severity	0.578	<0.001*
Physician's assessment		
Global question of patient's disease severity	0.318	0.002*

*A *p*-value of less than 0.05 indicates statistical significance
Abbreviations: DLQI; Dermatology Life Quality Index, FDLQI; Family Dermatology Life Quality Index, GqoLF; global QoL question for family members, GqoLP; global QoL question for patients

TABLE 4. Reliability analysis of the items of the Family Dermatology Life Quality Index (FDLQI)

Item number (FDLQI aspects)	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Emotional impact	0.604	0.823
Physical well-being)	0.697	0.813
Relationships	0.564	0.829
People's reaction	0.528	0.830
Social life	0.637	0.820
Leisure activities	0.553	0.828
Burden of care	0.441	0.841
Housework	0.372	0.844
Job/study	0.560	0.828
Financial burden	0.521	0.831

Abbreviation: FDLQI; Family Dermatology Life Quality Index

family members, respectively. This is in line with that of the Japanese version.[8] As expected, the DLQI score of patients with inflammatory diseases was significantly higher than those with non-inflammatory diseases.[9,30] However, this pattern was not consistent with the FDLQI results. The Thai version of the FDLQI showed high reliability, which corresponds to the original version and those of other countries, including Japan, Iran and Ukraine.[31] The Cronbach alpha was not significantly improved by removing any item of the FDLQI. Basra et al.[6] and Higaki et al.[8] also demonstrated that the FDLQI could be used to monitor the QoL of family members of patients with chronic skin diseases, such as eczema, psoriasis, and squamous cell carcinoma, etc. In a follow-up period of three to six months, the FDLQI could detect changes overtime.

Different culture, socioeconomic status, and educational levels could reflect different effects on the QoL of individuals.[3,9,32,33] This could be one of the reasons that the correlation between the DLQI and the FDLQI score in Thailand and other countries was not very close. The DLQI was completed by a patient while the FDLQI was completed by a patient's family member. During the process of our study, some participants explained why they had rated those scores. For example, some patients had horrible acnes while their family members felt little or no effect on their lives. In contrast, some family members, especially parents and partners, felt very worried and used a lot of time to care for the skin diseases (ex. alopecia areata, basal cell carcinoma, and pearly penile papules) while the patients did not feel that it was the problem of their lives.

Some limitations of this study should be noted. First, it had a small sample size. Second, it was carried out only in only urban area of Thailand, where daily life, culture, socioeconomic status, and educational levels are much different from the rural area.[34,35]

CONCLUSION

All three dimensions of skin burden must be taken into account to provide the best holistic care to a patient. FDLQI is one of the most widely used instruments for measuring the QoL of the dermatological patients. This study shows the acceptable validity and reliability of the Thai version of the FDLQI. It is a generic questionnaire that can be used to assess the QoL of family members of patients in any dermatological disease.

ACKNOWLEDGMENTS

The authors thank Assistant Professor Chulaluk Komoltri for statistical analysis consultation.

Data Availability

The data used to support the findings of this study are included within the article.

REFERENCES

1. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global Skin Disease Morbidity and Mortality: An Update From the Global Burden of Disease Study 2013. JAMA Dermatol. 2017;153:406-12.
2. Montero-Vilchez T, Sánchez-Díaz M, Martinez-Lopez A, Arias-Santiago S. Quality of Life in Patients with Skin Disease and Their Cohabitants. Health-Related Quality of Life - Measurement Tools, Predictors and Modifiers. doi:10.5772/intechopen.97450
3. Chogani F, Parvizi MM, Murrell DF, Handjani F. Assessing the quality of life in the families of patients with epidermolysis bullosa: The mothers as main caregivers. Int J Womens Dermatol. 2021;7:721-6.
4. Lifschitz C. The impact of atopic dermatitis on quality of life. Ann Nutr Metab. 2015;66 Suppl 1:34-40.
5. Rees J, O'Boyle C, MacDonagh R. Quality of life: impact of c hronic illness on the partner. J R Soc Med. 2001;94:563-6.
6. Basra MK, Sue-Ho R, Finlay AY. The Family Dermatology Life Quality Index: measuring the secondary impact of skin disease. Br J Dermatol. 2007;156:528-38.
7. Basra MK, Edmunds O, Salek MS, Finlay AY. Measurement of family impact of skin disease: further validation of the Family Dermatology Life Quality Index (FDLQI). J Eur Acad Dermatol Venereol. 2008;22:813-21.
8. Higaki Y, Tanaka M, Futei Y, Kamo T, Basra MKA, Finlay AY. Japanese version of the Family Dermatology Life Quality Index: Translation and validation. J Dermatol. 2017;44:914-9.
9. Safizadeh H, Nakhaee N, Shamsi-Meymandi S, Pourdamghan N, Basra MK. Preliminary reliability and validity of Persian version of the Family Dermatology Life Quality Index (FDLQI). Qual Life Res. 2014;23:869-75.
10. Chernyshov PV, Kaliuzhna LD, Reznikova AA, Basra MK. Comparison of the impairment of family quality of life assessed by disease-specific and dermatology-specific instruments in children with atopic dermatitis. J Eur Acad Dermatol Venereol. 2015;29:1221-4.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19:210-6.
12. Kulthana K JS, Wanitphakdeedecha R. The validity and reliability of the dermatology life quality index (DLQI) in Thais. Thai J Dermatol. 2004;20:113-23.
13. Nunnaly JC, BI. Psychometric theory. 3rd ed: NewYork: Mc Graw-Hill; 1994.
14. Schmitt N. Uses and Abuses of Coefficient Alpha. Psychological Assessment. 1996;8:350-3.
15. Gourraud PA, Le Gall C, Puzenat E, Aubin F, Ortonne JP, Paul CF. Why statistics matter: limited inter-rater agreement prevents using the psoriasis area and severity index as a unique determinant of therapeutic decision in psoriasis. J Invest Dermatol. 2012; 132:2171-5.
16. Finlay A. The three dimensions of skin disease burden: 'Now', 'long term' and 'family'. Br J Dermatol. 2013;169:963-4.
17. Sampogna F, Finlay AY, Salek SS, Chernyshov P, Dalgard FJ, Evers AWM, et al. Measuring the impact of dermatological conditions on family and caregivers: a review of dermatology-specific instruments. J Eur Acad Dermatol Venereol. 2017;31: 1429-39.
18. Köse S, Akelma Z, Özmen S. Severity of disease and the quality of life indexes in infants with atopic dermatitis. Allergol Immunopathol (Madr). 2022;50:55-61.
19. Martínez-García E, Arias-Santiago S, Valenzuela-Salas I, Garrido-Colmenero C, García-Mellado V, Buendía-Eisman A. Quality of life in persons living with psoriasis patients. J Am Acad Dermatol. 2014;71:302-7.
20. Kim E, Fischer G. Relationship between PASI and FDLQI in paediatric psoriasis, and treatments used in daily clinical practice. Australas J Dermatol. 2021;62:190-4.
21. Agarwal S, Jain C, Shaafie HI, Khalid A, Singh A. Impact on quality of life of family members of vitiligo patients in North India: A cross-sectional study using family dermatology life quality index. Indian J Dermatol Venereol Leprol. 2021;87: 869-72.

22. Bin Saif GA, Al-Balbeesi AO, Binshabaib R, Alsaad D, Kwatra SG, Alzolibani AA, et al. Quality of life in family members of vitiligo patients: a questionnaire study in Saudi Arabia. Am J Clin Dermatol. 2013;14:489-95.
23. Kouris A, Christodoulou C, Efstathiou V, Chatzimichail I, Zakopoulou N, Zouridaki E. Quality of life in Greek family members living with leg ulcer patients. Wound Repair Regen. 2015;23:778-80.
24. Sajedianfard S, Handjani F, Saki N, Heiran A. Family dermatology life quality index in patients with pemphigus vulgaris: A cross-sectional study. Indian J Dermatol Venereol Leprol. 2021;87:375-8.
25. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res. 1995;4:293-307.
26. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60:34-42.
27. Wamper KE, Sierevelt IN, Poolman RW, Bhandari M, Haverkamp D. The Harris hip score: Do ceiling effects limit its usefulness in orthopedics? Acta Orthop. 2010;81:703-7.
28. Uttl B. Measurement of Individual Differences: Lessons From Memory Assessment in Research and Clinical Practice. Psychol Sci. 2005;16(6):460-7.
29. Raat H, Landgraf JM, Oostenbrink R, Moll HA, Essink-Bot ML. Reliability and validity of the Infant and Toddler Quality of Life Questionnaire (ITQOL) in a general population and respiratory disease sample. Qual Life Res. 2007;16:445-60.
30. Zhang X-J, Wang A-P, Shi T-Y, Zhang J, Xu H, Wang D-Q, et al. The psychosocial adaptation of patients with skin disease: a scoping review. BMC Public Health. 2019;19:1404.
31. Ware JE, Jr., Gandek B. Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment. J Clin Epidemiol. 1998;51:945-52.
32. Yun J, Katelaris CH, Weerasinghe A, Adikari DB, Ratnayake C. Impact of chronic urticaria on the quality of life in Australian and Sri Lankan populations. Asia Pac Allergy. 2011;1:25-9.
33. Knafl KA, Gilliss CL. Families and Chronic Illness: A Synthesis of Current Research. J Fam Nurs. 2002;8:178-98.
34. Ariyaarpakamol N. Urban-rural inequality in Thailand: Differences in characteristics or returns? Kasetsart J Soc Sci. 2019;40:32-9.
35. Hitokoto H, Takahashi Y, Kaewpijit J. Happiness in Thailand: Variation between urban and rural regions. Psychologia. 2014;57:229-44.

Adverse Events of Traditional Medicines and Herbal Products in the Thai Health Product Vigilance Center Database and the Ayurved Clinic of Applied Thai Traditional Medicine, Siriraj Hospital

Suvimol Niyomnaitham, M.D.,*,, Narichat Chuensakun, B.ATM.***, Slita Prachakit, B.ATM.***, Chidapa Pakjamsai, B.ATM.***, Pravit Akarasereenont, M.D., Ph.D.*,***

**Department of Pharmacology, Faculty of Medicine Siriraj Hospital, **Siriraj Institute of Clinical Research, Faculty of Medicine Siriraj Hospital, Mahidol University, ***Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Objective: The aim of this study was to categorize adverse events (AEs) and symptoms related to traditional medicines (TMs) and herbal products (HPs) using the Thai Vigibase program (TVP).

Materials and Methods: TVP collected spontaneous AE reports including causality assessment of medical products in Thailand. For prospective data, Naranjo's algorithm (NJA) was used to determine the level of causality.

Results: There were a total of 1,133 AE case reports extracted from TVP and featured 1,229 TMs/HPs (310 TMs/HPs names) and 1,592 symptoms (204 symptom names). *Andrographis paniculata* was the product most frequently linked to AEs, with six cases of confirmed urticaria, 37 probable cases, and 24 possible causalities, 15 patients were given 23 TMs/HPs and this related to 33 AEs. The Ya Hom No.24 Tablets had the most reported AEs at 17.4% with only one causality, which was most probably linked to chest burning pain. There was also one case of herbal decoction relieving menopausal symptoms that was certainly related to chest fullness, feeling hot and cold, suffocation feeling, and sweating increase. Ayurved Siriraj Brand Ya Lom No.65 Pills, also reported one case that was linked to fatigue and drowsiness.

Conclusion: Reports from both data sources found a similar pattern in AE type and TMs/HPs. Naranjo's algorithm might be one of useful tools to help assess the causality between TMs/HPs and AEs. The results of this study serve as a good reference for causality between TMs/HPs and their AEs for all Thai traditional medicine practitioners.

Keywords: Traditional medicine; herbal product; adverse event; symptom name; and Naranjo's algorithm (Siriraj Med J 2023; 75: 377-391)

INTRODUCTION

Traditional medicines (TMs) and herbal products (HPs) are increasingly being used across the world. The Thai herbal industry grew from $US27 million in 2003 to $US300 million in 2014.[1,2] This acceleration of over 10% growth per year was the result of global exports of.[2] Although a great deal of research has been carried out to prove the benefits of TMs/HPs, adverse events (AEs) remain a concern. Minimal adverse effects of TMs/HPs have been recorded worldwide and systemically

Corresponding author: Pravit Akarasereenont
E-mail: pravit.auk@mahidol.edu
Received 24 February 2023 Revised 18 March 2023 Accepted 27 March 2023
ORCID ID:http://orcid.org/0000-0001-5743-3251
https://doi.org/10.33192/smj.v75i5.261512

categorized.[3-5] An understanding of AEs associated with TMs/HPs is essential for accurate prescriptions and to ensure user safety. Global organizations, such as the World Health Organization (WHO), have stored safety profile data of TMs/HPs use, including AE reports.[6] Regulatory authorities in many countries such as the Therapeutic Goods Administration (TGA) in Australia or even the China Food and Drug Administration (CFDA) in China, have tried to establish prospective surveillance in order to gain an understanding of the frequency, severity and causes of AEs involving TMs/HPs.[7-9] As a result of continuous data collection in studies from around the world, there is an abundance of results regarding herbal safety. For example, several studies have examined possible AEs linked to TMs/HPs through regulatory pharmacovigilance programs. A study of ADRs in Brazil[10], a prospective study with complementary medicine inpatients in Germany[11] and a study of AE using complementary and alternative medicine (CAM) products in Singapore[12] all looked at herbal drug ingredients.

In 1980, the Ministry of Public Health of Thailand began drug monitoring in hospitals with the founding of the Health Product Vigilance Center (HPVC), which in 1983 came under Thai Food and Drug Administration (Thai FDA). The Thai Vigibase Program (TVP) was created to collect AE reports of health products, including HPs from all over the country.[13] In Thailand, pharmacovigilance studies on the safety of herbal products have increased, especially of Traditional Thai medicine. A study conducted in 2000 at Lampang Hospital, in the north of Thailand reported hepatotoxic effects in Type 2 diabetes patients treated with *Tinospora crispa*.[14] Retrospective data from TVG between 2001-2012 described AEs, including hypersensitivity reactions to Andrographis products.[15] Studies looking at some specific TMs/HPs and serious AEs used the TVG which collects all AEs from health products, including TMs/HPs.[16,17] However, in this study, there was a plan to collect and analyze AE reports of HPs from two dimensions: retrospective data from database in Thailand and prospective visitors to Ayurved Clinic (AC) at Siriraj Hospital.

The Ayurved Clinic (AC) of Applied Thai Traditional Medicine under the Center of Applied Thai Traditional Medicine (CATTM), Faculty of Medicine Siriraj Hospital provides all types of traditional Thai treatments, including TMs/HPs to patients. Ingredients of TMs/HPs at the AC are not only known for their efficacy, but also manufactured following factory qualified standards or Good Manufacturing Practice (GMP) and the Pharmaceutical Inspection Co-operation Scheme (PICS). However, adverse effects caused by TMs/HPs need to be classified and incorporated with the national database of Thailand. Following a previous AE study, this report was designed to continuously and retrospectively collect AEs related to TMs/HPs.[16] This prospective collection of AEs at the AC provides a more complete picture of patient information compared to retrospective data of the former study. Therefore, the aim of this study was to describe characteristics of AEs using TVP and patients' data from AC.

MATERIALS AND METHODS

This study was approved by the Ethics Committee for Research in Humans via certificate of approval No. Si 410/2015, and ran at the Faculty of Medicine Siriraj Hospital between 2015 and 2017. There were two sets of data, including a retrospective part that looked at TVP data from the national database and a prospective part in which patients experienced AEs as a result of TMs/HPs at the AC.

Thai Vigibase Program (TVP)

Retrospective data was extracted from TVP, a database that collects spontaneous AE reports in the country. The reports were submitted either as an electronic form via an online reporting system or in paper format to the Health Product Vigilance Center (HPVC), Thai Food and Drug Administration (Thai FDA). The HPVC shares this data for use in pharmacovigilance studies. Each data point in the reports extracted characteristics of patients such as, names of products, terms and characteristics of AEs between January 2009 and July 2015.

Ayurved Clinic (AC)

A prospective study at the AC, Faculty of Medicine Siriraj Hospital was conducted between August 2015 and March 2016 and the prevalence of AEs in patients prescribed TMs/HPs was recorded. AEs were assessed by doctors who specialize in traditional Thai medicine and Western physicians, including follow-ups by telephone to record patients' sign and symptoms. The **World Health Organization's Adverse drug Reaction Terminology (WHO-ART)** was used to explain symptoms linked to AEs. **Naranjo's algorithm (NJA)** is a widely used tool among pharmacists to assess the ADRs of patients and the causality of adverse drug reactions through the answering of 10 questions.[18] Each question was answered and then categorized according to a scoring system divided into four levels of causality, including "Certain", "Probable", "Possible", and "Unlikely". The total score is shown as level of the causal relationship [9-13 points = certain, 5-8 points = probable, 1-4 point (s) = possible, or less than 1 point = unlikely/doubtful].[18,19]

Data analysis

Retrospective data from the TVP was imported into Microsoft Excel for data generation and preliminary analysis. The SPSS program was used for statistical analysis.[20] Descriptive statistics including mean, mode, and frequency were used to describe data in both retrospective and prospective studies.

RESULTS

Retrospective Results from Thai Vigibase Program and Prospective Results from Ayurved Clinic

Results from the TVP between January 2009 and July 2015 revealed, 1,131 patient reports, and a total of 1,229 products (310 product names) associated with 1,592 symptoms (204 symptom names). Some of the reports had just one product linked to one symptom, while some had one product linked to two or more symptoms. Some products also had contained more than one symptom associated to it.

According to data from the AC over the eight-month period from August 2015 to March 2016, 9,959 visitors were prescribed TMs/HPs. Of these, 15 visitors (0.15%) informed of an AE linked to clinical use of TMs/HPs use. Five of them had repeated AE after retaking the same products. There were 23 products (17 product names) linked to 33 symptoms (29 symptom names) and some of the reports were the same as in TVP or products that had more than one AE linked to it.

Fig 1 shows the characteristics of reports and patients in TVP and AC. The report characteristics include type, quality and seriousness. According to characteristics, data from the TVP and AC were presented as spontaneous in quality level 2 and non-serious events. All reports from AC were of the spontaneous type. No clinical trials have been performed using either sets of data. Referring to the seriousness of AEs, one "death" was associated to an AE in TVP. The most serious reported AE in TVP were "Initial or prolongation of hospitalization", which was similar to reports from AC where two serious AEs in this category were reported. According to patient characteristics from both sets of data, most of the patients were female and outpatient. All AE cases at the AC were outpatients. The age of TVP-patients mostly ranged from 46-60 whereas it was 61-75 at the AC.

Fig 2 shows the number, name and type of AE reported in products in TVP. The AE reports extracted 310 products, consisting of 64 known and 246 unknown ingredients, and 1,229 product reports. The 246 unknown ingredients may have been repeatedly reported by different events, so the exact total of unknown product names might be less than 246. The types of products included 27 single herbs and 37 herbal formulas. The single herb

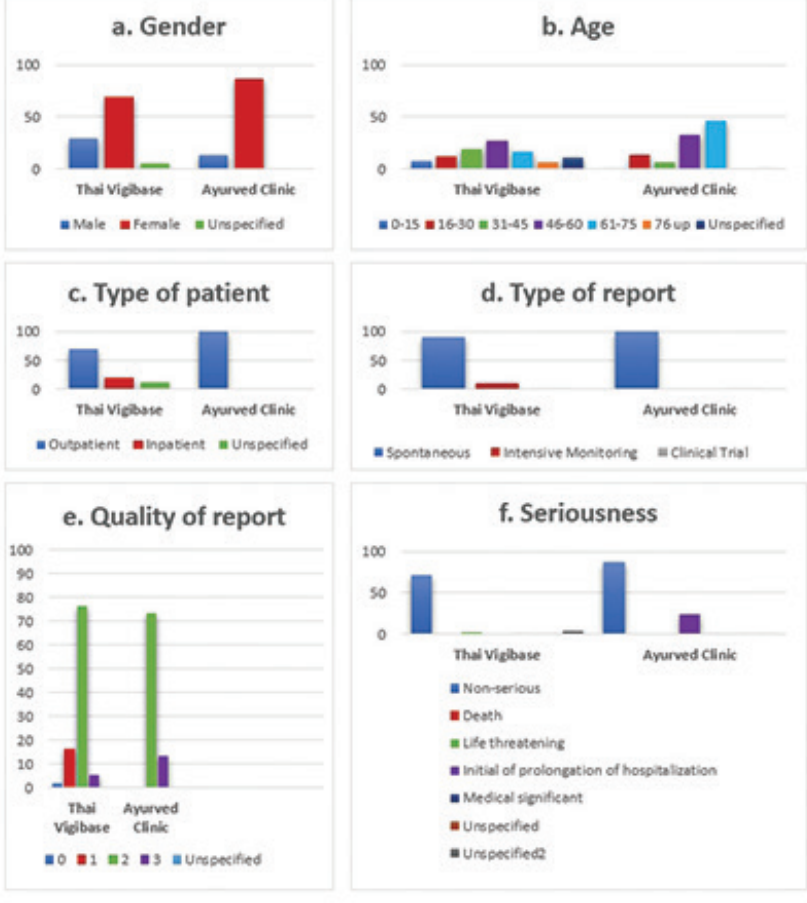


Fig 1. Report characteristics and patients from the Thai Vigibase Program between January 2009 and July 2015 and Ayurved Clinic between August 2015 and March 2016.

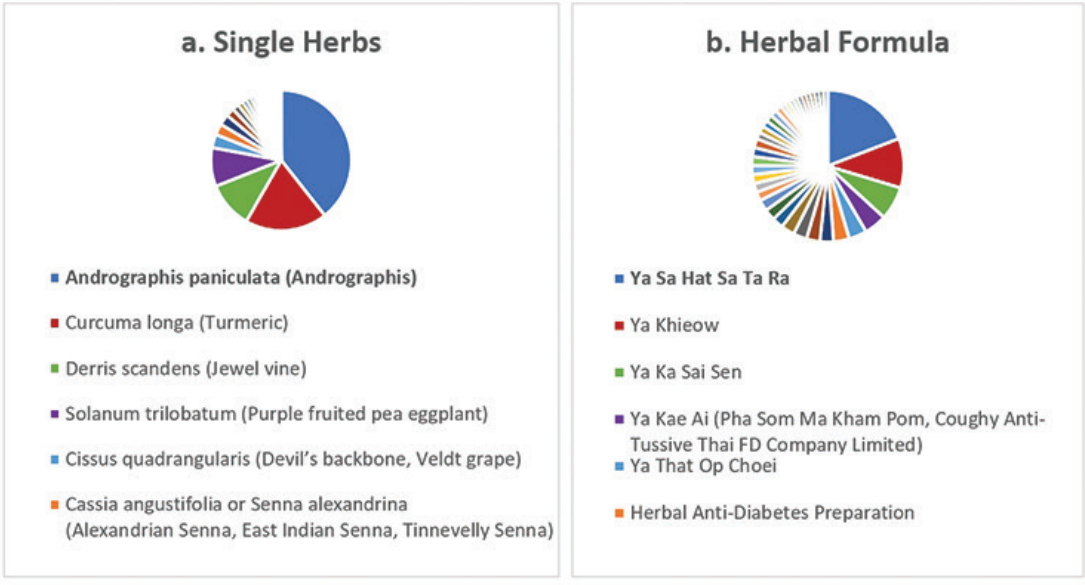


Fig 2. Products associated with adverse events from the Thai Vigibase Program between January 2009 and July 2015.

consisted of one HP while herbal formulas contained multiple single herbs. For the single herbs, the products were reported as scientific names, including their common names. The single herb product *"Andrographis paniculata"*, had the most AE associated with it. The top five on the chart mostly show four single herbs, and one herbal formula known as "Ya Sa Hat Sa Ta Ra". Although "Ya Sa Hat Sa Ta Ra" ranked fifth in the chart, it reported the most AEs among the herbal formula products. As seen in Table 2, the top 10 included 11 products in total. "Ya Ka Sai Sen" had and equal number of reports to *"Zingiber cassumunar"* in 10th place. The top 10 in the chart includes three herbal formulas "Ya Sa Hat Sa Ta Ra", "Ya Khieow", and "Ya Ka Sai Sen".

Table 1 shows the 11 products that had the most reported AEs, causalities, and symptom names. Each product had four levels of causalities, including an unspecified level. The four levels were; certain, probable, possible and unlikely. Each was calculated using Naranjo's algorithm assessment. The unspecified level included products that reported no causality. Most of the symptoms associated with these products fell in the probable level. In first place was *"Andrographis paniculata"*, which mostly led to urticaria. In second place was *"Curcuma longa"*, which mostly led to rash. However, for "Ya Sa Hat Sa Ta Ra", *"Cassia angustifolia* or *Senna alexandrina", "Momordica charantia"*, "Ya Ka Sai Sen", and "*Zingiber cassumunar*", there was no data at the certain level. Among all the data in the table, *"Andrographis paniculata"* was the only product to have an unspecified causality of two symptoms.

Fig 3 shows the name, type and the number of product reports from the AC. A total of 17 products reported 23 AEs. Of this, 17 TMs/HPs were single herbs and the rest herbal formulas. All products were named after the "Ayurved Siriraj Manufacturing Unit of Herbal Medicine and Products" so that reported AEs had a registered name even if there was no scientific name of a single herb. The mode of administration included pills, capsules, tablets and three different formulas of decoction. Almost all of the 17 products were herbal formula, except for "Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion", which was the only single herb causing AE. "Ayurved Siriraj Brand Ya Hom No.24 Tablets", a herbal formula was the product that reported the most AEs. In second place for AEs were three products, "Ayurved Siriraj Brand No.11 Antiflatulent Tablets", "Ayurved Siriraj Brand No.39 Antiflatulent Tablets" and "Ya Med Kae Nam Luang Sia, Ayurved Siriraj Brand". Most of the products were marked for internal-use except Ayurved Siriraj Brand Medicated Balm formula 1, which was meant for external use.

Table 2 shows the 17 products that had an AE associated with causalities and symptoms at the AC. "Ayurved Siriraj Brand Ya Hom No.24 tablets" had the most reported AEs. However, the "probable" category had the highest level of causalities in most products. Only two products reported a certain level of symptoms. "Herbal decoction relieving menopausal symptoms" was certainly related to chest fullness, feeling hot and cold, suffocation feeling, and sweating increase. "Ya Lom No.65 Pills, Ayurved Siriraj Brand" was also certainly related to drowsiness and fatigue.

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015.

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
1	*Andrographis paniculata* (Andrographis) 305 (24.81)	Certain	Urticaria (6), Pruritus (2), Angioedema (1), Fixed eruption (1), Macular rash (1), Oedema mouth (1), Papular rash (1), Rash (1), Rash maculo-papular (1)
		Probable	Urticaria (37), Rash maculo-papular (35), Angioedema (16), Pruritus (14), Rash (13), Oedema eyelid (12), Anaphylactic shock (11), Rash erythematous (11), Anaphylaxis (10), Face oedema (7), Itching (7), Dyspnoea (5), Nausea (5), Papular rash (5), Vomiting (5), Macular rash (4), Chest tightness (3), Chest fullness (2), Dizziness (2), Flatulence (2), Lips swelling non-specific (2), Oedema legs (2), Acute generalized exanthematous pustulosis (1), Anaphylactic reaction (1), Anaphylactoid reaction (1), Blisters (1), Bloating (1), Breath shortness (1), Chest discomfort (1), Coughing (1), Diarrhoea (1), Erythema (1), Eye discharge (1), Faintness (1), Fever (1), Gastro-intestinal disorder NOS* (1), Hearing impaired (1), Hepatic enzymes increased (1), Measly rash (1), Mouth ulceration (1), Muscle cramp (1), Oedema (1), Oedema generalized (1), Oedema genital (1), Oral mucosal eruption (1), Pain (1), Papulovesicular rash (1), Paralysis muscle local skeletal (1), Purpura allergic (1), Red eye (1), Skin flushed (1), Stevens Johnson Syndrome (1), Tongue disorder (1), Urticaria acute (1), Weariness (1)
		Possible	Urticaria (24), Rash (17), Rash maculo-papular (14), Angioedema (9), Rash erythematous (9), Face oedema (7), Oedema eyelid (7), Papular rash (6), Oedema mouth (5), Pruritus (5), Anaphylactic shock (2), Anaphylaxis (2), Dyspnoea (2), Itching (2), Macular rash (2), Nausea (2), Oedema (2), Stevens Johnson Syndrome (2), Vomiting (2), Anaesthesia mouth (1), Anaphylactic reaction (1), Arthritis rheumatioid aggravated (1), Burning sensation (1), Chest fullness (1), Chest tightness (1), Coughing (1), Dermatitis exfoliative aggravated (1), Diarrhoea (1), Dizziness (1), Eczema (1), Eosinophilia (1), Eye inflamed (1), Fever (1), Fixed eruption (1), Hepatitis (1), Inflammatory swelling (1), Morbilliform rash (1), Numbness oral (1), Oedema of extremities (1), Oedema peripheral (1), Pain (1), Palpitation (1), Skin vasculitis NOS* (1), Stomatitis (1), Sweating increased (1), Wheezing inspiratory (1)
		Unlikely	Constipation (1), Dizziness (1), Stool black (1)
		Unspecified	Rash (1), Urticaria (1)
2	*Curcuma longa* (Turmeric) 146 (11.88)	Certain	Burning sensation (1), Extrapyramidal disorder (1), Fixed eruption (1), Nausea (1), Rash maculo-papular (1), Vomiting (1), Weakness generalized (1)
		Probable	Rash maculo-papular (13), Urticaria (13), Rash (12), Pruritus (9), Angioedema (6), Dizziness (6), Itching (5), Nausea (5), Oedema legs (5), Dyspnoea (4), Palpitation (4), Face oedema (3), Headache (3), Oedema (3), Vomiting (3), Anaphylaxis (2), Chest tightness (2), Constipation (2), Diarrhoea (2), Macular rash (2),

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
			Mouth dry (2), Oedema eyelid (2), Rash erythematous (1), Abdominal pain (1), Anaphylactic shock (1), Breath shortness (1), Buccal mucosa ulceration (1), Burning sensation (1), Chest distress (1), Chest fullness (1), Coughing (1), Erythema (1), Faintness (1), Fixed eruption (1), Flatus (1), Fullness abdominal (1), Hearing impaired (1), Heat rash (1), Lip soreness (1), Mouth ulceration (1), Oedema mouth (1), Oedema peripheral (1), Oral mucosal eruption (1), Pain (1), Papular rash (1), Stevens Johnson Syndrome (1), Stomach upset (1), Tongue disorder (1), Weariness (1)
		Possible	Rash (10), Rash maculo-papular (6), Urticaria (6), Pruritus (3), Angioedema (2), Diarrhoea (2), Dyspnoea (2), Vomiting (2), Abdominal pain (1), Anaphylactic shock (1), Anorexia (1), Chest tightness (1), Constipation aggravated (1), Dizziness (1), Erythema multiforme (1), Fatigue (1), Flatulence (1), Headache (1), Itching (1), Lethargy (1), Macular rash (1), Mouth dry (1), Nausea (1), Oedema eyelid (1), Oral ulceration (1), Palpitation (1), Papulovesicular rash (1), Rash erythematous (1), Rash pustular (1), Stevens Johnson Syndrome (1), Throat dry (1)
		Unlikely	Allergic conjunctivitis (1), Dizziness (1), Hypoglycaemia (1), Oedema of extremities (1), Pruritus (1), Rash (1), Urticaria (1)
		Unspecified	-
3	*Derris scandens* (Jewel vine) 83 (6.75)	Certain	Angioedema (1), Anorexia (1), Burning sensation (1), Dizziness (1), Itching (1), Mouth dry (1), Nausea (1), Palpitation (1), Pruritus (1), Sleepiness (1), Throat dry (1)
		Probable	Rash (6), Urticaria (6), Angioedema (5), Palpitation (5), Face oedema (3), Itching (3), Urinary frequency (3), Vomiting (3), Diarrhoea (2), Dizziness (2), Macular rash (2), Nausea (2), Papular rash (2), Rash erythematous (2), Rash maculo-papular (2), Angioedema (1), Abdominal pain (1), Anaphylactic shock (1), Anaphylaxis (1), Bewilderment (1), Breathing difficult (1), Bruise (1), Convulsions (1), Bullous eruption (1), Debility (1), Eczema (1), Erythema multiforme (1), Eye irritation (1), Fixed eruption (1), Haemorrhage NOS* (1), Hypokalaemia (1), Mouth dry (1), Mouth ulceration (1), Numbness (1), Oedema mouth (1), Oedema of extremities (1), Oedema peripheral (1), Pruritus (1), Stools watery (1), Throat dry (1), Tiredness (1), Urinary retention (1)
		Possible	Angioedema (5), Urticaria (5), Itching (3), Abdominal pain (2), Dizziness (2), Rash (2), Anorexia (1), Bullous eruption (1), Chest tightness (1), Constipation (1), Convulsions (1), Diarrhoea (1), Erythema (1), Extremities hot feeling (1), Faecal abnormality NOS* (1), Headache (1), Insomnia (1), Mouth irritation (1), Muscle pain (1), Muscle rigidity (1), Oedema mouth (1), Papular rash (1), Rash erythematous (1), Throat irritation (1), Urinary frequency (1)
		Unlikely	Giddiness (1), Nausea (1), Vision blurred (1)
		Unspecified	-

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
4	*Solanum trilobatum* (Purple fruited pea eggplant) 69 (5.6)	Certain	Fixed eruption (1), Pruritus (1), Rash maculo-papular (1), Urticaria (1)
		Probable	Rash (9), Rash maculo-papular (7), Urticaria (6), Oedema eyelid (5), Pruritus (5), Angioedema (4), Chest fullness (3), Face oedema (3), Oedema mouth (3), Macular rash (2), Oedema (2), Rash erythematous (2), Stevens Johnson Syndrome (2), Anaesthesia local (1), Anaesthesia mouth (1), Anaesthesia tongue (1), Bronchospasm (1), Dermatitis exfoliative (1), Dizziness (1), Dyspepsia (1), Dyspnoea (1), Eye irritation (1), Flatulence (1), Gastro-intestinal disorders NOS* (1), Hot flushes (1), Joint pain (1), Lips dry (1), Lips swelling non-specific (1), Mouth dry (1), Mouth ulceration (1), Nausea (1), Palpitation (1), Papulovesicular rash (1), Rash bullous (1), Tiredness (1), Vomiting (1)
		Possible	Rash maculo-papular (5), Itching (2), Rash (2), Urticaria (2), Angioedema (1), Chest fullness (1), Diarrhoea (1), Face oedema (1), Gasping (1), Lips swelling non-specific (1), Oedema eyelid (1), Oral ulceration (1), Papular rash (1), Rash erythematous (1), Rash petechial (1)
		Unlikely	Lips swelling non-specific (1), Oedema (1), Pruritus (1), Rash erythematous (1)
		Unspecified	-
5	Ya Sa Hat Sa Ta Ra 40 (3.25)	Certain	-
		Probable	Abdominal pain (3), Diarrhoea (3), Throat dry (3), Flatulence (2), Mouth dry (2), Nausea (2), Pruritus (2), Anorexia (1), Bloating (1), Dizziness (1), Eczema (1), Hearing impaired (1), Peripheral oedema / Acute gout attack (1), Rash erythematous (1), Rash maculo-papular (1), Sleepiness (1), Stools loose (1), Tongue disorder (1), Urticaria (1), Vomiting (1)
		Possible	Abdominal pain (5), Anorexia (4), Diarrhoea (4), Dizziness (4), Mouth dry (4), Throat dry (4), Rash erythematous (3), Constipation (2), Pruritus (1), Rash (1), Urine discolouration (1), Urticaria (1), Vomiting (1), Weakness generalized (1)
		Unlikely	Abdominal pain (1)
		Unspecified	-
6	*Cissus quadrangularis* (Devil's backbone, Veldt grape) 24 (1.95)	Certain	Adult respiratory distress syndrome (1), Urticaria (1)
		Probable	Burning sensation (2), Dizziness (1), Dyspnoea (1), Headache (1), Lip soreness (1), Nausea (1), Pruritus (1), Rash erythematous (1), Rash maculo-papular (1)
		Possible	Chest tightness (2), Diarrhoea (2), Flatulence (2), Pruritus (2), Abdominal discomfort (1), Angioedema (1), Constipation aggravated (1), Dizziness (1), Nausea (1), Rash (1)
		Unlikely	-
		Unspecified	-
7	Ya Khieow 22 (1.79)	Certain	Anaphylaxis (1), Urticaria (1)
		Probable	Rash erythematous (2), Rash maculo-papular (2), Stevens Johnson Syndrome (2), Anaphylactic shock (1), Anaphylaxis (1), Burn (1), Erythema multiforme severe (1), Eye inflamed (1), Face oedema (1), Fever (1), Oedema eyelid (1), Pruritus (1), Rash (1)

TABLE 1. A list of the 11 products that reported the most adverse events with level of causalities, and symptom names from the Thai Vigibase Program between January 2009 and July 2015. (Continued)

No.	Product Report No. (%) [n=1,229]	Level of Causalities	Symptom Name (n) [n=1,732]
		Possible	Rash maculo-papular (2), Urticaria (2), Urticaria acute (2), Angioedema (1), Bronchospasm (1), Eye pain (1), Face oedema (1), Oedema eyelid (1), Oedema mouth (1), Rash (1), Toxic epidermal necrolysis (1)
		Unlikely	Choking (1), Rash maculo-papular (1), Unconsciousness (1)
		Unspecified	-
8	*Cassia angustifolia* or *Senna alexandrina* (Alexandrian Senna, East Indian Senna, Tinnevelly Senna) 20 (1.63)	Certain	-
		Probable	Urticaria (3), Dizziness (2), Dyspnoea (2), Oedema mouth (2), Rash erythematous (2), Rash maculo-papular (2), Anaphylactic shock (1), Anaphylactoid reaction (1), Anaphylaxis (1), Angioedema (1), Coughing (1), Itching (1), Pruritus (1), Rash (1), Rash erythematous aggravated (1), Wheezing inspiratory (1)
		Possible	Erythema multiforme (1), Fixed eruption (1), Hepatitis (1), Rash erythematous (1), Urticaria (1)
		Unlikely	-
		Unspecified	-
9	*Momordica charantia* (Bitter melon, Bitter gourd) 19 (1.55)	Certain	-
		Probable	Urticaria (2), Angioedema (1), Anorexia (1), Dizziness (1), Flatulence (1), Nausea (1), Rash erythematous (1), Rash maculo-papular (1), Vomiting (1)
		Possible	Dizziness (2), Anaesthesia mouth (1), Anaesthesia tongue (1), Diarrhoea (1), Face oedema (1), Faintness (1), Headache (1), Hepatitis (1), Insomnia (1), Nausea (1), Oedema mouth (1), Palpitation (1), Pruritus (1), Rash (1), Rash erythematous (1), Rash maculo-papular (1), Throat dry (1)
		Unlikely	Flatulence (2), Abdominal pain (1), Paraesthesia (1), Rash erythematous (1), Sleepiness (1), Stools loose (1), Urine discolouration (1)
		Unspecified	-
10	Ya Ka Sai Sen 15 (1.22)	Certain	-
		Probable	Urticaria (2), Anaphylaxis (1), Bradycardia (1), Face oedema (1), Gastrointestinal tract bleeding NOS* (1), Macular rash (1), Nausea (1), Oedema eyelid (1), Papular rash (1), Rash erythematous (1), Rash maculo-papular (1), Stevens Johnson Syndrome (1), Vesiculobullous rash (1)
		Possible	Pruritus (2), Urticaria (2), Angioedema (1), Papular rash (1)
		Unlikely	-
		Unspecified	-
11	*Zingiber cassumunar* or *Zingiber montanum* (Phlai, Cassumunar ginger) 15 (1.22)	Certain	-
		Probable	Rash (3), Itching (2), Angioedema (1), Application site reaction (1), Bullous eruption (1), Burning sensation (1), Burning skin (1), Dermatitis contact (1), Eruption (1), Erythema (1), Macular rash (1), Pruritus (1), Rash bullous (1), Rash maculo-papular (1), Urticaria (1), Vesicular rash (1)
		Possible	Abdominal pain (1), Anorexia (1), Dermatitis contact (1), Rash erythematous (1)
		Unlikely	-
		Unspecified	-

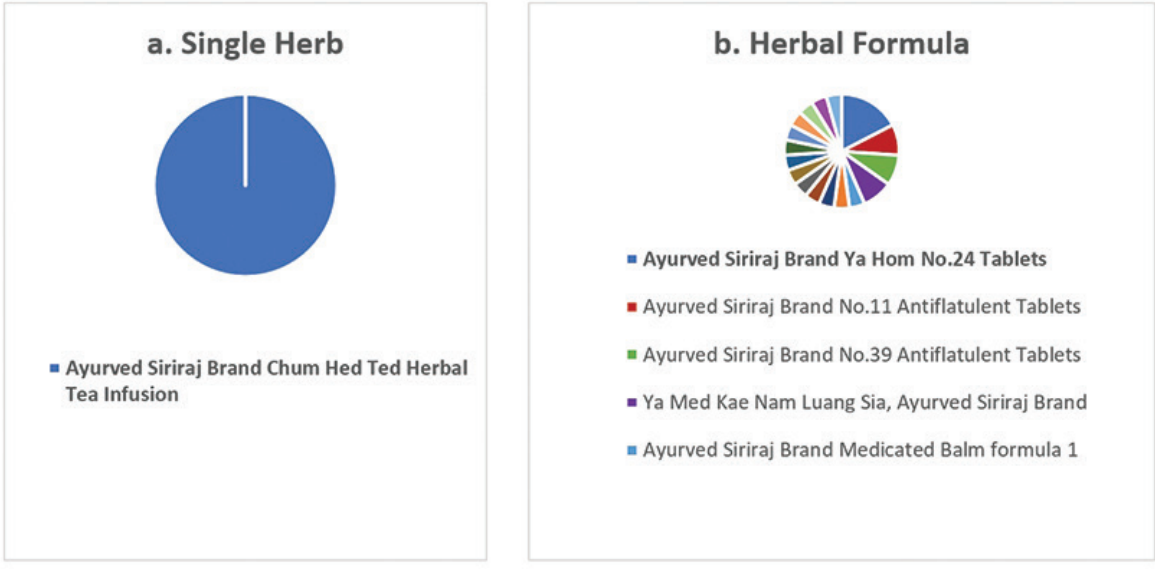


Fig 3. Products that reported adverse events at the Ayurved Clinic between August 2015 and March 2016.

TABLE 2. Products that reported level of causalities and symptom names at Ayurved Clinic between August 2015 and March 2016.

No.	Product report No. (%) [n=23]	Level of Causalities	Symptom Name (n) [n=51]
1	Ayurved Siriraj Brand Ya Hom No.24 Tablets 4 (17.4)	Certain	-
		Probable	Chest burning pain (1)
		Possible	Abdominal discomfort (1), Chest fullness (1), Debility (1), Dizziness (1), Feeling hot and cold (1), Headache (1), Pruritus (1), Sleeplessness (1), Suffocation feeling (1), Sweating increase (1), Urticaria (1)
		Unlikely	-
2	Ayurved Siriraj Brand No.11 Antiflatulent Tablets 2 (8.7)	Certain	-
		Probable	-
		Possible	Abdominal pain (1), Nausea (1), Large bowel obstruction (1)
		Unlikely	Leg cramps (1)
3	Ayurved Siriraj Brand No.39 Antiflatulent Tablets 2 (8.7)	Certain	-
		Probable	Chest burning pain (1)
		Possible	Burning mucosal (1), Nasal congestion (1), Throat dry (1)
		Unlikely	-
4	Ya Med Kae Nam Luang Sia, Ayurved Siriraj Brand 2 (8.7)	Certain	-
		Probable	Oedema eyelid (1), Oedema mouth (1), Urticaria (1)
		Possible	Face oedema (1), Oedema eyelid (1), Urticaria aggravated (1)
		Unlikely	-
5	Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion 1 (4.35)	Certain	-
		Probable	Dizziness (1)
		Possible	-
		Unlikely	-
6	Ayurved Siriraj Brand Medicated Balm formula 1 1 (4.35)	Certain	-
		Probable	Burning sensation (1), Itching (1)
		Possible	-
		Unlikely	-

TABLE 2. Products that reported level of causalities and symptom names at Ayurved Clinic between August 2015 and March 2016. (Continued)

No.	Product report No. (%) [n=23]	Level of Causalities	Symptom Name (n) [n=51]
7	Ayurved Siriraj Brand No.12 Pills 1 (4.35)	Certain Probable Possible Unlikely	- Abdominal pain (1), Nausea (1), Large bowel obstruction (1) - -
8	Ayurved Siriraj Brand No.30 Ya Satree Pills 1 (4.35)	Certain Probable Possible Unlikely	- - Face oedema (1), Oedema eyelid (1), Urticaria aggravated (1) -
9	Ayurved Siriraj Brand Ya Hom No.20 Tablets 1 (4.35)	Certain Probable Possible Unlikely	- Palpitation (1) - -
10	Ayurved Siriraj Brand Ya Hom No.47 Tablets 1 (4.35)	Certain Probable Possible Unlikely	- - Burning mucosal (1), Nasal congestion(1), Throat dry (1) -
11	Bantaoridsidwangthawan Pills, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- - Dizziness (1) -
12	Herbal decoction relieving joint pain or inflammation (fruit instead stem of khi ka daeng formula) 1 (4.35)	Certain Probable Possible Unlikely	- Abdominal discomfort (1) - -
13	Herbal decoction relieving menopausal symptoms 1 (4.35)	Certain Probable Possible Unlikely	Chest fullness (1), Feeling hot and cold (1), Suffocation feeling (1), Sweating increase (1) - - -
14	Herbal decoction relieving menopausal symptoms (Benjakool formula, remove Ha-rak ingredients) 1 (4.35)	Certain Probable Possible Unlikely	- Pruritus (1), Urticaria (1) - -
15	Ya Lom No.65 Pills, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	Drowsiness (1), Fatigue (1) - - -
16	Ya Sahatsatara Tablets, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- - Papulovesicular rash (1) -
17	Ya Sattakavata, Ayurved Siriraj Brand 1 (4.35)	Certain Probable Possible Unlikely	- Leg cramps (1) - -

DISCUSSION

This study examined AEs relating to TMs/HPs by looking at retrospective data in the TVP database over a seven-year period and prospective data from the AC over an eight-month period. In the TVP, some of the 1,133 patients had a poly-medicine regimen, so 1,229 and 1,732 symptoms were reported as seen in Table 1 and Table 2. Differences of AE relations were reported. Each report from both datasets used either a product or poly-medicine. Some reports showed a product with a symptom or more than one symptom while other reports showed more than a product with a symptom or more than a symptom.

As seen in data from TVP and AC data in Fig 1, most reports and patient characteristics were similar. As a result of establishing a routine for AE assessment in TMs/HPs among health professionals, there was not a clinical trial that reported on a data or intensive monitoring of TVP. Due to this reason, it would be beneficial to collect more AE data in a further study to learn about AEs linked to TMs/HPs. To improve patient safety standards, proactive collecting of AEs from clinical-trial studies at the AC should be promoted. Both sets of data were recorded at quality level two or three, which means it was mostly complete when compared to data from TVP. Even though the number of non-serious AEs was high in both datasets, there was one death in the TVP dataset and two cases of "initial or prolongation of hospitalization" at AC. No inpatient was reported at the AC because the clinic serves only outpatients. Also, patients over 45 in both datasets had more AEs reports.

As TVP-product data shows in Fig 2, TMs/HPs consist of drug such as "Thai Thip O-Soth Herbal Medicine" or food supplements such as the "Dietary Supplement Product (Sun Clara)" manufactured in Thailand. However, some products have their origin in Chinese traditional medicine or products such as "Jiu Jeng Pushen Jiao Nang" and "Yong Heng Herb Solution". Some of those products are also sold in other countries such as "Garcinia extract + Emblica extract plus several vitamins and amino acids (Ketosteril, Amiyu)" and "Pudina Satva (A Blend of Mint Oils)". These various forms have both internal and external use. This shows the variety in behaviors of use of TMs/HPs as either drugs or food supplements among Thais. The three single herbal products, *"Andrographis paniculata"*, *"Curcuma longa"*, and *"Derris scandens"*, are in the list of top three most frequently used products. Moreover, they are listed in the Thailand National List of Essential Medicines (Thailand NLEM) and observed under an intensive monitoring program by HPVC.[6] The wide use of the first of these products, *"Andrographis paniculata"*, is due to its properties of relieving sore throat, fever, cough and other inflammations, and it is a nationwide-reported herb in HPVC.[6] When comparing AE data from TVP to the former study, *Andrographis paniculata, Curcuma longa,* and *Derris scandens* still ranked in the top 10 during this study period. One possible explanation is that these products are known and popular among users and easily accessible over the counter via drugstores or convenient stores.

"Ya Sa Hat Sa Ta Ra", a popular drug used to relieve muscle pain had the most AEs reported among all herbal formulas. "Ya Sa Hat Sa Ta Ra" is manufactured by AC and has 21 single herbs.[23-25] The four main ingredients of "Ya Sa Hat Sa Ta Ra" are *"Piper nigrum, Piper retrofractum, Plumbago indica,* and *Acorus calamus"*, all of which have a hot tasted." In the Thai NLEM, "Ya Sa Hat Sa Ta Ra" is prescribed in the form of capsules, powder, tablets or pills. Its properties list the ability to expel wind which obstructs your muscles and causes pain.[22] A result that was different in this study from the former (6) was an increase in the number of AEs linked to *"Andrographis paniculata"* and *"Derris scandens"*. This could be due to awareness amongst users of the latest information about, *"Cissus quadrangularis, Centella asiatica,* and *Zingiber cassumunar"* having less AEs compared to the former 5.

According to symptoms of TVP-products in Table 1, *"Andrographis paniculata"* had the most AEs associated to it, leading mostly to urticaria in certain, probable and possible level of causalities. According to MEDSAFE – a New Zealand Medicines and Medical Devices Safety Authority[26], TGA and the WHO, *"Andrographis paniculate"* was reported as the leading cause of allergic reactions, including urticaria. A study from Thailand looking at *"Andrographis paniculata"* mostly reported cases of urticarial.[15] As seen in reports from many other countries, *"Andrographis paniculata"* should be carefully used. Due to its strongly cold taste in Thai traditional medicine, the body may rapidly respond by generating heat and express it out via the blood and skin through conditions such as urticaria and rash. According to traditional Thai pharmaceutical knowledge, the tastes of herbal medicine is divided into nine groups or three main groups.[27] On the other hand, AE reports linked to use of "Ya Sa Hat Sa Ta Ra" ranked fifth on the chart, but it was the highest rank among herbal formulas. AEs linked to "Ya Sa Hat Sa Ta Ra" were the mostly linked to the gastro-intestinal system, such as abdominal pain, diarrhoea, and throat dry. Moreover, the hot taste of "Ya Sa Hat Sa Ta Ra" can also disturb the internal body system, especially the gastrointestinal system.[22] However, there were no symptoms at the certain level of data in the first period.

There needs to be an increase in the number of reports collected to support a higher causality.

According to the 17 AC-products listed in Fig 3, most AEs were the result of herbal formulas and prescriptions that require use of more than one herb. Most of the data, 13 out of 17 product names to be precise, equally reported one symptom each, so the data shows a spread of AEs linked to each TM/HP. Among the 17 product names, "Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion" was the only a single herb that had AE reports. The top four products on the chart have a blended-hot tasted which can generate most of the symptoms linked to use of TM/HPs. "Ayurved Siriraj Brand Ya Hom No.24 Tablets" had the most reported AEs. The four main ingredients of this product included *"Nigella sativa, Coriandrum sativum, Aquilaria crassna,* and *Jasminum sambac"*. However, causality assessment of AEs of single herbs will lead to better conclusion of the result of an adverse event than herbal formulas with multiple compounds.

According to data from AC in Table 2, most of the 17 products had a hot taste or blended-hot taste that led to AEs. "Ayurved Siriraj Brand Ya Hom No.24 Tablets" is frequently used because of its various medicinal properties in stimulating blood circulation, but it also leads to a high number of AEs. In one case it related to chest burning pain. Even though the AE wasn't assessed as the highest causality (certain level), the reliability of the event was strong enough to elicit careful use of this product as supported by data from ADRs in Thailand NLEM regarding a burning gastrointestinal system.[22] The main ingredient, known as Benjakool, is one of the five hot tasting herbs which consists of *Piper longum, Piper sarmentosum, Piper wallicii, Plumbago indica,* and *Zingiber officinale*. Each of them was involved in causing AE symptoms as reported in the table. Similar to Ayurved Siriraj Brand Chum Hed Ted Herbal Tea Infusion, Thailand NLEM recorded how "Ya Chum Hed Ted", prescribed as a stimulant laxative could lead to abdominal pain or abdominal discomfort due to its effect on the contraction of the large intestine. However, in this report, only one case was probably linked to dizziness caused by the nine tastes of traditional Thai medicines. "Chum Hed Ted" has a nauseating taste and among the three patients prescribed herbal formulas, the first patient reported an AE from "Herbal decoction relieving joint pain or inflammation (fruit instead stem of Khi Ka Daeng formula)" which caused abdominal discomfort because the fruit of "Khi Ka Daeng" (*Gymnopetalum integrifolim*) stimulates the bowel system. Meanwhile, the second patient experienced "Herbal decoction relieving menopausal symptoms: Harak formula" which led to an AE relating to her *Imperata cylindica* allergy, which was one of the ingredients of the formula. Lastly, the third patient experienced an AE from "Herbal decoction relieving menopausal symptoms: Benjakool formula" which is made up of 32 crude drugs, including five hot tasting herbs as in "Ya Sa Hat Sa Ta Ra" and "Ayurved Siriraj Brand Ya Hom No.24 Tablets". According to AE results from the herbal formula, Benjakool would be an interesting choice for further pharmacovigilance. In Table 2, almost all of the reports were assessed as possible causality, so that more cases of AE could be gathered to improve our understanding.

TVP-products in Fig 2 and AC products in Fig 3 show AE data from both single herbs and herbal formulas from former study that only presented from single herbs.[6] There was an increase in AEs linked to herbal formulas in this study which had single herbs in both the TVP and AC. Following HPVC policy, promoting careers in health instead of reporting on AEs caused by TMs/HPs led to the increase in reports of herbal formulas in the period this study was conducted. However, across Thailand, single herbs still had more representation in TVP as they were heavily and extensively promoted in the health system for a long period of time. As a result of herbal formulas with many herbs, it was difficult to figure out which herb directly caused symptoms.

In Table 1 and Table 2, products and their causalities relating to symptoms are listed. What is certain that the highest level of causalities which were mostly in TVP rather than at AC. The reason for this is the abundance of data and reports that helped make a strong assessment of those products and their symptoms. The more AE reports that were analyzed, the more statistics there were on hand to study products and symptom causalities. Previous AE reports of the same symptoms resulting from the same product can support the decision of causality results. However, a lowe number of certain results in AC products proved data collection is just in the starting stages and more AE reports are required to ensure causality. With a total of 305 AE reports for *"Andrographis paniculata"*, it far outnumbered the 40 AE reports of "Ya Sa Hat Sa Ta Ra". Meanwhile, collection of AE reports of "Ya Sa Hat Sa Ta Ra" use just started in the first period which means the results are probably to a certain level.

NJA is a convenient tool that helps assess causality between AEs and TMs/HPs in AC. In order to group causality, the tool helped answer and calculate the score of questions. This conventional and scientific method helped interpret AE information relating to herbs. However,

many of the AEs lacked some basic information to answer questions 1, 6, 7, and 10 which caused an incomplete assessment of those reports. The first question was about AE reported for all collection but there was little evidence of it being recorded. Meanwhile, question six was about AEs treated by a placebo to compare symptoms of TMs/HPs, however, this process was not done at AC. Question number seven was about AEs that found a toxic amount of the drug in blood or other fluids but AC did not process these results before the patients were informed. Last but not least, question number 10 was not marked because the event ended before confirmation of any objective evidence. Even though there was no marked point on these four questions, some reports could be calculated to a certain level. NJA is a professional and international assessment tool, however, a proper tool is required for specific assessment of TMs/HPs in the future.

For herbal formulas or combinations of TVP and AC, it was difficult to identify individual herbs that most likely caused an AE. However, expertise in prescribing traditional Thai medicine is required to consider which herbal ingredients cause AE. Using herbs in the early stages of traditional Thai Medicine did not result in systemic records as national evidence. So, details of AEs from herbs were confirmed by experts' experience along with collection of more reports of the same product. For precise assessment, AEs related to a culpable herb, and research about each herb is needed.

Even though pharmacovigilance studies of herbs have been conducted worldwide, this study was designed to look at collected data of AEs at the AC. According to AEs from TVP, there was enough variety for interpretation. Most AE reports showed a high use of herbs and promotion of health careers paying attention to reports. Meanwhile regarding data collection at AC mostly had essential data because of systemically planning ensured patients received a case record form.

Despite the existing TVP reporting systems, the numbers do not represent the incidence of AEs related to TMs/HPs. There are many limitations of our spontaneous reporting system.[28] Regulatory authority programs were unable to capture all occurrences linked to TMs/HPs. The healthcare professionals and consumers' decision on reporting depended on many factors such as their awareness, incentive, as well as the convenience of reporting system. Another limitation was the causality assessment, which depends on expertise of health professionals and other contributing factors (comorbidity, concomitant drugs, and timing). Thus, data from reporting systems can only serve as a screening tool for generating a hypothesis. In spite of these challenges, AE data from TVP and prospective surveillance can provide insight into occurrences of AEs involving TMs/HPs. A well-established program is needed to collect information and systemically categorize association between TMs/HPs and AEs.[29] This program will help ensure the safe use of TMs/HPs. The government should create a policy urging the health professionals to report and collect more AEs. This will ensure the safety of each drug and help to promote product exports from Thailand.

CONCLUSION

The findings show AEs and level of causalities associated with TMs/HPs products in Thailand. More details of each AE symptom and its link to individual single herbs or herbal formula had been seen at the AC. These would help increase the awareness of possible AEs when use some specific TMs/HPs.

It is difficult to identify which herb in a formula may link to occurred AEs. We still need to collect more reports and study each type of herb in vitro, in vivo and in a clinical study.[30-34] Moreover, individual pharmacological studies of each herb serve as strong supporting evidence. The gathering of information of each herb could help clarify the real causality between their AE symptoms. NJA might be a potential tool in assessing the causality between AEs and TMs/HPs. Other specific tool for assessing AEs/ADRs in a single herb, herbal formula, or even combinations of herbs should also be studied.

In order to establish risk-benefit profiles of TMs/HPs, a further study and systemic analyses of the existing information, and intense prospective surveillance is needed. Updated information of the top products associated with AEs, would help promote cautious consumption and reduce AE symptoms in the future.

ACKNOWLEDGEMENTS

We are grateful for the help provided by the Health Product Vigilance Center, Technical & Planning Division, Thai Food and Drug Administration, Ministry of Public Health for retrospective data collection through the national system known as the, Thai Vigibase Program. Regarding the valuable assessment process, we thank the specialist team of Ms.Wimon Suwankesawong, Dr.Sareeya Wechwitan and Dr.Pakawadee Sriphiromya for making the best decisions and providing useful comments regarding the application of Naranjo's alogorithm to score adverse events at Ayurved Clinic. We are also thankful for cooperation in research between the Center of Applied Thai Traditional Medicine and Department of Pharmacology, Faculty of Medicine Siriraj Hospital. We would also like to thank lecturer Suwat Tangjitjaroen,

a traditional Thai medicine expert, and senile teachers at CATTM who provide advice and shared experiences about symptoms caused by traditional medicine. We are also thankful to Miss Phutsadee Pudchakan and Mrs.Panadda Swasdimongkol from the Adverse drug reaction center, Siriraj Hospital for advising the use of NJA to assess causality of AEs in complementary and traditional medicine. We also thank our Adverse Drug Reaction team for creating a routine for the greater unit in CATTM; Ms.Patthanin Sathiansri, Ms.Kalayaporn Termnark, Mrs.Panida Smith, Ms.Natchaya Ziangchin, Mr.Niismael Doloh, Ms.Viewwadee Boonleang, Mr.Pasin Pantuwanich and Mr.Patpanat Hutapaet. Lastly, we thank the Routine to Research unit, Faculty of Medicine Siriraj Hospital for funding this project.

REFERENCES

1. Riewpaiboon A. Increasing herbal product consumption in Thailand. Pharmacoepidemiol Drug Saf. 2006;15(9):683-6.
2. Thailand Center of Excellence for life Sciences. Three-year strategy plan 2016-2019 แผนยุทธศาสตร์การดำเนินงานในระยะ 3 ปี (2559-2561). 2016 [10 April 2017]; Available from: draft_manuscript.docx 3 ปี (2559-2561).pdf.
3. World Health Organization (WHO) [Internet]. World alliance for patient safety: WHO draft guidelines for adverse event reporting and learning systems: from information to action. 2020 [cited 2020 Oct 4]. Available from: https://apps.who.int/iris/handle/10665/69797
4. Australian Government, Department of Health, Therapeutic Goods Administration (TGA) [Internet]. Reporting Adverse Events. 2019 [updated 2019 Oct 30; cited 2020 Oct 4]. Available from: https://www.tga.gov.au/reporting-adverse-events
5. Administrative Regulation on Reporting and Monitoring of Adverse Drug Reaction. Expedite reporting of adverse events: the agency CFDA (China FDA). Pharma Mirror [Internet]. 2014 [cited 2020 Oct 4]. Available from: https://www.pharmamirror.com/pharmaceutical-articles/expedite-reporting-adverse-events-agency-cfda-china-fda/
6. World Health Organization (WHO) [Internet]. Pharmacovigilance. 2019 [cited 2020 May 22]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
7. Australian Government, Department of Health, Therapeutic Goods Administration (TGA) [Internet]. About the TGA. [cited 2020 May 22]. Available from: https://www.tga.gov.au/about-tga
8. Australian Government, Department of Health, Therapeutic Goods Administration (TGA) [Internet]. Safety information. [cited 2020 May 22]. Available from: https://www.tga.gov.au/safety-information
9. Zhang L, Wong LY, He Y, Wong IC. Pharmacovigilance in China: current situation, success and challenges. Drug Saf. 2014;37(10):765-70.
10. Soares Neto JA, Galduroz JC, Marques LC, Kato ET, Macrini T, Rodrigues E. Possible adverse reactions to herbal products: a study with individuals who resort to popular medicine in the city of Diadema, SP, Brazil. Phytother Res. 2014;28(3):405-11.
11. Susskind M, Thurmann PA, Luke C, Jeschke E, Tabali M, Matthes H, et al. Adverse drug reactions in a complementary medicine hospital: a prospective, intensified surveillance study. Evid Based Complement Alternat Med. 2012;2012:320760.
12. Patel DN, Low WL, Tan LL, Tan MM, Zhang Q, Low MY, et al. Adverse events associated with the use of complementary medicine and health supplements: an analysis of reports in the Singapore Pharmacovigilance database from 1998 to 2009. Clin Toxicol (Phila). 2012;50(6):481-9.
13. Health Product Vigilance Center [Internet]. Introduction of Health Product Vigilance Center. 2015 Oct 1 [cited 2020 May 22]. Available from: http://thaihpvc.fda.moph.go.th/thaihvc/Public/Webpage/main.jsf
14. Sangsuwan C, Udompanthurak S, Vannasaeng S, Thamlikitkul V. Randomized controlled trial of *Tinospora crispa* for additional therapy in patients with type 2 diabetes mellitus. J Med Assoc Thai 2004;87(5);543-6.
15. Suwankesawong W, Saokaew S, Permsuwan U, Chaiyakunapruk N. Characterization of hypersensitivity reactions reported among *Andrographis paniculata* users in Thailand using Health Product Vigilance Center (HPVC) database. BMC Complement Altern Med. 2014;14:515.
16. Saokaew S, Suwankesawong W, Permsuwan U, Chaiyakunapruk N. Safety of herbal products in Thailand: an analysis of reports in the thai health product vigilance center database from 2000 to 2008. Drug Saf. 2011;34(4):339-50.
17. Wechwithan S, Suwankesawong W, Sornsrivichai V, McNeil B E, Jiraphongsa C, Chongsuvivatwong V. Signal detection for Thai traditional medicine: examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk. Regul Toxicol Pharmacol. 2014;70(1):407-12.
18. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
19. Zaki SA. Adverse drug reaction and causality assessment scales. Lung India. 2011;28(2):152-3.
20. IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
21. Lindquist M. Documentation grading of ICSRs and improved data quality management in Vigibase [abstract]. Drug Saf 2007;30(10):953.
22. National Drug Information, Food and Drug Administration of Thailand. National List of Essential Medicines. 2018 Jan 19 [cited 2021 Jan 8]. Available from: http://ndi.fda.moph.go.th/uploads/main_drug_file/20180529192247.pdf
23. Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University. Ayurved Siriraj Drug Guideline (Version 1). Bangkok; 2020.p.36.
24. The Botanical Organization, Ministry of Natural Resource and Environment Thailand. BGO Plant Databases, The Botanical Garden Organization. 2011 [cited 2021 Mar 1]. Available from: http://www.qsbg.org/database/botanic_book full option/search_page.asp
25. Forest Botany Division, Thailand. Thai Plant Names. 2021 [cited 2021 Mar 1]. Available from: http://www.dnp.go.th/botany/mplant/index.html
26. New Zealand Medicines and Medical Devices Safety Authority, Ministry of Health, New Zealand Government. *Andrographis paniculata* – Potential Risk for Allergic Reactions. 2017 Mar

24 [cited 2020 Oct 4]. Available from: https://www.medsafe.govt.nz/safety/EWS/2017/Andrographis Paniculata.asp

27. Ayurved Thamrong School, Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University. Drug compounding. Thai Traditional Medicine in the Faculty of Medicine Siriraj Hospital. First edition. Bangkok: Supavanich Press; 2009.p.11-2.
28. Meyboom RH, Lindquist M, Egberts AC, Edwards IR. Signal selection and follow-up in pharmacovigilance. Drug Saf. 2002; 25(6):459-65.
29. Gryzlak BM, Wallace RB, Zimmerman MB, Nisly NL. National surveillance of herbal dietary supplement exposures: the poison control center experience. Pharmacoepidemiol Drug Saf. 2007;16(9):947-57.
30. Bunnan K, Chaikomin R, Lohsiriwat S, Chomchai S, Chomchai S, Akarasereenont P. Effect of Ayuraved Siriraj Herbal Recipe "Wattana" on Gastric Emptying Rate. Siriraj Med J. 2020;64(3): 89-93. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/244165
31. Akarasereenont P, Thitilertdecha P, Palo T, Seubnooch P, Wattanarangsan J, Phadungrakwitya R, et al. Chromatographic Fingerprint Development for Quality Assessment of "Ayurved Siriraj Prasachandaeng", Antipyretic Drug. Siriraj Med J. 2020; 62(1):4-8. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/243638
32. Seubnooch P, Wattanarangsan J, Thamsermsang O, Booranasubkajorn S, Laohapand T, Akarasereenont P. Chemical Profiling of an Antipyretic Drug, Thai Herbal Harak Formula, by Liquid Chromatography Coupled with Quadrupole Time-of-Flight Mass Spectrometry. Siriraj Med J. 2018;70(2):159-68. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/127514
33. Wattanarangsan J, Akarasereenont P, Lumlerdkij N, Chotewuttakorn S, Wattanapornchai K, Laohapand T. Ultrasonication Extraction and Solid Phase Extraction Clean-up for Quantification of Aristolochic Acid I in the Thai Herbal Antitussive 3 Formula by High Performance Liquid Chromatography with Photodiode Array Detection. Siriraj Med J. 2018;70(3):227-32. Available from: https://he02.tci-thaijo.org/index.php/sirirajmedj/article/view/129727
34. Booranasubkajorn S, Kanlaya H, Huabprasert S, Lumlerdkij N, Akarasereenont P, Tripatara P. The Effect of Thai Herbal Ha-Rak Formula (HRF) on LPS-Induced Systemic Inflammation in Wistar Rats. Siriraj Med J. 2017;69(6):356-62. Available from: https://he02.tci thaijo.org/index.php/ sirirajmedj/article/view/ 106179

Sleep Quality and Associated Factors in Elderly Patients with Type-2 Diabetes Mellitus

Sitthichai Khamchet, M.D.*, Nida Buawangpong, M.D.*, Kanokporn Pinyopornpanish, M.D.*, Teerapat Nantsupawat, M.D.**, Chaisiri Angkurawaranon, M.D., Ph.D.*, Yanee Choksomngam, M.D.*, Nopakoon Nantsupawat, M.D.*

**Department of Family Medicine, **Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.*

ABSTRACT

Objective: The prevalence of poor sleep quality has been greatly escalating over the past years, along with the surging of type 2 Diabetes Mellitus (DM). The aging population is most concerned as sleep quality is notably impaired and influences the diabetic condition. This study aimed to observe the sleep quality and factors related to poor sleep quality in elderly patients with type-2 DM.

Materials and Methods: A cross-sectional study of patients with type 2 DM, aged 60 years and above was conducted. The questionnaires included demographic data, the Thai version of the Pittsburgh Sleep Quality Index (T-PSQI), the Thai version of the Diabetic-39, and the Thai Geriatric Depression Scale-15. Factors associated with sleep quality were analyzed using the logistic regression model.

Results: Among 385 participants with a mean age of 67 years old was 63.90% female. The prevalence of poor sleep quality was 9.88%. No association was found between sleep quality and glycemic levels. The related factors for poor sleep quality were sex (aOR = 2.57, p = 0.035, 95%CI = 1.06-5.93), body mass index (aOR =1.09, p = 0.028, 95% CI = 1.00-1.20), and diabetic complications. Diabetic retinopathy showed highest odd ratio (aOR = 6.28, p = 0.021, 95% CI = 1.32-29.94).

Conclusion: The prevalence of poor sleep quality was low in the current study. We found a strong association between diabetic complications and poor sleep quality. Evaluation of sleep quality may help to enhance overall health and care for diabetic geriatric patients.

Keywords: Sleep quality; poor sleep quality; diabetes mellitus type 2; elderly, geriatric (Siriraj Med J 2023; 75: 392-398)

INTRODUCTION

Sleep problem is a common public health concern around the world.[1,2] Sleep problem affects overall health, leads to lethargy, lack of enthusiasm, decreased immunity, increased stress, and reduced quality of life.[2] Sleep problem was classified into different groups by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and the core features of each group encompass sleep quality. Sleep quality relates to timing, amount of sleep, daytime distress, and self-reported satisfaction regarding the quality of sleep which has been divided into seven dimensions in consonance with The Pittsburgh Sleep Quality Index (PSQI).[3] These include subjective sleep quality, sleep latency (how long it takes the person to fall asleep), sleep duration (hours of actual sleep), habitual sleep efficiency (the percentage of time in bed that the person is asleep), sleep disturbance (any issues, feelings, and symptoms that disturb sleep), use of sleep medications, and daytime consequences (concentration, daily performance).[4] Poor sleep quality is one of the major psychosocial issues that impact all aspects of health and quality of life.[5]

Corresponding author: Nopakoon Nantsupawat
E-mail: nopakoon.n@cmu.ac.th
Received 10 January 2023 Revised 1 April 2023 Accepted 3 April 2023
ORCID ID:http://orcid.org/0000-0002-7548-8616
https://doi.org/10.33192/smj.v75i5.260818

The prevalence of poor sleep quality is considerably high in elderly patients[6], especially elder with chronic illnesses, such as hypertension, heart disease, and diabetes.[7,8] Diabetes is one of the major chronic conditions which has high morbidity and mortality in the elderly and all ages.[1,9] reveal that poor sleep quality increases insulin resistance, reduces the acute insulin response to glucose and is associated with glucose intolerance[10,11] results in higher blood sugar levels and increases diabetes complications.[11] Other explanations for poor sleep quality sequences establishing endothelial dysfunction, aggravating inflammatory markers, and activating of systemic inflammation.[12] It has been reported that more than half of patients with diabetes mellitus have poor sleep quality with the prevalence of poor sleep quality is greater in type 2 diabetes patients than in the general population.[13] Many elderly patients with type-2 diabetes confront challenges to their sleep, still, they do not bring sleep issues when they come to a health institution for a follow-up. Consequently, poor sleep quality is usually unrecognized in elderly with diabetes, also, studies on this issue are scarce. This study aimed to examine the sleep quality and factors related to poor sleep quality in elderly diagnosed with type-2 diabetes.

MATERIALS AND METHODS

Consent and Ethical Approval

The study was approved by the Human Research Ethics Committee of the Phrae Hospital (No: 21/2019). Informed consent was obtained from all participants.

Participants

This cross-sectional study recruited elderly patients who received outpatient clinic follow-up at the outpatient clinic of Phrae Tertiary care Hospital. Inclusion criteria included age of 60 years and older who were diagnosed with type 2 diabetes based on ADA criteria and Thai diabetes guidelines 2018. The exclusion criteria were unwillingness to enroll, severe hearing or vision impairment, dementia, or any other conditions affecting the ability to understand and complete the questionnaire regardless of assistance from the clinic nurse.

Sample Size Determination

The sample was calculated using the Thorndike formular (Thorndike, 1978), $N \geq 10K + 50$, where N is the sample size, and K is the total studied variables. Study variables were reviewed and finalized to 30 variables.[7,11,14,15] Also for 10% of the non-response rate of 350, the total sample size was 385. Purposeful sampling from outpatient clinic by nurse, 9-12.00 am during clinic operating time. 400 meet criteria exclude 15 due to missing data. Final sample was 385.

Data collection and questionnaires

Data were collected between November 2019 and April 2020. The questionnaire consisted of basic information, the Thai version of the Pittsburgh Sleep Quality Index (T-PSQI) (16), and the disturbing factors of the sleep questionnaire.[7,11,14,15] The Thai version of the Diabetic-39 (D-39) was used to collect quality of life in diabetes patients (a reliability of 0.85).[17] D-39 composed of 6 dimensions: diabetes control, energy and mobility, anxiety and worry, social burden, sexual functioning and overall quality of life, higher number rated in each dimensions indicated larger effect from the disease to quality of life. And the Thai Geriatric Depression Scale-15 (TGDS-15, a sensitivity of 0.92 and a specificity of 0.87) was used to determine depression.[18]

Data analysis

Statistical data were analyzed using STATA for Windows version 15. The prevalence of poor sleep quality was analyzed as frequency and percentage. The disturbing factors of sleep were analyzed using the Chi-square test and factors associated with poor sleep quality were analyzed by Logistic regression. A P value of < 0.05 was considered statistically significant.

Operation Definition

1. The elderly was defined as people age 60 years and older. (WHO Criteria for Asian)

2. Good sleep quality was defined as T-PSQI scores 5 or less than 5.

3. Major depression suspected was defined as the TGDS-15 scores more than 4.

4. Diabetic complications were defined as follows:

- Diabetic neuropathy included having symptom of paresthesia, numbness, restless leg syndrome caused by diabetes and diagnosed by physicians.
- Diabetic retinopathy diagnosed by ophthalmologists via full ophthalmic examination.
- Diabetic nephropathy with impairment in creatinine clearance of eGFR less than 80.
- Chronic wound was described as a wound that fails to proceed through the normal phases of wound healing and with proper treatment over one month.[19]

RESULTS

Patient characteristics

Of the total 385 diabetic patients, 63.90 percent were female, and the mean age was 67.31 ± 5.76 years old. The

mean global score of T-PSQI were 2.8 in average, and 2.3 in the good sleep quality group versus 7.5 in the poor sleep quality group ($p < 0.001$). Marital, income, exercise, alcohol drinking and smoking status were similar in both groups. Body mass index (BMI) between the good and poor sleep quality groups were statistically significant differences (mean 23.68 ± 3.35 in good sleep vs 25.69 ± 4.88 in poor sleep group, $p = 0.004$).

Disease factors and quality of life in diabetic patients

The poor sleep quality group had 2.6 times higher for diabetic complications than the good sleep quality group, 36.84% vs 14.12%, $p = 0.001$. Two types of diabetic complications that yielded a significant difference between the two groups were diabetic neuropathy and retinopathy ($p < 0.001$). No difference was shown in the type of pharmacological treatment and the laboratory results. The energy mobility dimension in the quality of life for diabetic patients showed a significant difference ($p = 0.007$).

Environmental factors

All the environmental factors including noise, light, roommate, and animals or insects provided statistically significant differences between groups ($p = 0.012$, 0.006, 0.027, and 0.046, respectively).

Prevalence of poor sleep quality among elderly with diabetes was 9.88%. More than 70% had very good subjective sleep quality and sleep efficiency (self-rated sleep efficacy for more than 85%). Half of the patients had sleep latency between 16-30 minutes. Eighty-six percent had a sleep duration of more than 7 hours per night. The sleep disturbance score was in the low range (0-1). Sleep disturbances from question lists; have to get up to use the bathroom, cannot breathe comfortably, and having pain at nighttime, were mainly reported less than once a week. Most of the participants did not use sleep medicine. Daytime dysfunction score was calculated, this component was scored low (score = 0) in 77% of the participants. There were statistically differences of all components in PSQI between good and poor sleep quality groups ($p = 0.001$). PSQI score could also indicate sleep hygiene which lower score imply to less sleep difficulty. In our study, higher PQSI (marked sleep difficulty) were consistence with poor sleep quality. These results were demonstrated in Table 2.

On logistic regression (Table 3), we selected variables with p-value <0.05 and two universal variables (sex, age) from table 1 to analyze. The significant associated factors of poor sleep quality were sex (female) (AOR 2.57, 95% CI 1.06 - 5.93), body mass index (AOR 1.09, 95% CI 1.1-6.2), diabetic neuropathy (AOR 4.12, 95% CI 1.70 – 9.99), and diabetic retinopathy (AOR 6.28, 95% CI 1.32 - 29.94).

DISCUSSION

The current study focused on sleep quality in the context of elderly patients with diabetes by examining PSQI and factors related to poor sleep quality. The prevalence of poor sleep quality in this study was approximately 10% which is very low compared to other studies in the different races and topography that varied from 36.5% to 73.2%.[1,15,20] The rural residence was positively associated with good sleep quality.[21] The quality of sleep results from T-PSQI: overall sleep quality was very good. And thoroughly subcomponents of T-PSQI showed good sleep efficacy, short sleep latency, suitable sleep duration, and low sleep disturbances, which explained the good level of baseline sleep status in our population.

When comparing between the good and poor sleep quality groups, significant differences in mean BMI, diabetic complications, energy mobility dimension of quality of life, and environmental factors was noted. These factors received further logistic regression analysis.

Analyzing factors associated with poor sleep quality using the logistic regression adjusted by sex, body mass index, diabetic complications, noise, light, roommate, animal or insects, and energy mobility (dimension of quality of life) showed four factors associated with poor sleep quality. 1) Females are more likely than males to report poor sleep, inconsonant with previous studies which identified between 50-70% of insomnia prevalence which possibly an effect from hormonal change after postmenopause.[5,22] 2) Higher BMI was associated with poor sleep quality. This finding rationalized that increasing BMI magnified the likelihood of obstructive sleep apnea syndrome (OSAS),[23] which causes intermittent sleep apnea and periodic wakefulness (poor sleep quality and efficacy). However, there was also bidirectional effects, short sleep duration and sleep fragmentation could result in low leptin, high appetite, and decrease in energy expenditure, caused weight gain, obesity and precipitated OSAS. Therefore, monitoring BMI and overweight status may help physicians for early detection or preventing development of OSAS which affect sleep quality. And also, encouraging healthy sleep hygiene may help reducing body weight and insulin resistance in elderly patients with diabetes. 3) The odds of having poor sleep quality are increased when presented with diabetic neuropathy. Common manifestation of diabetic neuropathy liked paresthesia, restless leg syndrome which were usually worsen during nighttime could

TABLE 1. Patient characteristics and associated factors in good and poor sleep quality groups.

Patient characteristics	Total N (%) (N=385)	Good quality N (%) (N=347)	Poor quality N (%) (N=38)	P-value
Sex - Female	246 (63.90)	217 (62.54)	29 (76.32)	0.093
Age (years) (Mean ± SD)	67.31 ± 5.76	67.48 ± 5.80	65.71 ± 5.17	0.071
T-PSQI score (Mean ± SD)	2.79 ± 2.10	2.28 ± 1.36	7.50 ± 1.84	<0.001
Marital status - Married	312 (81.04)	285 (82.13)	27 (71.05)	0.098
Income per month				
< 10,000 baht	309 (80.26)	276 (79.54)	33 (86.84)	0.283
≥ 10,000 baht	76 (19.74)	71 (20.46)	5 (13.16)	
Exercise frequency				
1-5 times a week	229 (59.48)	203 (58.50)	26 (68.42)	0.497
Everyday	143 (37.14)	132 (38.04)	11 (28.95)	
Alcohol drinking	55 (14.28)	51 (14.70)	4 (10.53)	0.485
Smoking	6 (1.56)	5 (1.44)	1 (2.63)	0.574
Body mass index (kg/m^2)				0.010
< 18.5	11 (2.86)	9 (2.59)	2 (5.26)	
18.5 – 22.9	171 (44.42)	162 (46.69)	9 (23.68)	
23.0 – 24.9	91 (23.64)	83 (23.92)	8 (21.05)	
≥ 25.0	112 (29.09)	93 (26.80)	19 (50.00)	
Mean BMI ± SD	23.88 ± 3.57	23.68 ± 3.35	25.69 ± 4.88	0.004
Disease factors				
Years since diabetes diagnosis mean ± SD	7.76 ± 4.37	7.67 ± 4.22	8.57 ± 5.58	0.227
Comorbidities - yes	326 (84.67)	292 (84.15)	34 (89.47)	0.387
Major depression	137 (35.58)	121 (34.87)	16 (42.11)	0.376
Any diabetic complications	63 (16.36)	49 (14.12)	14 (36.84)	0.001
Type of diabetic complications				
Diabetic neuropathy	54 (14.03)	40 (11.53)	14 (36.84)	<0.001
Diabetic retinopathy	9 (2.34)	5 (1.44)	4 (10.53)	<0.001
Diabetic nephropathy	6 (1.56)	5 (1.44)	1 (2.63)	0.57
Chronic wound	6 (1.56)	5 (1.44)	1 (2.63)	0.57
DM Treatment				
Oral medications only	385 (98.96)	343 (98.85)	38 (100)	0.506*
Oral medications and insulin	4 (1.04)	4 (1.15)	0 (0)	
HbA1c (Mean ± SD)	7.25 ± 1.49	7.22 ± 1.50	7.49 ± 1.40	0.305
FBS (Mean ± SD)	135.93 ± 34.95	136.38 ± 35.83	131.78 ± 25.57	0.442
LDL (Mean ± SD)	97.57 ± 29.76	96.87 ± 29.88	103.92 ± 28.29	0.166
TG (Mean ± SD)	136.00 ± 82.58	136.54 ± 85.73	131.05 ± 44.96	0.697
Quality of life for diabetic patients				
Diabetes Control	16.41 ± 8.65	16.49 ± 8.63	15.69 ± 8.91	0.589
Anxiety and worry	15.85 ± 9.55	15.72 ± 9.29	17.01 ± 11.72	0.432
Social Burden	14.68 ± 7.98	14.78 ± 8.03	13.75 ± 7.57	0.453
Sexual Function	14.10 ± 8.66	14.21 ± 8.65	13.15 ± 8.83	0.478
Energy Mobility	16.60 ± 9.09	16.33 ± 8.69	19.07 ± 12.02	0.007
Environmental factors				
Noise	58 (15.06)	47 (13.54)	11 (28.95)	0.012
Light	62 (16.10)	50 (14.41)	12 (31.58)	0.006
Roommate	63 (16.25)	52 (14.99)	11 (28.95)	0.027
Animals or Insects	51 (13.25)	42 (12.10)	9 (23.68)	0.046

Abbreviations: HbA1c = Hemoglobin A1C, FBS = Fasting Blood Sugar, LDL = Low Density Lipoprotein, TG = Triglycerides
* Fisher's exact test

TABLE 2. Sleep quality among elderly with diabetes.

Sleep Quality	Total N (%) (N=385)	Good quality N (%) (N=347)	Poor quality N (%) (N=38)	P-value
n (% in row)	385 (100)	347 (90.12)	38 (9.88)	
T-PSQI mean ± SD	2.79 ± 2.11	2.28 ± 1.36	7.50 ± 1.84	<0.001
min , max	0 , 14	0 , 5	6 , 14	
Subjective sleep quality				<0.001
Very good	302 (78.44)	295 (85.01)	7 (18.42)	
Fairly good	64 (16.62)	46 (13.29)	18 (47.37)	
Fairly bad	18 (4.68)	6 (1.73)	12 (31.58)	
Very bad	1 (0.26)	0 (0)	1 (2.63)	
Sleep efficiency (%)				<0.001
≥ 85	288 (74.81)	274 (78.96)	14 (36.84)	
75-84	71 (18.44)	60 (17.29)	11 (28.95)	
65-74	19 (4.94)	11 (3.17)	8 (21.05)	
< 65	7 (1.82)	2 (0.58)	5 (13.16)	
Sleep latency (min)				0.001
≤ 15	122 (31.69)	114 (32.85)	8 (21.05)	
16-30	185 (48.05)	175 (50.43)	10 (26.32)	
31-60	74 (19.22)	58 (16.71)	16 (42.11)	
> 60	4 (1.04)	0 (0)	4 (10.53)	
Sleep duration (hr)				<0.001
> 7	331 (85.97)	314 (90.49)	17 (44.74)	
6-7	44 (11.43)	29 (8.36)	15 (39.47)	
5-6	9 (2.34)	4 (1.15)	5 (13.16)	
< 5	1 (0.26)	0 (0)	1 (2.63)	
Sleep disturbance score				<0.001
0	168 (43.64)	162 (46.69)	6 (15.79)	
1	178 (46.23)	156 (44.96)	22 (57.89)	
2	38 (9.87)	28 (8.07)	10 (26.32)	
3	1 (0.26)	1 (0.29)	0 (0)	
Have to get up to use the bathroom				0.001
Not during the past month	101 (26.23)	93 (26.80)	8 (21.50)	
Less than once a week	198 (51.43)	183 (52.74)	15 (39.47)	
Once or twice a week	80 (20.78)	68 (19.60)	12 (31.58)	
Three or more times a week	6 (1.56)	3 (0.86)	3 (7.89)	
Cannot breathe comfortably				0.001
Not during the past month	199 (51.69)	183 (52.74)	16 (42.11)	
Less than once a week	168 (43.64)	151 (43.52)	17 (44.74)	
Once or twice a week	16 (4.16)	12 (3.46)	4 (10.53)	
Three or more times a week	2 (0.52)	1 (0.29)	1 (2.63)	
Have pain				<0.001
Not during the past month	197 (51.17)	184 (53.03)	13 (34.21)	
Less than once a week	156 (40.52)	138 (39.77)	18 (47.37)	
Once or twice a week	30 (7.79)	24 (6.92)	6 (15.79)	
Three or more times a week	2 (0.52)	1 (0.29)	1 (2.63)	
Use of sleep medication				<0.001
Not during the past month	357 (92.73)	336 (96.83)	21 (55.26)	
Less than once a week	18 (4.68)	9 (2.59)	9 (23.68)	
Once or twice a week	6 (1.56)	2 (0.58)	4 (10.53)	
Three or more times a week	4 (1.04)	0 (0)	4 (10.53)	
Daytime dysfunction score				<0.001
0	296 (76.88)	287 (82.71)	9 (23.68)	
1	51 (13.25)	36 (10.37)	15 (39.47)	
2	29 (7.53)	17 (4.90)	12 (31.58)	
3	9 (2.34)	7 (2.02)	2 (5.26)	

TABLE 3. Logistic regression analysis of factors associated with poor sleep quality.

Variables	Crude OR	95% CI	P value	Adjusted OR	95% CI	P-value
Sex (female)	1.93	0.88 - 4.20	0.098	2.57	1.06 - 5.93	0.035
Age	0.93	0.87 - 1.00	0.072	0.93	0.86 - 1.00	0.050
Body mass index	1.13	1.05 - 1.23	0.002	1.09	1.00 - 1.20	0.028
Diabetic neuropathy	3.55	1.72 - 7.33	0.001	4.12	1.70 - 9.99	0.002
Diabetic retinopathy	8.04	2.06 - 31.39	0.001	6.28	1.32 - 29.94	0.021
Noise	2.90	1.49 - 5.61	0.002	1.00	0.24 - 4.58	0.947
Light	3.15	1.67 - 5.93	<0.001	3.15	0.82 - 11.24	0.080
Roommate	2.66	1.33 - 5.31	0.005	1.54	0.49 - 4.77	0.460
Animal or Insects	2.45	1.14 - 5.27	0.021	1.18	0.31 - 4.13	0.795
Energy Mobility	1.02	0.99 - 1.06	0.082	1.00	0.96 - 1.03	0.949

affect patients' sleep quality.[23] 4) The study indicated that elderly patients who have diabetic retinopathy were six times more likely to encounter poor sleep quality compare to those who did not have any complications. As previous studies[2,24,25] poor sleep quality was associated with diabetic retinopathy. Tan NYQ et al. (2018), showed that patients who developed a short duration of sleep can affect the development of all diabetic complication such as retinopathy.[23-25] Some studies found that other complications such as chronic wound related to poor sleep quality[26], however, two types of diabetic complications were associated with poor sleep quality significantly in this study. Additionally, high blood glucose level in the past could be represented to the diabetic complications despite good ranges of current laboratory results.[22] This simplified that the appearance of diabetic complication or previously poor disease controlled resulted in disturbing symptoms and poor sleep quality in the present study. Nevertheless, the other underlying diseases or confounding variables such as the use of anxiolytics, antidepressants, caffeinated drink, and other metabolic abnormalities could affect the association between sleep quality, DM, and the examined factors, which should be investigated in further research.

Limitations

The cross-sectional study design of the study is a limitation as recall bias may appear. As a consequence of the low prevalence of poor sleep quality, the result in the study may be unable to generalize to other population which have different prevalence or patients' characteristic. Moreover, the sleep quality and disturbance factors were subjectively assessed, and no clinically objective measurements were conducted, like overnight polysomnography, daytime multiple sleep latency tests, and CPAP titration studies which offered more accurate diagnosis of sleep problems and other co-morbidities such as OSAS.[27] The result in older population from this study may not be able to extrapolate to other age groups.

CONCLUSION

Poor sleep quality in this study was low compared with other settings. Our study showed a strong association between diabetic complications and poor sleep quality. As discussed in preceding sections, the etiology of poor sleep quality in elder patients with diabetes is usually multifactorial and multidirectional. Hence, a comprehensive history, cautious examination, complete laboratory investigations and efficacy follow-up blood glucose level[28] will be required for successful evaluation and subsequent management of poor sleep quality in this population. Other clinical measuring such as overnight polysomnography, multi-setting studies and longitudinal cohort design would be suggested for future research.

ACKNOWLEDGMENTS

The authors would like to thank the Research Unit of the Department of Family Medicine, Chiang Mai University, the Primary Care Unit Nurse Team of Phrae Hospital, and Ms. Pichayaporn Sunthornmuang for all assistance and support. We gratefully acknowledge all the participants who made this project possible.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution: All authors have made substantial contributions to conception, drafting. All authors approved the final version and agreed to be accountable for all aspects of the study.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Khorasani ZM, Ravan VR, Hejazi S. Evaluation of the Prevalence of Sleep Disorder Among Patients with Type 2 Diabetes Mellitus Referring to Ghaem Hospital from 2016 to 2017. Curr Diabetes Rev. 2021;17(2):214-21.
2. Ogunbode AM, Adebusoye LA, Olowookere OO, Owolabi M, Ogunniyi A. Factors Associated with Insomnia among Elderly Patients Attending a Geriatric Centre in Nigeria. Curr Gerontol Geriatr Res. 2014;2014:780535.
3. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.
4. 3rd CFR, O'Hara R. DSM-5 Sleep-Wake Disorders Classification: Overview for Use in Clinical Practice. Am J Psychiatry. 2013;170(10):1099-101.
5. Yoshida K, Otaka H, Murakami H, Nakayama H, Murabayashi M, Mizushiri S, et al. Association between insomnia and coping style in Japanese patients with type 2 diabetes mellitus. Neuropsychiatr Dis Treat. 2018;14:1803-9.
6. Tufan A, Ilhan B, Bahat G, Karan MA. An under-diagnosed geriatric syndrome: sleep disorders among older adults. Afr Health Sci. 2017;17(2):436-44.
7. Zhu B-Q, Li X-M, Wang D, Yu X-F. Sleep quality and its impact on glycaemic control in patients with type 2 diabetes mellitus. International Journal of Nursing Sciences. 2014;1(3):260-5.
8. Birhanu TE, Getachew B, Gerbi A, Dereje D. Prevalence of poor sleep quality and its associated factors among hypertensive patients on follow up at Jimma University Medical Center. J Hum Hypertens. 2021;35(10):94-100.
9. McClellan SP, Haque K, Garcia-Pena C. Diabetes multimorbidity combinations and disability in the Mexican Health and Aging Study, 2012-2015. Arch Gerontol Geriatr. 2021;93:104292.
10. Leproult R, Deliens G, Gilson M, Peigneux P. Beneficial impact of sleep extension on fasting insulin sensitivity in adults with habitual sleep restriction. Sleep. 2015;38(5):707-15.
11. Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. J Appl Physiol (1985). 2005;99(5):2008-19.
12. Krishnasamy S, Abell TL. Diabetic Gastroparesis: Principles and Current Trends in Management. Diabetes Ther. 2018;9(Suppl 1):1-42.
13. Luyster FS, Dunbar-Jacob J. Sleep quality and quality of life in adults with type 2 diabetes. Diabetes Educ. 2011;37(3):347-55.
14. Zuo X, Dong Z, Zhang P, Zhang P, Chang G, Xiang Q, et al. Effects of cognitive behavioral therapy on sleep disturbances and quality of life among adults with type 2 diabetes mellitus: A randomized controlled trial. Nutr Metab Cardiovasc Dis. 2020;30(11):1980-8.
15. Edmealem A, Degu SG, Haile D, Gedfew M, Bewket B, Andualem A. Sleep Quality and Associated Factors among Diabetes, Hypertension, and Heart Failure Patients at Debre Markos Referral Hospital, Northwest Ethiopia. Sleep Disord. 2020;2020:6125845.
16. Sitasuwan T, Bussaratid S, Ruttanaumpawan P, Chotinaiwattarakul W. Reliability and validity of the Thai version of the Pittsburgh Sleep Quality Index. J Med Assoc Thai. 2014;97 Suppl 3:S57-67.
17. Songraksa K, Lerkiatbundit S. Development of a disease specific quality of life instrument: Thai version of the Diabetic-39. Songkla Med J. 2009;27(1):35-49.
18. Wongpakaran N, Wongpakaran T, Reekum RV. The Use of GDS-15 in detecting MDD: a comparison between residents in a Thai long-term care home and geriatric outpatients. J Clin Med Res. 2013;5(2):101-11.
19. Sheehan P, Jones P, Giurini JM, Caselli A, Veves A. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Plast Reconstr Surg. 2006;117(7 Suppl):239S-44S.
20. Sridhar GR, Madhu K. Prevalence of sleep disturbances in diabetes mellitus. Diabetes Res Clin Pract. 1994;23(3):183-6.
21. Gu D, Sautter J, Pipkin R, Zeng Y. Sociodemographic and health correlates of sleep quality and duration among very old Chinese. Sleep. 2010;33(5):601-10.
22. Telford O, Diamantidis CJ, Bosworth HB, Patel UD, Davenport CA, Oakes MM, et al. The relationship between Pittsburgh Sleep Quality Index subscales and diabetes control. Chronic Illness. 2018;15(3):210-9.
23. Grandner MA, Sands-Lincoln MR, Pak VM, Garland SN. Sleep duration, cardiovascular disease, and proinflammatory biomarkers. Nat Sci Sleep. 2013;5:93-107.
24. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res. 2011;30(5):343-58.
25. Tan NYQ, Chew M, Tham Y-C, Nguyen QD, Yasuda M, Cheng C-Y, et al. Associations between sleep duration, sleep quality and diabetic retinopathy. PLoS One. 2018;13(5):e0196399.
26. Situm M, Kolić M, Spoljar S. Quality of Life and psychological aspects in Patients with Chronic leg ulcer. Acta Med Croatica. 2016;70(1):61-3.
27. Rungmanee S, Banhiran W, Keskool P, Assanasen P, Chotinaiwattarakul W, Nujchanart N. Characteristics and Clinical Presentations of Patients at the Siriraj Snoring Clinic. Siriraj Med J. 2020;72(3):202-8.
28. Wongwutthiwet P, Bosittipichet T, Leesri T. The Efficacy of Follow-up Phone Calls for Capillary Blood Glucose Lowering in Diabetic Patients in Primary Care Unit. Siriraj Med J. 2021;73(12):801-7.

Current Physical Therapy Management and Clinical Evaluation for Achilles Tendinopathy

Sangarun Dungkong, B.Sc. (Physical therapy)

Department Orthopedic Surgery, Faculty of Medicine Siriraj Hospital Mahidol University Bangkok 10700, Thailand.

ABSTRACT

Achilles tendinopathy (AT) is common in both the general population and athletes, especially in running and jumping sports. The incidence of AT is 43% in athletes, but as high as 83% in middle-distance runners. However, 30% of patients have a sedentary lifestyle. Currently, the physical therapy (PT) is an effective conservative treatment and more widely population. Objective this review article is update the most effective physiotherapy treatment and the most validity and reliability clinical evaluation for AT. Destination is to provide physical therapist guideline for select appropriate clinical practice. The results of the literature review found that key treatment recommendation for AT is to follow an eccentric exercise protocol, which is the most common intervention for the management of functional limitations in AT. Extracorporeal shockwave therapy (ESWT) is the most commonly used next step when patients do not respond to eccentric exercise. Also, eccentric exercise combined with ESWT and eccentric exercise combined with ankle joint mobilization can improve immediately enhance their quality of life more than either treatment alone. Clinical evaluation can utilize many tools but the VISA-A questionnaire was developed as a validity and reliability assessment for AT. A limitation of the VISA-A questionnaire is that it was designed for athletes only, and so is inappropriate for the general population.[3,4,8,13,16] The FAOS questionnaire has been accepted as a valid and reliable tool for evaluating foot and ankle injuries.[1,14] Clinical evaluation is recommended to choose the appropriate assessment tool each patient (for the general population or athletes).

Keywords: Achilles tendinopathy; physical therapy; conservative treatment; eccentric exercise; clinical evaluation (Siriraj Med J 2023; 75: 399-406)

INTRODUCTION

Achilles tendinopathy (AT) is common in both the general population and athletes, especially in running and jumping sports.[1,2,4] The incidence of AT was reported to be 43% in athletes, and as high as 83% in middle-distance runners.[4] However, 30% of patients have a sedentary lifestyle. The etiology of AT may be related to intrinsic factors or extrinsic factors or a combination of both. Intrinsic factors comprise biomechanical abnormalities of a lower extremity, underlying disease, such as obesity or gout, and patient characteristics, such as age.[2,5,10] Extrinsic factors comprise training errors and immoderate mechanical overload.[2,5,10] AT is classified into insertion or midportion tendinopathy based on the location of the pain. Midportion tendinopathy is most commonly characterized by pain 2 to 7 cm proximal to the calcaneus attachment. Insertion tendinopathy is pain at the posterior calcaneus.[4,5,8,9] AT tends to involve a gradual onset of pain, swelling, morning stiffness, a range of motion limitation, and impaired function. Finally, AT can obstruct patients from performing sports and decrease their quality of life.[1,3,4] Treatment for AT can be divided into conservative and surgical treatments. Conservative treatment can involve various methods,

Corresponding author: Sangarun Dungkong
E-mail: sangarun.dun@gmail.com
Received 18 January 2023 Revised 31 March 2023 Accepted 31 March 2023
ORCID ID:http://orcid.org/0000-0002-5292-1720
https://doi.org/10.33192/smj.v75i5.260948

such as acupuncture[5], medicine[1], injection[3], orthosis[4], and physical therapy.[2] Surgical treatment is suggested if conservative treatment fails, or for tendons requiring debriding, augmentation, or reconstruction.[1,3,5,10] Currently, the physical therapy (PT) is an effective conservative treatment and more widely population.

PT can involve various treatments, such as exercise, mobilization treatments, and modalities (shock waves, ultrasound, laser, e.g.,).[5] and clinical evaluation can utilize many tools.

Focused clinical question

Currently, what is the most effective physiotherapy treatment (exercise, manual therapy or modality) for AT? What is the most validity and reliability clinical evaluation for AT?

Conservative treatments:

1. Exercise

There is strong evidence of the effectiveness of exercise rehabilitation as a primary treatment option of AT.[3,4] Indeed, there are several exercise protocols in AT, including the Silbernagel protocol, heavy–slow resistance protocol, Stanish protocol, and eccentric exercise protocol.[2,3] The eccentric exercise protocol is the most common intervention in the management of pain and functional limitations in AT,[6,7,9,10,12] and the rates of a successful outcome after treatment have been reported to range from 56% to 89% for midportion AT and 28%–32% for insertion AT.[9] The purpose of eccentric exercise is to decrease pain, improve the healing process, improve calf muscle strengthening, lengthen the myotendinous junction, and improve the tendon structure in AT.[4,8,10,12] In particular, patients can benefit from performing exercises with the knee extended or the knee slightly flexed[9,13] as both positions activate the calf muscle, while having the knee slightly flexed activates the soleus muscle.[13] Patients are usually instructed to perform eccentric exercises in 3 sets of 15 repetitions per session and 2 sessions per day in both positions.[1,2,9,11-13] In the first eccentric exercise, the patients stand with their weight on the affected side of the foot with a neutral ankle position with the knee extended as the starting position (Fig 1A) and then they move their heel up to the end range of ankle plantarflexion (Fig 1B), and then slowly lower their heel down to the end range of ankle dorsiflexion in a count of 5 (Fig 1C). The sound side of the foot assists the patient to return to the starting position.[1,11-13] In the second eccentric exercise, the patients stand with their weight on the affected side of the foot with a neutral ankle position with the knee slightly flexed as the starting position (Fig 2A) and then they move the heel up to the end range of ankle plantarflexion (Fig 2B), and then slowly lower the heel down to the end range of ankle dorsiflexion in a count of 5 (Fig 2C). The sound side of the foot assists the patient to return to the starting position.[1,11-13] In the event that the patients are unable to complete the protocol of 3 sets of 15 repetitions, the patients are instructed to begin with a lower number of sets or/and repetitions, such as 2 sets of 10 repetitions, and then to increase the number up to the full protocol when the patients are ready to complete the full exercise program.[9,11] In the first phase, the patient's bodyweight acts as the resistance for the exercise. When the patients are able to stand on the affected side with no pain or discomfort, they can progress by increasing the resistance

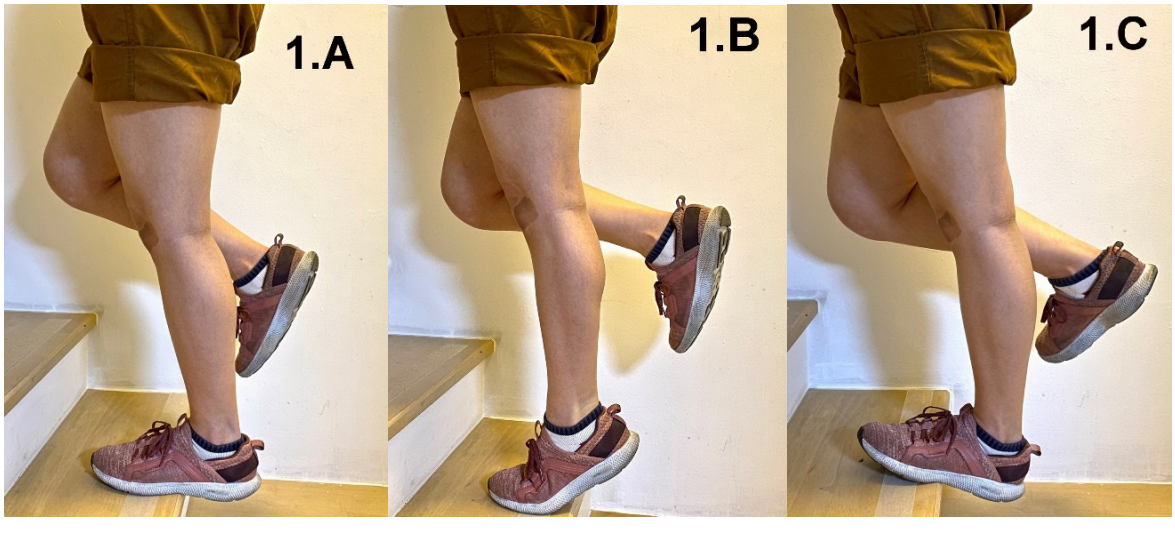


Fig 1. Eccentric exercise with the knee extended. In the starting position, the knee is extended with the ankle in a neutral position (1A). Controlled movement of the ankle into end range plantarflexion (1B). Controlled movement of the ankle into slow end range dorsiflexion (1C).

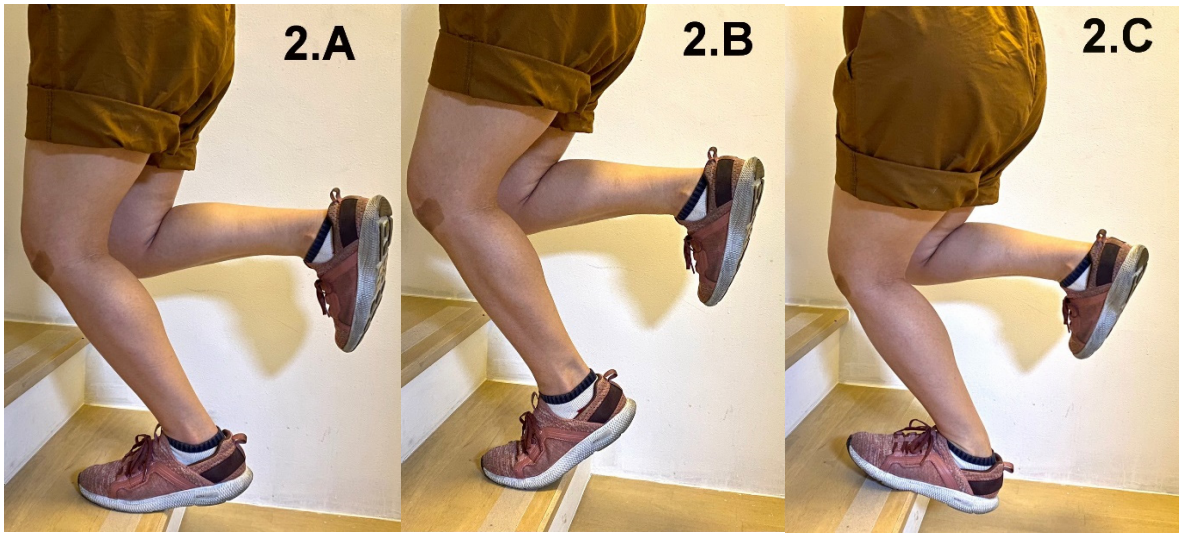


Fig 2. Eccentric exercise with the knee slightly flexed. In the starting position, the knee is slightly flexed with the ankle in a neutral position (2A). Controlling the ankle in end range plantarflexion (2B). Controlling the ankle in slow end range dorsiflexion (2C).

in the exercises.[1,12,13] Patients are able to increase the load by wearing a backpack weighing 5 kg. Later, they can increase the weight when the pain during and in finishing the exercises is minimal.[1,11,13] Patients may experience some muscle soreness for a couple of weeks after completing the exercises.[13] However, if patients have increased pain that makes them unable to complete the eccentric exercise program, they should discontinue the program and be referred to a doctor.[13]

2. Manual therapy

2.1 Mobilization therapy

Manual therapy has been shown to be a safe and effective intervention for the treatment of AT.[8] AT can involve limited ankle dorsiflexion mobility, hypomobility in the subtalar joint, and weakness of the ankle plantar flexor group muscle.[8,15] Ankle joint mobilization therapy appears to be a suitable treatment in AT because it can improve ankle mobility, decease pain, and improve plantar flexor group muscle endurance for the purpose of decreasing overloading of the Achilles tendon when walking or running.[8,15] Biomechanically, limited ankle dorsiflexion during walking or running has been related to subtalar joint overpronation, and overpronation of the subtalar joint has been reported to be associated with the development of AT. Improvement in ankle dorsiflexion has been reported to be associated with a normal gait pattern in weight-bearing lower extremities, and decreased compensatory subtalar joint pronation, causing a decrease in abnormal loading of the Achilles tendon.[15] Movements involving hip rotation during walking or running are related to the position of the ankle in terms of supination and pronation. Impaired movement in hip extension has been reported to be related to the development of AT. Examination, treatment, and evaluation are recommended for hip movement issues in AT. Hip mobilization for extension therapy can improve the normal foot position for more effective push-off during walking or running.[15] Joint mobilization therapy can provide a hypoalgesia effect to decrease pain and weakness. Evaluation is usually made based on a pain scale and the performance of the patient in doing heel raise repetitions.[15] Talocrural joint therapy is performed to address secondary limitations in ankle dorsiflexion. Talocrural joint mobilization therapy aims to improve talocrural joint mobility by promoting the plantar flexor mechanism and functional force generation through decreasing pain by anterior–posterior gliding of the talocrural joint (grade III–IV glides), for about 4 min or for more joint mobility[8,15] (Fig 3). Similarly, subtalar joint lateral gliding mobilization therapy aims to improve subtalar joint mobility by promoting the plantar flexor mechanism and functional force generation through decreasing pain by lateral gliding of the subtalar joint (grade III–IV glides), for about 4 min or for more joint mobility[8,15] (Fig 4). Self-mobilization exercises for subtalar joint lateral gliding mobilization can be an added component of a home program taking up 5 minutes once a day[15] (Fig 5). Hip joint extension mobilization therapy aims to improve hip mobility for promoting a normal pattern of walking and running by performing posterior–anterior gliding of the hip joint (grade III–IV glides), for about 4 min or for more joint mobility[8,15] (Fig 6).

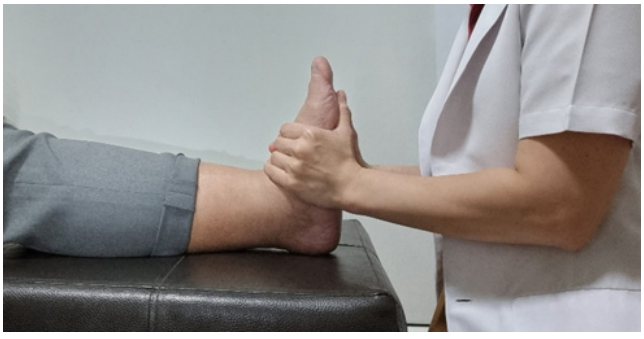


Fig 3. Talocrural joint long-axis thrust mobilization. With the patient in a supine lying position, the PT practitioner grasps the plantar aspect of the involved foot with his thumbs, while grasping the talus with the ring finger. Talocrural joint distraction is added, with concurrent ankle dorsiflexion. Ankle inversion or eversion is added, as required, to increase tissue resistance. A long-axis thrust is performed.[8]

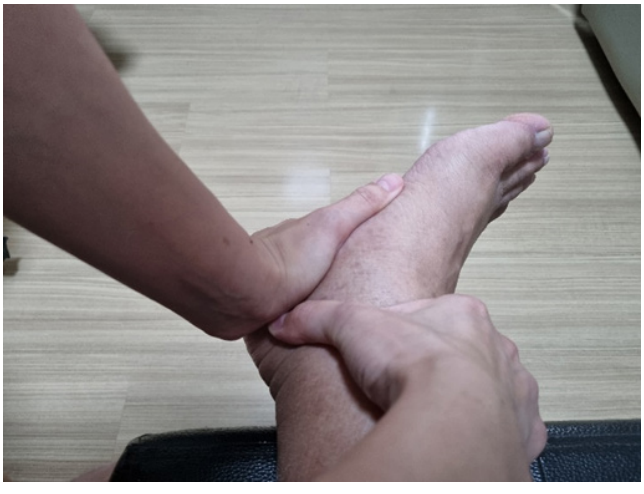


Fig 4. Subtalar joint lateral gliding mobilization. With the patient in a side lying position on their effected side, the PT practitioner stabilizes the distal tibia and fibula with one hand, while with the other hand, the PT practitioner grasps the calcaneus, distal to the talus, and provides a mobilization force vertical to the ground.[8,15]

Fig 5. Self-mobilization of the subtalar joint lateral gliding mobilization. With the patient crossing the effected leg side over the opposite thigh, the stabilization hand grasps the distal fibula and lateral aspect of the talus, while the mobilization hand grasps the calcaneus and directs a lateral force vertical to the ground.[15]

Fig 6. Hip joint extension mobilization. With the patient lying in a prone position, the PT practitioner mobilizes a posterior–anterior force directed to the hip joint, while concurrently taking the distal femur superiorly into extension.[15]

2.2 Deep friction massage

Deep friction massage is widely used to treat AT.[16,20] Deep friction massage is an effective treatment in AT as it can promote the healing process, activate the regeneration of damaged tissue, facilitate the normal alignment of soft tissue fiber, decrease muscle tightness, improve the range of motion in the ankle joint, improve function, relieve pain, reduce abnormal part injury adhesive fibrous tissue, and increase scar tissue movement in subacute and chronic injuries.[10,16,19] Some research has indicated that issues with the range of motion in the ankle joint could increase the risk of overuse symptoms in the musculotendinous junction of the calf muscle. For instance, calf muscle tightness is related to a decreased range of motion, but the range of motion in the ankle joint could be increased after the release of certain trigger points in the gastrocnemius and soleus muscle. Trigger points at the soleus muscle can cause pain that can indicate AT. Deep friction massage can release the gastrocnemius and soleus muscle through thumb pressure massage applied to the painful and tense calf muscle area until the pain has started to decrease or the muscle has started to relax, but not for more than 60 seconds per point. Pressure applied on the muscle should help control the patient's pain to be more tolerable. However, if the patient's pain means that they cannot fully tolerate the pressure, the PT practitioner should remove the applied pressure and apply this at another point and start to apply the minimal pressure there. The PT practitioner should use palpation by the thumb to search for a tender point, trigger point, and taut band on the medial and lateral side of the soleus muscle and gastrocnemius muscle. In most common cases, the patients should sense a

decrease in pain at the calf muscle and Achilles tendon immediately after the deep friction massage. If this is not the case, the treatment should be repeated with a little increased pressure, and if the patient still cannot sense that, it is recommended to consider another treatment. Despite this, it is suggested that deep friction massage to the calf muscle is a useful future treatment for AT, because trigger points may be related to pain in AT.[16,22]

3. Novel Physical modality - Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) is conservative treatment in AT.[2,14] ESWT is most commonly used as a next step if patients have not responded to other conservative treatments, such as eccentric exercise, ultrasound, cold pack, laser, or injections.[6] ESWT comprises two types when applied in AT: focused-ESWT (F-ESWT) and radial-ESWT (R-ESWT).[5,14] F-ESWT is used in deep or small area tissue focus point.[5,14] R-ESWT is used in superficial or large area tissues.[5,14] Currently, there is no evidence-based consensus on whether F-ESWT or R-ESWT is better for AT.[2] The mechanism stimulation process of ESWT starts with Achilles tendon regeneration in AT by promoting the proinflammation process and catabolic process, which are associated with removing damaged matrix components.[10] ESWT can decrease pain, promote the healing process, improve the function, and increase the patient's quality of life and satisfaction with treatment.[4,14] The effective application of ESWT can comprise different doses and durations. R-ESWT uses a number of pulses per session, typically from 2,000 to 3,000, a frequency of 15 Hz, with energy increasing from 1.4 to 3.0 bar, for 3 to 5 sessions, but once a week.[5] F-ESWT uses 1500 pulses per session, a frequency of 2.3 Hz, with the energy increasing from 0.12 to 0.4 mJ/mm^2, for 3 to 5 sessions, but once a week.[5] There is recent evidence supporting combining ESWT and eccentric exercise for AT showing that combined treatments are more effective than lone treatments.[2,4-6,14] After treatment, some skin reddening and a little to intermediate discomfort may be found, but no bruising.[5]

4. Conventional physical modality

4.1 Cryotherapy

Cryotherapy is a general management approach for musculoskeletal injury. The physiological effects of AT on the Achilles tendon include a reduction in the metabolic rates of cells, reduction in the expanded capillary blood flow, decreased conduction velocity of the nerve, and reduced muscle spindle activity.[10,19] The compression in cryotherapy can be effective by increasing oxygen saturation in AT.[18] The physiological response to this treatment is conducive to decreasing cell hypoxia injury, relieving pain, and relieving muscle spasms.[10,18,19,21] Recently, evidence is less supporting its practice in AT.

4.2 Low level laser therapy

Low level laser therapy can stimulate tenocyte proliferation, increase the collagen bundle, increase the number of small blood vessels, and decrease the capillary flow neovascular. Finally, low level laser therapy can conserve the elasticity of the Achilles tendon. In the future, new quality research is expected to prove and support the further application of low-level laser therapy in AT.[10,17] Recently, low level laser therapy has drawn conflicting evidence for its support, but some research has reported low level laser therapy combined with exercise to have beneficial effects for the treatment of AT.[4]

4.3 Ultrasound

Ultrasound is a common modality of physical therapy. Ultrasound techniques can be divided into the pulse mode and continuous mode. The pulse mode can improve the healing process by non-thermal effects, while the continuous mode increases the blood circulation and causes muscle relaxation by thermal effects. Therapeutic ultrasound can decrease swelling, relieve pain, and increase the function in AT. However, the evidence base for the use of ultrasound for AT is insufficient to support its practical use in clinic.[10]

4.4. Superficial heat therapy

Superficial heat therapy has been traditionally used in chronic cases for AT management for decreasing pain and improving joint mobility. Thermotherapy can help relieve muscle spasms, improve local blood flow, and assist the inflammation process of infiltrates, swelling, and chemical exudation. Some evidence supports its use for vasodilation, to increase blood flow, and for the warming of superficial tissue and to improve cell metabolism.[19]

5. Prevention

AT prevention measures in impact sport participation include Achilles stretching and plantar flexors group muscle strengthening. Posterior kinetic chain strengthening exercises include erector spinae muscle strengthening exercise, gluteus group muscle strengthening exercise, hamstring group muscle strengthening exercise, gastrocnemius muscle strengthening exercise, and soleus muscle strengthening exercise, and have been found to

be beneficial for preventing AT. High-impact loading athletes should optimize their tibiotalar joint and subtalar joint mobility. Balance training has been suggested in athletes as a successful prevention tactic.[2] In sport participation, athletes should be careful not to overload joints at the early stage. Athletes and PT practitioners should be aware of the signs and symptoms of AT in the early stage. Monitoring the training load would be advantageous for detecting changes in training load as a way to decrease the risk factors of AT. Changes in the tendon structure, such as a tendon tear or tendinopathy, are risk factors for developing AT. The clinician could use ultrasound imaging for information to grade training and performance measures to assess whether an athlete can take part in heavy practice. The optimal prevention is to recognize the early symptoms and adjust the training loads as required, as the earlier the injury detection, the shorter the period for recovery.[4]

Clinical evaluation:

1. Visual analog scale (VAS)

The visual analog scale (VAS) is the most commonly used patient measure for pain (on a scale of 0–10, where 0 indicates no pain and 10 indicates the worst pain imaginable). The VAS has been used to indicate pain at rest, pain during palpation, and pain on movement. VAS has also been associated with estimating clinical improvement.[1,4,5,23]

2. Observation

Clinical evaluation can include observing the static and dynamic alignment of the foot and ankle. AT has been related to either percavus or perplanus combined hyperpronation.[2] Midportion AT can specifically present with a localized thickening (fusion pattern).[2]

3. Range of motion

The range of motion can be measured as non-weight bearing by a goniometer and weight bearing by the ankle lunge test. The ankle lung test entails the patient adopting a standing position with the knee joint straight and then performing slight flexion of the knee joint. The recommendation is to evaluate the ankle dorsiflexion range of motion, because a limited dorsiflexion range of motion may be characteristic of AT.[2,4,16] In assessing hip joint mobility for a case with a decreased hip extension, an assessor movement test involving a posterior–anterior glide showed hypomobility of the hip joint.[15] The movement was assessed at the talocrural joint and subtalar joint, because these may often be found to be restricted in the assessed movement.[15]

4. Palpation

Palpations may be found at tender points or a thickness at the Achilles tendon and a taut band at the gastrosoleus muscle.[15] Palpations may act as guidance for detecting myofascial pain of the gastrocnemius muscle and soleus muscle.[24] Sometimes, myofascial pain syndrome may be combined with AT or may be separate, so the palpation may be distinguished in the referred zone pain as myofascial pain syndrome or AT.

5. Muscle power

Calf muscle strength is affected by AT, because the reduction in plantar flexor muscle strength is an important risked factor for AT. A dynamometer can be used to measure the ankle plantar flexor muscle and dorsi flexor muscle strength, both for concentric and eccentric contraction.[4]

6. Functional evaluation

Functional evaluation can be performed using the heel rise test. The heel rise test assesses endurance for the calf muscle. The starting position requires the patient to stand with their knee straight. The PT practitioner allows the patient to place 2 fingertips per hand on the wall to maintain balance. The PT practitioner instructs the patient to raise each heel as high as they are able until they feel fatigued. A metronome is used with an approve consistent rhythm with the frequency of heel rise performed at 30 per min based on literature measures for using this endurance test. The amount of repetitions, maximum height of heel rise, and total number of patients able to perform the test are used to calculate and compare the degree of functional impairment between the normal side and abnormal side.[4,23,24]

7. Questionnaire

The Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire was developed as a validity and reliability assessment for AT. The VISA-A questionnaire is easy to use to self-report pain and functional disability. It comprises 8 questions related to pain, function, and sporting activities. The scores range between 0 to 100, with 100 indicating good physical activity. A higher VISA-A score indicates decreased pain and improved function. A limitation of the VISA-A questionnaire is that it was designed for athletes only, and so may be inappropriate for the general population.[3,4,8,13,16] The Foot and Ankle Outcome Score (FAOS) questionnaire has been accepted as valid and reliable for the evaluation of foot and ankle injuries. The FAOS questionnaire was responsive when assessed in AT. It defines five subscales of pain, activities

of daily living, sport and diversion functions, foot and ankle related quality of life, and other symptoms. Scores range from 0–100, with 100 illustrating no symptoms.[1,14]

CONCLUSION

Exercise is accepted to have the highest level of evidence, encouraging its use as a key management strategy for AT.[6] In case exercise is not successful in treatment, ESWT is considered as the next step treatment option.[6] Further, eccentric exercise combined with ESWT and eccentric exercise combined with ankle joint mobilization can improve immediately enhance patients quality of life more than either treatment alone for AT.[8,14] Prospective recommendation follow the treatment for AT with high laser pawer therapy and peripheral magnetic stimulation are new intervention and have not currently been studied. Clinical evaluation can utilize many tools but the VISA-A questionnaire was developed as a validity and reliability assessment for AT. A limitation of the VISA-A questionnaire is that it was designed for athletes only, and so is inappropriate for the general population.[3,4,8,13,16] The FAOS questionnaire has been accepted as a valid and reliable tool for evaluating foot and ankle injuries.[1,14] Clinical evaluation is recommended to choose the appropriate assessment tool each patient (for the general population or athletes).

ACKNOWLEDGMENTS

The authors thank the Siriraj Medical Journal and reviewer for provide review article make this more complete. Thank you, Miss Sangarun Dungkong for subject exercise pictures and Mr. Dittapong Thanompan for subject mobilization pictures.

REFERENCES

1. Al-Ani Z, Meknas D, Kartus TJ. Radiofrequency microtenotomy or physical therapy for Achilles tendinopathy: results of a randomized clinical trial. Orthop J Sports Med. 2021;9(12): doi: 10.1177/23259671211062555
2. Rickenbach KJ, Borgstrom H, Tenforde A, Borg-Stein J, McInnis KC. Achilles tendinopathy: evaluation, rehabilitation, and prevention. Curr Sports Med Rep. 2021; 20:327-34.
3. Griffin c, Daniels K, Hill C, Franklyn-Miller A, Morin JB. A criteria-based rehabilitation program for chronic mid-portion Achilles tendinopathy: study protocol for a randomised controlled trial. BMC Musculoskelet Disord. 2021;22:1-14.
4. Silbernagel KG, Hanlon S, Sprague A, Current clinical concepts: conservative management of Achilles tendinopathy. J Athl Train. 2020;55(5):438-47.
5. Stania M, Juras G, Chmielewska D, Polak A, Kucio C, Król P. Extracorporeal shock wave therapy for Achilles Tendinopathy. Biomed Res Int. 2019. doi: 10.1155/2019/3086910.
6. Dilger CP, Chimenti RL. Nonsurgical treatment options for insertional Achilles tendinopathy. Foot Ankle Clin. 2019;24(3): 505-13.
7. Murphy M, Travers M, Gibson W. Is heavy eccentric calf training superior to wait-and-see, sham rehabilitation, traditional physiotherapy and other exercise interventions for pain and function in mid-portion Achilles tendinopathy? Syst Rev. 2018;7:58. doi: 10.1186/s13643-018-0725-6.
8. Jayaseelan DJ, Kecman M, Alcorn D, Jayaseelan DJ. Manual therapy and eccentric exercise in the management of Achilles tendinopathy. J Man Manip Ther. 2017;25(2): 106-14.
9. McCormack JR, Underwood FB, Slaven EJ, TA Cappaert. Eccentric exercise versus eccentric exercise and soft tissue treatment (Astym) in the management of Insertional Achilles Tendinopathy: a randomized controlled trial. Phys Ther Res. 2016;8(3):230-7.
10. Li HY, Hua YH. Achilles Tendinopathy: current concepts about the basic science and clinical treatments. Biomed Res Int. 2016;2016:6492597. doi: 10.1155/2016/6492597.
11. Kedia M, Williams M, Jain L, Barron M, Bird N, Blackwell B, et al. The effects of conventional physical therapy and eccentric strengthening for insertional Achilles tendinopathy. Int J Sports Phys Ther. 2014;9(4):488-97.
12. Jayaseelan DJ, Mischke JJ, Strazzulla RL. Eccentric exercise for Achilles Tendinopathy: a narrative review and clinical decision-making considerations. J Funct Morphol Kinesiol. 2019;4(2):34.
13. Rabusin CL, Menz HB, McClelland JA, Evans AM, Landorf KB, Malliaras P, et al. Efficacy of heel lifts versus calf muscle eccentric exercise for mid-portion Achilles tendinopathy (the healthy trial): study protocol for a randomized trial. J Foot Ankle Res. 2019;12:20.
14. Burton I. Combined extracorporeal shockwave therapy and exercise for the treatment of tendinopathy: A narrative review. Sports Med Health Sci. 2021;4(1):8-17.
15. Jayaseelan DJ, Post AA, Mischke JJ, Sault JD. Joint mobilization in the management of persistent insertion Achilles tendinopathy: a case report. Int J Sports Phys Ther. 2017;12(1):133-43.
16. Stefansson SH, Brandsson S, Langberg H, Arnason A. Using Pressure Massage for Achilles Tendinopathy a Single-Blind, Randomized Controlled Trial Comparing a Novel Treatment Versus an Eccentric Exercise Protocol. Orthop J Sports Med. 2019; 7(3):2325967119834284. doi: 10.1177/2325967119834284.
17. Joensen J, Gjerdet NR, Hummelsund S, Iversen V, Alvaro BR, Martins L, et al. An experimental study of low-level laser therapy in rat Achilles tendon injury. Lasers Med Sci. 2012;27(1):103-11.
18. Morales CR, Martín-Llantino PJ, Calvo-Lobo C, Palomo-López P, López-López D, Fernández-Carnero J, et al. Ultrasonography effectiveness of the vibration vs cryotherapy added to an eccentric exercise protocol in patients with chronic mid-portion Achilles tendinopathy: A randomized clinical trial. Int Wound J. 2019;16(2):542-9.
19. Miners AL, Bougie TL. Chronic Achilles tendinopathy: a case study of treatment incorporating active and passive tissue warm-up, Graston Technique, ART, eccentric exercise, and cryotherapy. J Can Chiropr Assoc. 2011;55(4):269-79.
20. Imai K, Ikoma K, Chen Q, Zhao C, An KN, Gay RE. Biomechanical and histological effects of augmented soft tissue mobilization therapy on Achilles tendinopathy in a rabbit model. J Manipulative Physiol Ther. 2015;38(2):112-8.

21. Zhanga J, Pana T, Wanga JH-C. Cryotherapy suppresses tendon inflammation in an animal model. J Orthop Translat. 2014;2(2): 75-81.
22. Borda J, Selhorst M. The use of compression tack and flossing along with lacrosse ball massage to treat chronic Achilles tendinopathy in an adolescent athlete: a case report. J Man Manip Ther. 2017;25(1):57-61.
23. Tenforde AS, Vogel KEL, Tam J, Silbernagel KG. Research protocol to evaluate the effectiveness of shockwave therapy, photobiomodulation and physical therapy in the management of non-insertional Achilles tendinopathy in runners: a randomised control trial with elective cross-over design. BMJ Open Sport Exerc Med. 2022:27;8(3):e001397.
24. Koszalinski A, Flynn T, Hellman M, Cleland JA. Trigger point dry needling, manual therapy and exercise versus manual therapy and exercise for the management of Achilles tendinopathy: a feasibility study. J Man Manip Ther. 2020;28(4):212-21.