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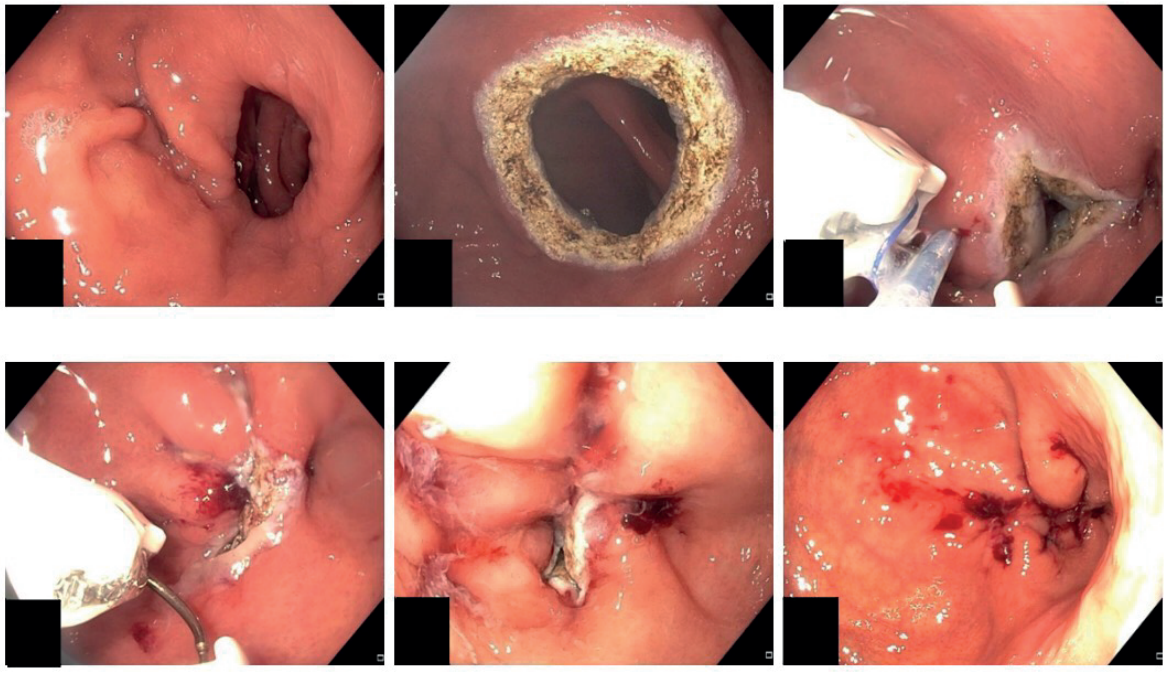

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Quality of Life of Stroke Patients at One Year after Discharge from Inpatient Rehabilitation: A Multicenter Study

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ABSTRACT

Objective: To investigate the quality of life (QoL) and factors significantly associated with QoL of stroke patients at 1 year after discharge from post-stroke inpatient rehabilitation.

Materials and Methods: This study included patients from 9 rehabilitation centers. QoL of stroke patients was evaluated using the World Health Organization Quality of Life Instrument - Brief Version. Patient QoL scores at the 1-year follow-up were compared with those recorded at discharge from inpatient rehabilitation. Factors related to QoL at one year after discharge were identified using univariate analysis and multiple linear regression.

Results: One hundred and ninety-seven patients were recruited with a mean age of 63.3±12.4 years. Of the 197 patients that were recruited, 21 (10.7%) were readmitted during the 1-year post-discharge period. Of those, there were 16 single readmissions, and 5 double readmissions. The mean QoL score at one year after discharge was significantly lower than the score at discharge. Multiple linear regression analysis revealed 5 factors as being independently associated with QoL, including having a leisure activity, modified Barthel (Activity of Daily Living, ADL) Index (mBI) at the 1-year follow-up, needing a caregiver, anxiety score, and depression score with regression coefficients of 6.42 (95% CI: 2.32, 10.51), 0.64 (95% CI: 0.07, 1.21), -7.88 (95% CI: -12.25, -3.52), -0.79 (95% CI: -1.41, -0.18), and -1.14 (95% CI: -1.71, -0.56), respectively.

Conclusion: At one year after discharge from inpatient rehabilitation, stroke patients had poorer QoL, and five factors were found to be associated with post-discharge QoL. Strategies to enhance post-discharge QoL are urgently needed.

Keywords: Quality of life; stroke patients; discharge; inpatient rehabilitation (Siriraj Med J 2021; 73: 216-223)

INTRODUCTION

Stroke is a major worldwide public health problem that often leads to chronic disability. Results from the Epidemiologic Stroke Study of Thailand that was conducted in 2011 revealed a crude prevalence of stroke among adults aged ≥65 years of 2.7%.[1] Stroke survivors suffer from functional dependency, and they have adversely affected abilities in daily life, including inability to perform self-care, transfer, and ambulation.[2] The long-term consequences of stroke have a negative impact on the quality of life (QoL) of both stroke patients and their caregivers.[3] A 2015 study from Korea reported that stroke was ranked

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as the 3rd highest cause of quality-adjusted life-year loss.[4] Moreover, poor QoL can cause depressive symptoms in patients with chronic stroke[5], and post-stroke depression has a negative impact on functional outcomes and the QoL of patients with stroke.[6] Godwin, *et al.* reported a higher level of depression to be associated with a lower mental QoL among stroke survivors.[7]

Some studies reported improved QoL after stroke at durations of follow-up that varied by study. For example, van Mierlo, *et al.* conducted a multicenter prospective longitudinal cohort study specific to the course of QoL from 2 months up to 2 years after stroke.[8] Their results revealed that QoL, participation, and life satisfaction improved during the first year after stroke, with most changes occurring during the first 6 months.[8] In contrast, Paredes, *et al.* studied the QoL of stroke patients at 12 months and found that all indices of QoL were lower over time compared to healthy controls.[9] Laurent, *et al.* reported the QoL of stroke survivors at the 2-year follow-up and found QoL to be significantly impaired compared to controls.[10] In 2017, Kusambiza-Kiingi and colleagues conducted a study in stroke survivors at community health centers, and they found poor QoL among their study population.[11]

The consequences after stroke attack were reported to be motor paralysis, dependency in self-care and ambulation, communication disorder, swallowing problem, and serious cognitive decline.[12-14] Factors reported to be significantly related to poor QoL included age, gender, body functional impairment, comorbidities, and depressive mood.[10,15-16] However but importantly, some of these factors can be prevented or minimized to improve QoL after stroke. Although most stroke patients achieve better functional outcomes after rehabilitation[17], some patients remain unsatisfied with the lowered QoL they experience due to residual disabilities after stroke. QoL is a subjective measurement of patient well-being that should be considered in the assessment of stroke survivors. A study of the QoL of stroke survivors during admission for inpatient rehabilitation showed significant improvement in patient QoL.[18-19] However, studies specific to QoL in Thai stroke patients after receiving inpatient rehabilitation are scarce. Accordingly, the aim of this study was to investigate the QoL and factors significantly associated with QoL of stroke patients at one year after discharge from post-stroke inpatient rehabilitation.

MATERIALS AND METHODS

This prospective multi-center study was a part of the Thai Stroke Rehabilitation Registry (TSRR), which was a 1-year follow-up project. This study was conducted during January 2008 to June 2009. The study protocol was approved by the institutional review boards of all 9 centers that participated in this study, and the study fully complied with the principles and standards set forth in the Declaration of Helsinki and all of its subsequent amendments. Siriraj Hospital was the center that initiated this multicenter trial, and approval to conduct this study was given by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 316/2006).

Our research assistant called stroke participants in the TSRR who had received inpatient stroke rehabilitation one year earlier and invited them to participate in this study. The same research assistant contacted and interviewed all eligible participants at each center.[20] Patients who were unwilling or unable to join this study were excluded, and the reasons for exclusion are presented in Fig 1. Written informed consent was obtained from all participants prior to their inclusion in the study.

Demographic and clinical data of participants at discharge and at the 1-year follow-up were recorded, including personal data, physical abilities, and psychological data. Collected data included age, gender, type of stroke (ischemic or hemorrhagic), and having complications, including musculoskeletal pain, contracture, spasticity (measured by modified Ashworth Scale; MAS ≥3), pressure ulcer, deep vein thrombosis (DVT), bowel-bladder incontinence, and/or infections. The proportion of patients who developed one or more complications during the year after discharge was recorded, and the rate of readmission during 1 year was assessed. Additional data that was collected included discharge location, employment status, source of income, having leisure activity, and needing a caregiver.

Physical abilities consisted of functional score, motor recovery stage, using wheelchair, walking ability, and urinary control. Patient functional score was evaluated by modified Barthel Index (mBI), which is a commonly used and widely accepted activities of daily living (ADL) assessment tool. The mBI is used to assess physical abilities, such as feeding, dressing, bathing, transferring, and ambulation (range score 0-20). A higher mBI score reflects greater independence.[21] Brunnstrom Motor Recovery Stage (BMRS) was used to assess motor recovery stage due to its simple and practical applicability. It is categorized into 6 stages, and a higher stage of BMRS represents better recovery.[22]

Psychological data consist of anxiety and depression information that was determined using the Hospital Anxiety and Depression Scale (HADS) screening tool.[23] The scores of each domain range from 0-21, and a score

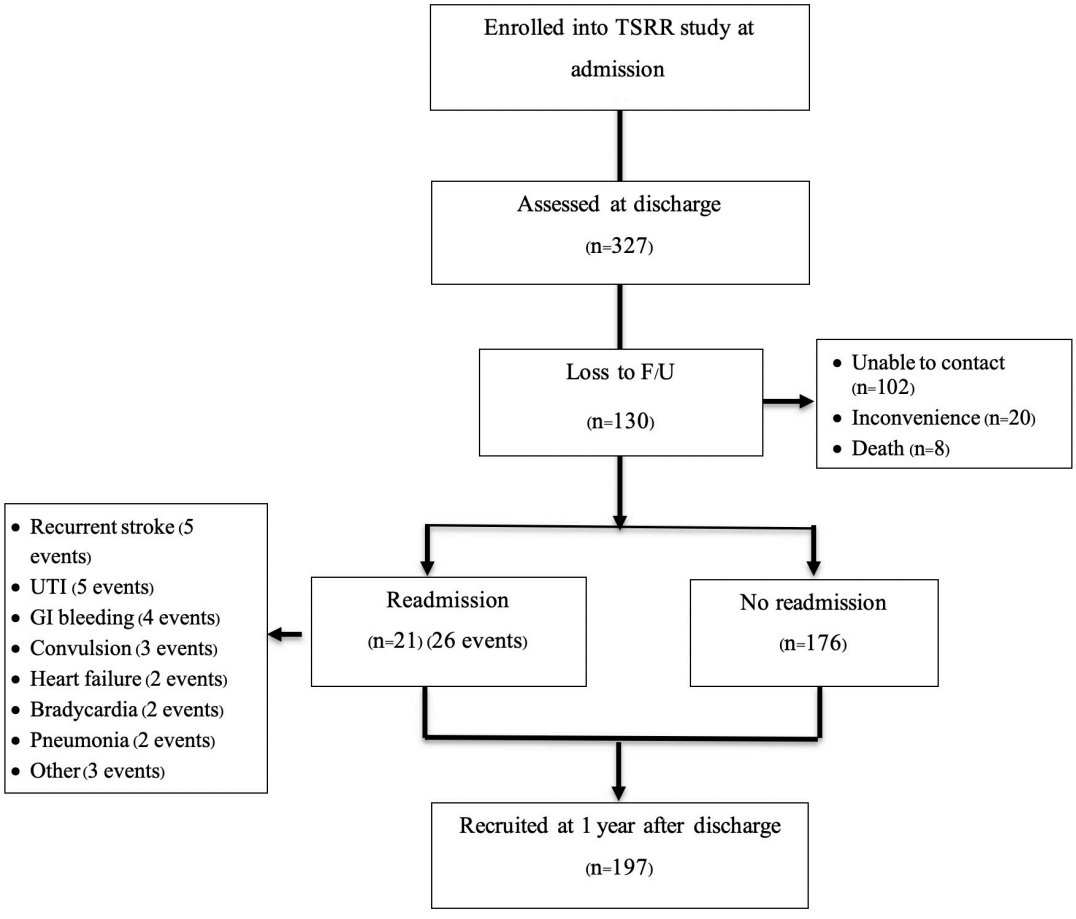

Fig 1. Flowchart of the study recruitment process

Abbreviations: TSRR, Thai Stroke Rehabilitation Registry; F/U, follow-up; UTI, urinary tract infection; GI, gastrointestinal

≥11 defines the presence of anxiety or depression. This scale was translated into Thai language and was reported to have good psychometric properties.[24]

Patient quality of life, the main outcome of this study, was assessed using the World Health Organization Quality of Life – Brief Version (WHOQOL-BREF) questionnaire.[25] It comprises 4 dimensions, including physical (7 items), psychological (6 items), environment (8 items), and social (3 items). The QoL score is continuous data that ranges from 26-130, with a higher score indicating better QoL. The total QoL score was analyzed. This questionnaire has good psychometric properties, and it was translated into Thai language and validated.[26] At one year after discharge, enrolled study participants were interviewed to obtain the previously described information, and to be assessed using the WHOQoL-BREF, mBI, and HADS tools.

Factors, including personal factors, physical abilities, and psychosocial factors, were compared between discharge and 1 year after discharge from inpatient stroke rehabilitation to assess their impact on patient QoL.

Statistical analysis

Continuous data, including age, functional score (mBI), anxiety, depression, and QoL score, are presented as mean plus/minus standard deviation (SD). Categorical variables are presented as number and percentage (%). Paired *t*-test or McNemar's was used to analyze demographic data at discharge and at the 1-year follow up. Concerning univariate analysis, unpaired *t*-test and Pearson's correlation coefficients (r) were used to analyze factors related to QoL. Factors that were statistically significant ($p<0.05$) in univariate analysis were included into multiple linear regression analysis. The results of that analysis are presented as regression coefficient (b), and were used to determine the effect of QoL score after adjusting for confounding factors. Data were analyzed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). A p-value < 0.05 was regarded as being statistically significant.

RESULTS

The number of patients at discharge in the TSRR project was 327. In this 1-year follow-up study, only 197

(60.25%) patients could be followed-up. Among the 197 patients recruited, 21 patients (10.7%) were readmitted. Of those, there were 16 cases of single readmission, and 5 cases of double readmission (26 events total). The reasons that patients could not be followed-up, and the causes of readmission are presented in Fig 1. The demographic and clinical characteristics of stroke patients compared between discharge and the one-year follow-up are given in Table 1. The mBI, BMRS, HADS-anxiety, and WHOQoL-BREF scores were all statistically significantly different between discharge and one year. The mBI and BMRS were both significantly improved, whereas the percentage of patients with anxiety increased and the QoL score decreased from discharge to one year. A comparison of age, gender, and type of stroke between those who could (n=197) and who could not (n=130) be followed-up is shown in Table 2.

Factors related to QoL at 1 year are shown in Table 3. Univariate analysis showed the following factors to be significantly associated with QoL: being employed, having a leisure activity, having no caregiver, having complications at follow-up, mBI at follow-up, BMRS of arm and leg, using a wheelchair, ability to walk, urinary incontinence, having anxiety, and having depression. All of those factors were then entered into multiple linear regression analysis. That analysis revealed 5 factors as being independently associated with QoL. Having a leisure activity and high mBI score at one year were associated with good QoL with regression coefficients (b) of 6.42 (95% CI: 2.32, 10.51) and 0.64 (95% CI: 0.07, 1.21). In contrast, needing a caregiver, having anxiety, and having depression were associated with poor QoL with regression coefficients (b) of -7.88 (95% CI: -12.25, -3.52), -0.79 (95% CI: -1.41, -0.18), and -1.14 (95% CI: -1.71, -0.56), respectively.

DISCUSSION

The results of this study revealed that the mean QoL score of stroke patients declined during the 1-year period after discharge from inpatient rehabilitation and this is consistent with the finding of Kusambiza-Kiingi and colleagues who conducted a similar study in the Johannesburg area of South Africa. They evaluated QoL among 108 stroke survivors at community health centers with physiotherapists on staff, and they found poor QoL among stroke patients, and positive correlation between community reintegration and QoL.[11] In contrast, Shyu, *et al*. performed a longitudinal study of stroke survivors in Taiwan and evaluated QoL at 1, 3, 6, and 12 months after discharge. They found that even though the QoL of stroke patients improved from 1 to 12 months after discharge, the QoL scores were considerably lower than in normal populations, especially relative to activities and participation.[27]

One of the main reasons why the QoL of stroke patients in our study declined over the 1-year post-discharge period may be that more than three-fourths (76.8%) of patients in the TSRR had developed at least one complication during that period, and nearly 60% of patients with complications at discharge still had the same complications one year later.[28] It is, therefore, clear that strategies need to be developed and implemented that will improve and maintain the QoL of stroke patients after discharge from inpatient rehabilitation. An example strategy may be to educate patients and their families/caregivers in how to prevent complications after discharge.

Concerning factors related to improving the QoL of stroke patients, the present study found high mBI score at the 1-year follow-up, low anxiety score, low depression score, having leisure activity, and no need for caregiver all to be independently associated with QoL. Heikinheimo and Chimbay reported age, gender, and functional recovery to be factors associated with QoL.[15] Mutai, *et al*. found younger age and better function related to better QoL, and depression related to poorer QoL.[16] Laurent, *et al*. found life satisfaction and QoL of stroke patients to be significantly impaired in all life domains.[10] Patient QoL was strongly correlated with functional independence, persistence of hemiplegia, and depressed mood.[10] Similar to the findings of our study, functional recovery was reported by many studies to be associated with QoL.[10,15-16] Even though higher mBI score was one of positive factors associated with QoL, its effect was not large (b=0.63). This might be due to the fact that the change in mBI score between discharge and 1 year was 2.4±3.9.[20] The mBI score at the 1-year follow-up was greater than the mBI at discharge (mean mBI at 1 year and at discharge were 16.04±4.30 and 13.66±4.34, respectively).

Two previous studies reported greater anxiety and depression scores to be the most important factors related to QoL.[29-30] Anxiety and depression may be a barrier to the rehabilitation process and patient outcomes, and may predict poorer post-rehabilitation QoL of stroke patients. Previous study reported that QoL can be improved over the long-term if physicians can detect and adequately treat anxiety and depression.[31] Concerning anxiety, Tang and colleagues measured anxiety using HADS to evaluate its effect on stroke patients, and they found anxiety to be significantly associated with QoL (r=-0.154).[31] Our study also found that anxiety could affect QoL in stroke patients, but not by much (b=-0.79). In contrast,

TABLE 1. Demographic and clinical characteristics of stroke patients at discharge and at one year after discharge (N=197).

Characteristics	At discharge	1-year after discharge	*p*-value[#]
Age (years), mean±SD	62.3±12.4	63.3±12.4	-
Gender: Male, n (%)	113 (57.4%)	113 (57.4%)	-
Type of stroke: Ischemic, n (%)	143 (72.6%)	143 (72.6%)	-
Complications (n=186), n (%)	134 (72.0%)	123 (66.1%)	0.222
mBI (n=180), mean±SD	13.7±4.3	16.0±4.3	***<0.001***
BMRS arm (n=177), n (%)			***<0.001***
Stage I-III	104 (58.8%)	81 (45.8%)	
Stage IV-VI	73 (41.2%)	96 (54.2%)	
BMRS leg (n=177), n (%)			***0.001***
Stage I-III	78 (44.1%)	57 (32.2%)	
Stage IV-VI	99 (55.9%)	120 (67.8%)	
Anxiety ≥11 (n=167), n (%)	8 (4.8%)	20 (12.0%)	***0.023***
Depression ≥11 (n=167), n (%)	25 (15.0%)	36 (21.6%)	0.135
WHOQoL-BREF score, mean±SD	85.2±11.5	81.1±14.5	***0.001***
LOS (days), mean±SD	25.8±15.2	-	-

A *p*-value<0.05 indicates statistical significance

[#]Paired *t*-test for continuous data, and McNemar's test for categorical data

Abbreviations: SD, standard deviation; mBI, modified Barthel Index; BMRS, Brunnstrom Motor Recovery Stage; WHOQoL-BREF, World Health Organization Quality of Life Instrument - Brief Version; LOS, length of stay

TABLE 2. Patient characteristics compared between those loss to follow-up and those included at one year after discharge.

Characteristics	Loss to FU (n=130)	One year after discharge (n=197)	*p* [#]
Age (years), (mean±SD)	63.2±11.7	63.3±12.4	0.975
Gender: Male, n (%)	80 (61.5%)	113 (57.4%)	0.491
Type of stroke: Ischemic, n (%)	91 (70.0%)	143 (72.6%)	0.619

A *p*-value<0.05 indicates statistical significance

[#] Unpaired *t*-test for continuous data, and chi-square test for categorical data

Abbreviations: FU, follow-up; SD, standard deviation

TABLE 3. Univariate and multivariate analysis to identify factors significantly associated with improvement in the quality of life of stroke patients at one year after discharge.

	Univariable analysis[#]		Multiple linear regression			
	Mean±SD of QoL	*p*	b	95% CI of b	SE (b)	*p*
Age (years)	r=0.116	0.115				
Gender		0.262				
Male (n=113)	80.1±15.7					
Female (n=84)	82.5±12.9					
Discharge location		0.071				
Nursing home	73.8±19.0					
Home	81.6±14.2					
Employment		***<0.001***				
No	79.5±14.4					
Yes	90.3±12.6		2.02	(-2.96, 7.00)	2.52	0.425
Source of income		0.054				
Themselves/spouse	83.6±15.6					
Others	79.4±13.6					
Having leisure activity		***0.004***				
No	74.3±15.0					
Yes	82.5±14.2		6.42	(2.32, 10.51)	2.07	***0.002***
Need caregiver		***<0.001***				
No	93.8±9.9					
Yes	77.9±13.8		-7.88	(-12.25, -3.52)	2.21	***0.001***
Complications		***<0.001***				
No	87.7±13.4					
Yes	78.4±13.9		-2.10	(-5.69, 1.50)	1.82	0.273
Readmission		0.169				
No (n=176)	81.6±14.5					
Yes (n=21)	76.7±15.1					
mBI	r=0.466	***<0.001***	0.64	(0.07, 1.21)	0.29	***0.027***
BMRS arm		***<0.001***				
Stage IV, V, VI	85.1±14.2					
Stage I, II, III	77.1±13.6		-1.34	(-5.61, 2.93)	2.16	0.535
BMRS leg		***<0.001***				
Stage IV, V, VI	84.4±13.9					
Stage I, II, III	75.3±13.8		-0.49	(-5.29, 4.30)	2.43	0.839
Using wheelchair		***0.001***				
No	77.4±14.2					
Yes	84.5±13.9		-1.64	(-5.54, 2.26)	1.98	0.407
Walking ability		***<0.001***				
Unable	71.7±14.2					
Able	83.3±13.8		1.74	(-3.65, 7.14)	2.73	0.524
Urinary incontinence		***<0.001***				
No	83.1±14.3					
Yes	72.2±11.6		-0.92	(-5.66, 3.83)	2.40	0.703
Anxiety	r=-0.575	***<0.001***	-0.79	(-1.41, -0.18)	0.31	***0.012***
Depression	r=-0.661	***<0.001***	-1.14	(-1.71, -0.56)	0.29	***<0.001***

A *p*-value<0.05 indicates statistical significance

[#] Unpaired *t*-test and Pearson's correlation coefficients (r)

Abbreviations: SD, standard deviation; QoL, quality of life; CI, confidence interval; b, regression coefficient; SE, standard error; mBI, modified Barthel Index; BMRS, Brunnstrom Motor Recovery Stage

Morris, *et al*. reported that anxiety appears to be more important than depression in predicting poor QoL at 6 months after stroke.[32]

Many studies reported the impact of depression on the QoL of stroke patients.[10,16,33-34] QoL in stroke patients with depression was more severely impaired than in non-depressed stroke patients.[33] Depression after stroke has a negative impact on outcomes, including self-care functions and QoL after stroke.[6,33-34] Since depression is a common consequence after stroke, medical personnel should maintain a high level of vigilance to early detect these conditions by using simple screening tools, such as HADS or Patient Health Questionnaire-9 (PHQ-9).

Leisure activities are important for stroke patients because they promote happiness and relaxation, and these effects help to promote healing for both the mind and the body. Our study found having a leisure activity to be a factor that positively influences patient QoL. Our research group found that creative art therapy consisting of art and music therapy enhanced inpatient rehabilitation among 118 inpatient stroke patients. More specifically, we found that creative art therapy twice a week for four weeks (8 sessions) combined with conventional physical therapy (20 sessions) could significantly decrease depression, improve physical functions, and increase QoL compared to physical therapy alone.[35]

Another factor independently related to QoL of stroke survivors was not having a need for a caregiver. This may indirectly imply that those participants had better functions, which meant that they did not need a caregiver. A study conducted in Mongolia reported being single to be a factor associated to low QoL.[36] The situation in Eastern countries is not like in Western countries. Being discharged to home to live with their family as opposed to a nursing home or other type of care facility, is common among Thai stroke patients.

This study had some limitations. First, the relatively small sample size may have limited our ability to identify all statistically significant relationships and differences. Second, all facilities from which the patients for this study were recruited were defined as tertiary care centers, so our study population may not be representative of general stroke patient population. Third, there are many tools available for assessing QoL, including the Stroke Impact Scale, the Stroke Specific Quality of Life scale, the Burden of Stroke Scale, and the WHOQOL-BREF questionnaire - all of which are specific health-related QoL instruments that were developed during the last decade[37]; therefore, direct comparison of QoL between our study and previously published studies could not be performed. Fourth and last, only 60% of subjects from the TSRR project could be followed-up for a full 12 months after discharge. This high loss to follow-up rate was influenced by factors that may include difficulty in contacting the patient, transportation-related problems, inconvenience to be or disinterest in being followed-up at the evaluating hospital, and failure to remember to attend. It should be noted that nearly 40% of our patients reside in a rural area, which would have made travel to the evaluating center more difficult and inconvenient. Future studies should include this limitation into the study design and consider physician visits to increase the follow-up rate, which will strengthen the integrity of the study findings.

CONCLUSION

The QoL of patients with stroke in the Thai Stroke Rehabilitation Registry declined at 1 year after discharge from inpatient rehabilitation. Factors strongly associated with better QoL were having leisure activities and having a high modified Barthel Index score at discharge. The factors strongly associated with decreased QoL were needing a caregiver, having anxiety, and having depression. Strategies to improve the post-inpatient rehabilitation QoL of stroke patients need to be urgently developed and implemented.

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Conflict of Interest Declaration:

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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REFERENCES

1. Hanchaiphiboolkul S, Poungvarin N, Nidhinandana S, Suwanwela NC, Puthkhao P, Towanabut S, et al. Prevalence of stroke and stroke risk factors in Thailand: Thai Epidemiologic Stroke (TES) Study. J Med Assoc Thai 2011;94:427-36.
2. Sturm JW, Dewey HM, Donnan GA, Macdonell RA, McNeil JJ, Thrift AG. Handicap after stroke: how does it relate to

disability, perception of recovery, and stroke subtype?: the north North East Melbourne Stroke Incidence Study (NEMESIS). Stroke 2002;33:762-8.
3. Opara JA, Jaracz K. Quality of life of post-stroke patients and their caregivers. J Med Life 2010;3:216-20.
4. Ock M, Han JW, Lee JY, Kim SH, Jo MW. Estimating quality-adjusted life-year loss due to noncommunicable diseases in Korean adults through to the year 2040. Value Health 2015;18:61-6.
5. Taylor-Piliae RE, Hepworth JT, Coull BM. Predictors of depressive symptoms among community-dwelling stroke survivors. J Cardiovasc Nurs 2013;28:460-7.
6. De Ryck A, Fransen E, Brouns R, Geurden M, Peij D, Mariën P, et al. Poststroke depression and its multifactorial nature: results from a prospective longitudinal study. J Neurol Sci 2014;347:159-66.
7. Godwin KM, Ostwald SK, Cron SG, Wasserman J. Long-term health-related quality of life of stroke survivors and their spousal caregivers. J Neurosci Nurs 2013;45:147-54.
8. van Mierlo ML, van Heugten CM, Post MW, Hajós TR, Kappelle LJ, Visser-Meily JM. Quality of life during the first two years post stroke: the Restore4Stroke Cohort Study. Cerebrovasc Dis 2016;41:19-26.
9. Paredes AM, Landa LO, Chagualá AC, Peralta HC, Torres GV, Perrin PB, et al. Health-related quality of life trajectories over the first year after stroke in Colombia, South America. Top Stroke Rehabil 2016;23:341-7.
10. Laurent K, De Sèze MP, Delleci C, Koleck M, Dehail P, Orgogozo JM, et al. Assessment of quality of life in stroke patients with hemiplegia. Ann Phys Rehabil Med 2011;54:376-90.
11. Kusambiza-Kiingi A, Maleka D, Ntsiea V. Stroke survivors' levels of community reintegration, quality of life, satisfaction with the physiotherapy services and the level of caregiver strain at community health centres within the Johannesburg area. Afr J Disabil 2017; doi:10.4102/ajod.v6i0.296.
12. Chaurasia RN, Sharma J, Pathak A, Mishra VN, Joshi D. Poststroke cognitive decline: A longitudinal study from a tertiary care center. J Neurosci Rural Pract 2019;10:459-64.
13. García Carretero R, Romero Brugera M, Rebollo-Aparicio N, Rodeles-Melero J. Dysphagia and aspiration as the only manifestations of a stroke. BMJ Case Rep 2016;2016: bcr2015213817. doi: 10.1136/bcr-2015-213817.
14. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol 2010;9:105-18.
15. Heikinheimo T, Chimbayo D. Quality of life after first-ever stroke: an interview-based study from Blantyre, Malawi. Malawi Med J 2015;27:50-4.
16. Mutai H, Furukawa T, Nakanishi K, Hanihara T. Longitudinal functional changes, depression, and health-related quality of life among stroke survivors living at home after inpatient rehabilitation. Psychogeriatrics 2016;16:185-90.
17. Kuptniratsaikul V, Kovindha A, Dajpratham P, Piravej K. Main outcomes of stroke rehabilitation: a multi-centre study in Thailand. J Rehabil Med 2009;41:54-8.
18. Manimmanakorn N, Vichiansiri R, Nuntharuksa C, Permsirivanich W, Kuptniratsaikul V. Quality of life after stroke rehabilitation among urban vs. rural patients in Thailand. J Med Assoc Thai 2008; 91:394-9.
19. Piravej K, Konjen N, Cowintaveewat V, Kuptniratsaikul V, Srisa-an Kuptniratsaikul P: Early interdisciplinary intensive rehabilitation significantly improves the quality of life of stroke survivors : A multi-center study. Asian Biomed 2014;8:1-9.
20. Kuptniratsaikul V, Kovindha A, Massakulpan P, Piravej K, Suethanapornkul S, Dajpratham P, et al. An epidemiologic study of the Thai Stroke Rehabilitation Registry (TSRR): a multi-center study. J Med Assoc Thai 2008;91:225-33.
21. Wade DT, Hewer RL. Functional abilities after stroke: measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry 1987;50:177-82.
22. Sawner K, LaVigne J. Brunnstrom's movement therapy in hemiplegia: a neurological approach, 2nd ed. Philadelphia: JB Lippincott Company; 1992.
23. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70.
24. Nilchaikovit T, Lotrakul M, Phisansuthideth U. Development of Thai version of Hospital Anxiety and Depression Scale in cancer patients. J Psychiatr Assoc Thai 1996;41:18-30.
25. Skevington SM, Lotfy M, O'Connell KA; WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 2004;13:299-310.
26. Mahatnirundrkul S, Tantipiwatanasakul W, Pumpaisalchai W, Wongsuwan K, Promanajirungkul R. Comparison of the WHOQOL-100 and the WHOQOL-BREF (26 items). J Ment Health Thai 1998;5:4-15.
27. Shyu YI, Maa SH, Chen ST, Chen MC. Quality of life among older stroke patients in Taiwan during the first year after discharge. J Clin Nurs 2009;18:2320-8.
28. Kuptniratsaikul V, Kovindha A, Suethanapornkul S, Manimmanakorn N, Archongka Y. Long-term morbidities in stroke survivors: a prospective multicenter study of Thai stroke rehabilitation registry. BMC Geriatr 2013;13:33. doi: 10.1186/1471-2318-13-33.
29. Howitt SC, Jones MP, Jusabani A, Gray WK, Aris E, Mugusi F, et al. A cross-sectional study of quality of life in incident stroke survivors in rural northern Tanzania. J Neurol 2011;258:1422-30.
30. Katona M, Schmidt R, Schupp W, Graessel E. Predictors of health-related quality of life in stroke patients after neurological inpatient rehabilitation: a prospective study. Health Qual Life Outcomes 2015;13:58-64.
31. Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS. Impact of anxiety on health-related quality of life after stroke: a cross-sectional study. Arch Phys Med Rehabil 2013;94:2535-41.
32. Morris JH, van Wijck F, Joice S, Donaghy M. Predicting health related quality of life 6 months after stroke: the role of anxiety and upper limb dysfunction. Disabil Rehabil 2013;35:291-9.
33. Žikić TR, Divjak I, Jovićević M, Semnic M, Slankamenac P, Žarkov M, et al. The effect of post stroke depression on functional outcome and quality of life. Acta Clin Croat 2014;53:294-301.
34. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the Bergen Stroke Study. Vasc Health Risk Manag 2012;8:407-13.
35. Kongkasuwan R, Voraakhom K, Pisolayabutra P, Maneechai P, Boonin J, Kuptniratsaikul V. Creative art therapy to enhance rehabilitation for stroke patients: A randomized controlled trial. Clin Rehabil 2016;30:1016-23.
36. Chuluunbaatar E, Chou YJ, Pu C. Quality of life of stroke survivors and their informal caregivers: A prospective study. Disabil Health J 2016;9:306-12.
37. Carod-Artal FJ. Determining quality of life in stroke survivors. Expert Rev Pharmacoecon Outcomes Res 2012;12:199-211.

The Study of Prevalence and Associated Factors of Dementia in the Elderly

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ABSTRACT

Objective: To study the prevalence and related factors of dementia in elderly.

Methods: A descriptive study of 295 elderlies was studied in Bangkruai subdistrict, Nonthaburi. According to the definition in Thailand, elderly is people who is older than 60 years old. Tools for this study were MMSE-Thai 2002 for screening dementia and calculating prevalence and general information questionnaires for related factor.

Results: The prevalence of dementia in elderly in Bangkruai subdistrict, Nonthaburi was 18 percent. The related factors of dementia in elderly were male sex, high age, low education, diabetes mellitus, no mobile phone, no computer skill, no internet skill, rarely social participation and rarely religion participation. However, factors that had no statistically significant were weight, height, BMI, marital status, occupation, hypertension, dyslipidemia, daily medicine, alcohol consumption, smoking, coffee, exercise, daily television use and family category.

Conclusion: The prevalence of dementia in elderly was 18 percent and the related factors that have statistically significant were male sex, high age, low education, diabetes mellitus, no mobile phone, no computer skill, no internet skill, rarely social participation and rarely religion participation. The study showed size of problem and made the good plans for elderly health such as technology assessment and motivation for social participation.

Keywords: Dementia; Prevalence; Related factor; Elderly (Siriraj Med J 2021; 73: 224-235)

INTRODUCTION

Currently, the number of senior populations aged 65 years and older is 703 million people which is 9 percent of overall global population.[1] By definition, this conveys that the world is going to enter an aging society. Similarly, there are also a considerable number of senior residents in Thailand, and the number is projected to increase consistently. From population statistics in 2018, the number of elderly residents in Thailand was 10 million, accounting for 16 percent. Hence, Thailand is in a state of entering an aging society, and it will become a complete aging society by 2021. It is expected for Thailand to see the greatest proportion of elderly people in the next 20 years.[2]

Dementia is one of the most common health issues among the elderly. Regarding to the prevalence of dementia in Thailand, there were 600,000 patients with dementia in 2015, and it is expected to surge to 1,117,000 people by 2030 and to 2,007,000 people by 2050.[3] Dementia can result in a loss of both memory and ability in making

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decisions and using language, and it also causes a change in personalities, behaviors and emotions. When dementia progresses and becomes severe, the patients are usually required 24-hour supervision and assistance.[4] As dementia significantly impairs person's memory and skills, this severely affects their abilities in performing daily-routine tasks. According to the report of Thai population's conditions of diseases and injuries (2013), as health problems can affect person's happiness, dementia is stated as one of major causes regarding diseases, which can deprive person's happiness. Dementia ranked the 13th among the male populations as it accounted for 1.7 percent of all diseases, which caused person's loss of happiness. For female counterparts, dementia ranked the 7th, and it made up for 4.6 percent of overall physical causes. In addition, dementia can also affect care providers in many aspects, including their personal time, stress, expenses and so on. These consequences can worsen both of care provider's and patient's quality of life.

According to Health Data Center under the Department of Public Health[5], the number of senior population in Bang Kruai Sub-District, Bang Kruai District, Nonthaburi Province was 6,794 people, and this accounted for 22.5 percent which was higher than the nation's proportion. This area, hence, can be categorized as a complete aging society. While working in a primary medical center, the researcher has been working with a considerable number of the elderly patients. It was found that many of them have a dementia, and some of them can perform their daily-routine tasks normally. Hence, the researcher is interested in identifying the number of patients with a dementia and the associated factors of the disease. The existing issue is that even though the prevalence of dementia is significantly high, the medical service to access the patients is quite passive. There is still a lack in an active study of a primary medical service's level. Due to the limits of commuting, some errors may occur with the use of the passive study. Hence, the researcher is interested in studying the prevalence of dementia in this area as well as associated factors of the disease in a more active manner.

Objective

To study the prevalence and related factors of dementia in elderly.

MATERIALS AND METHODS

Study design and population

This cross-sectional study explored 295 people aged 60 years and older, in Bang Kruai Sub-District, Bang Kruai District, Nonthaburi Province between January and March 2020. The Inclusion Criteria include participant's ability in communicating with Thai language in four skills (speaking, listening, reading and writing) as well as their voluntariness of consent to research. The Exclusion Criteria entail having an impairment regarding seeing or hearing, which can affect participant's ability in performing a test, and having nervous system or mental diseases.

Study size estimation

The previous studies[6-8] showed that average prevalence of dementia is 23.3 percent. Study size estimation by previous prevalence of dementia data was 265, calculated by by the following formula: Elderly Population (N) = 6,749, Error (d) = 0.05, Alpha (α) = 0.05, Z(0.975) = 1.959964 and Prevalence of Dementia Proportion (p) = 0.23. Also, 10% of the average samples are additionally collected to prepare for a case of participant's withdrawal, so the total number of samples in this study was 295.

The formular for calulating sample size of the study

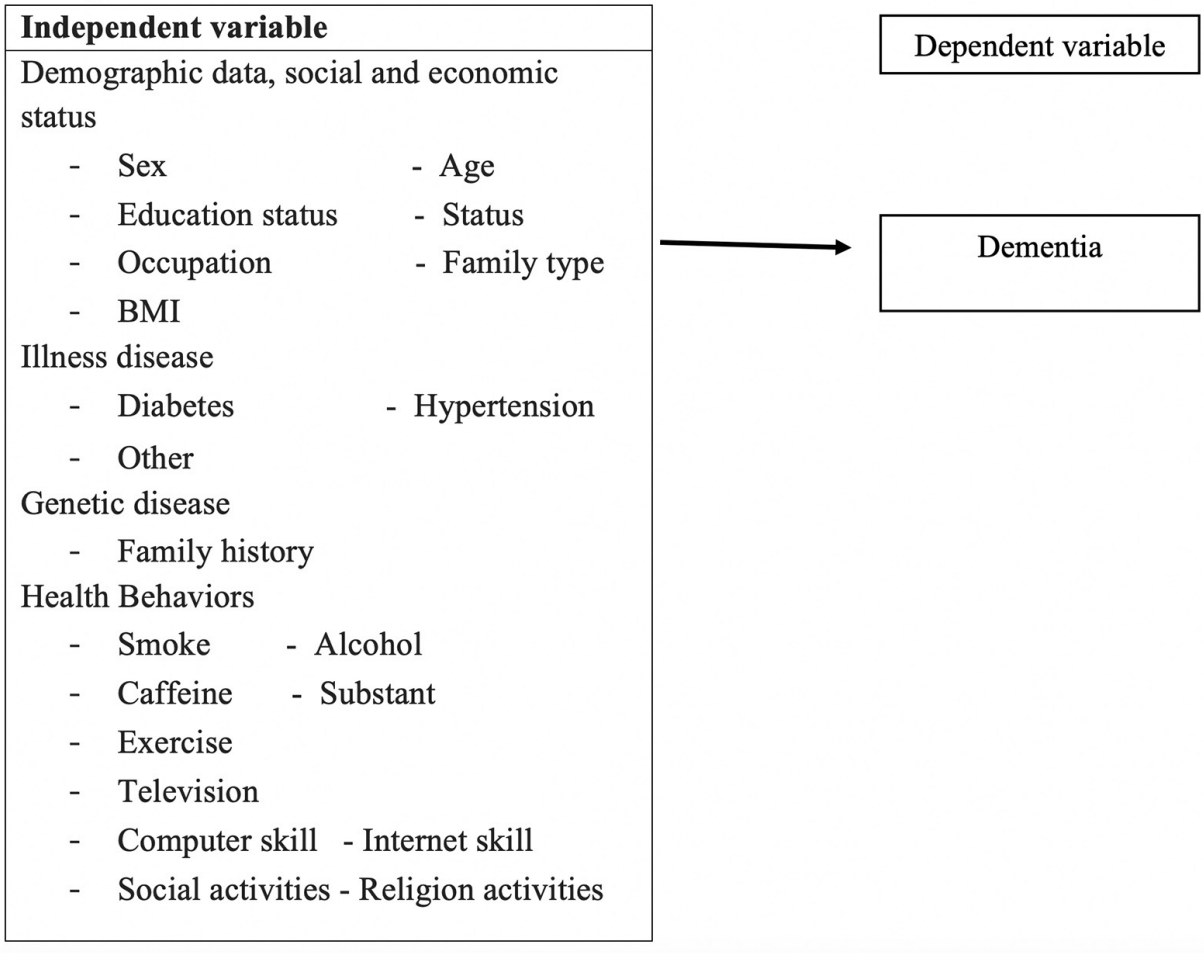
$$n = \frac{Np(1-p)z^2_{1-\frac{\alpha}{2}}}{d^2(N-1)+p(1-p)z^2_{1-\frac{\alpha}{2}}}$$

Measurement and tools

Tools for data collection include MMSE-Thai Questionnaire 2002 and a record of general personal data, covering participant's gender, occupation, marital status, education level, Body Mass Index (BMI), chronic disease and regular medication. A record of general personal data also include a study of participant's habits, such as drinking, smoking, coffee-intake, drug abusing, exercising, TV watching, computer using and internet surfing, as well as their participation in family, social and religious activities. The history of dementia in participant's family is also required for the record.

The diagnosis of dementia was defined by MMSE Score less than 14 in no education group, less than 17 in primary school group and less than 22 in higher primary school group.

Conceptual Framework



Data analysis

Data is analyzed by the statistical software, and the general data are presented in a form of a frequency table and percentage. The analysis of connections between associated factors of dementia is examined by Chi-square test and Fisher's exact test. The study of connections between associated factors of dementia is analyzed by multiple logistic regressions, and the free influences of each variable are examined by calculating crude and adjusted Odd Ratio.

Right to protection and research ethics

This study has a right to protection and research ethics as all participants' voluntariness of consent to research are given. In addition, all participants' personal data are recorded in a closed record. The data are, hence, kept confidential, and there will be no disclosure of the data to the third party. One year after the completion of research, all data will be disposed.

The benefits received by the participants are that the participants will immediately receive medical service if they are diagnosed with a dementia and that the participants will get their records from the study for the self-prevention of a dementia. The researcher has submitted a requirement for research approval from the committee of research ethics regarding to human study of Nonthaburi Public Health Office, and it has been approved by the document no. 1/2563, certified at January 14, 2020 before the conduct of the study.

RESULTS

It is found that the majority of samples are females as there are 233 people (79.0%) while there are 62 males (21.0%). The average age is 70.23±6.90 years old. The average weight is 60.85±12.33 kilograms. The average height is 157.23±7.55 centimeters. The average body mass index (BMI) is 24.53±4.31 kg/m^2. Regarding to marital status, 164 people of participants are married (55.6%). The numbers of widows, unmarried people and divorcees are 67 (22.7%), 45 (15.3%) and 19 (6.4%) people, respectively. Regarding to educational levels, 166 of them hold a primary school degree (56.3%). The number of holders of a high school degree, a bachelor's degree and a diploma degree are 61 (20.7%), 33 (11.2%) and 22 (7.5%)

people respectively. 8 people of participants (2.7%) are non-graduates while 5 of them (1.7%) hold a master degree. Regarding to occupations, 103 participants are unemployed (34.9%) while 94 participants are retirees (31.9%). The number of employed participants is 52 people (17.6%) whereas the figures for those who are in a trade business and who do other occupations are 32 (10.8%) and 14 (4.8%) people respectively. Regarding to chronic diseases, 218 participants (73.9%) report that they have high blood pressure while 111 participants (37.6%) have diabetes. 159 participants (53.9%) report that they have dialysis. About alcohol consumption, 220 participants (74.6%) state that they have never drunk alcohol. 55 participants (18.6%) said that they quit drinking alcohol while 20 participants (6.8%) still drink alcohol on a regular basis. Regarding to smoking habits, 264 participants (89.5%) state that they have never smoked. 31 participants (10.5%) said that they quit smoking while none of them still smoke on a regular basis. It is reported that none of them have been addicted to drugs. Regarding to exercising habits, 176 participants (59.7%) report that they do not exercise on a regular basis whereas the other 119 participants (40.3%) state that they do. 240 participants (81.4%) report that they watch a television regularly whereas the other 55 participants (18.6%) state that they do not watch a television on a regular basis. About mobile phones, 158 participants (53.6%) use smart phones whereas the other 90 participants (30.5%) use regular mobile phones. The other 47 participants (15.9%) do not use mobile phones. Regarding to computer skills, 253 participants (85.8%) are not able to use a computer while the other 42 participants (14.2%) know how to use a computer. About the Internet usage, it is found that 175 participants (59.3%) do not know how to use the Internet while the other 120 participants (40.7%) use the Internet on a regular basis. Regarding to social participations, 221 participants (74.9%) have regular social participations, while the other 74 participants (25.1%) admitted that they rarely participate in social activities. About a dementia history in participant's family, 277 participants (93.3%) reported that they do not have any relatives who have a dementia, while the other 18 participants (6.1%) do. Regarding to religious participations, 165 participants (55.9%) participate in religious activities frequently, whereas the other 130 participants (44.1%) do not. Regarding to family types, 164 participants (55.6%) live in nucleus families, while the other 98 participants (33.2%) live in extended families. The other 33 participants (11.2%) report that they live alone. The prevalence of dementia found is 53 participants (18.0%). (Table 1)

The represents participant's educational level and dementia prevalence. It is found that 50 percent of participants who are non-graduates have a dementia. It is found that 22 percent of primary-school degree and 10 percent of high school degree holders have a dementia. The majority of participants are a primary-school degree holder. From the results retrieved from MMSE Thai 2002, the sensitivity of the group (primary-school degree holders) is lower than the group of those holding a higher degree. (Table 2)

The demonstration of the comparative analysis of sample's personal data and having dementia. It is found that there are many personal features associated with having a dementia in the elderly, as those features show the statistical significance at 0.05. Firstly, males are more associated to have a dementia than females (OR 2.07 [95%CI 1.07, 4.01]), and those who are older are more associated to have a dementia than the younger ones (OR 1.08 [1.04, 1.13]). In addition, those who hold a primary-school degree or lower are more associated to have a dementia than those whose degrees are higher than a primary-school degree (OR 6.60 [95%CI 1.24, 35.23]), and the participants with diabetes are more associated to have a dementia than those who do not have a symptom of diabetes (OR 2.36 [95%CI 1.29, 4.31]). It is also found that those who use regular mobile phones are more associated to have a dementia than those who use smart phones (OR 5.69 [95%CI 2.59, 12.53]), and an inability in using computers is more associated to have a dementia than a keen ability in using computers (OR 10.61 [95%CI 1.43, 78.93]). Similarly, an inability in using the Internet is more associated to have a dementia than a keen ability in using the Internet (OR4.14 [95%CI 1.94, 8.86]), and infrequent social participations are more associated to have a dementia than frequent participations (OR 2.11 [95%CI 1.21, 3.97]). Last but not least, infrequent religious participations are more associated to have a dementia than frequent participations (OR 2.24 [(95%CI 1.22, 4.11]). Meanwhile, it is found that many personal features, including weight, height, body mass index (BMI), marital status, occupations, chronic diseases (high blood pressure and dialysis), regular medications, alcohol consumption, habits (smoking, exercising, watching TV) and family types, are not associated with having a dementia in the elderly due to the low statistical significance ($p>0.05$). Nevertheless, as none of the samples have family history related to a dementia, this cannot be applied to calculate in the statistics. (Table 3)

The multivariate analysis is applied to analyze personal features associated with dementia in the elderly who live in Bang Kruai Sub-District, Bang Kruai District,

TABLE 1. General Demographic Information (N=295).

	Number	Percentage
Sex		
Male	62	21.0
Female	233	79.0
Age (year old), mean±SD	70.23±6.90	
Body weight (kg.), mean±SD	60.85±12.33	
Height (cm.), mean±SD	157.23±7.55	
BMI (kg/m^2), mean±SD	24.53±4.31	
Marital Status		
Single	45	15.3
Married	164	55.6
Widow	67	22.7
Separated	19	6.4
Educational level		
No education	8	2.7
Primary school	166	56.3
Secondary school	61	20.7
Diploma	22	7.5
Bachelor degree	33	11.2
Master degree	5	1.7
Occupation		
Unemployed	103	34.9
Retried	94	31.9
Employment	52	17.6
Trade	32	10.8
Other	14	4.8
Comorbility		
Hypertension	218	73.9
Diabetes	111	37.6
DLP	159	53.9
Drug use	264	89.5
Alcohol consumption		
Regularly	20	6.8
Stopped	55	18.6
Never	220	74.6
Smoking		
Stopped	31	10.5
Never	264	89.5
Caffeine intake		
Regularly	176	59.7
Stopped	16	5.4
Never	103	34.9
Substant		
Never	295	100.0

TABLE 1. General Demographic Information (N=295). (continue)

	Number	Percentage
Exercise		
Regularly	119	40.3
Sometime	176	59.7
Television uses		
Regularly	240	81.4
Sometime	55	18.6
Mobile uses		
Never	47	15.9
Classic version	90	30.5
Smart phone	158	53.6
Computer skill		
Yes	42	14.2
No	253	85.8
Internet Skill		
Yes	120	40.7
No	175	59.3
Social Participation		
Regularly	221	74.9
Sometime	74	25.1
Family history of dementia		
Yes	18	6.1
No	277	93.9
Participating in religious activities		
Normally	165	55.9
Sometime	130	44.1
Family Type		
Nuclear Family	164	55.6
Extended Family	98	33.2
Alone	33	11.2
Dementia present		
Yes	53	18.0
None	242	82.0

TABLE 2. Dementia separated by Educational level.

Educational Level	MMSE Score	Dementia present (n=53)	Dementia absent (n=242)
None	< 14	4 (7.5)	4 (1.7)
Primary school	< 17	37 (69.8)	130 (53.7)
Higher primary school	< 22	12 (22.7)	108 (44.6)

TABLE 3. The analysis for comparing the general information with dementia.

	Dementia presented (n=53)	Dementia absented (n=242)	Odds ratio (95%CI)	p-value
Sex				
Male	17 (32.1)	45 (18.6)	2.07 (1.07, 4.01)	<0.05*
Female	36 (67.9)	197 (81.4)	ref.	
Age (Years)	73.45±6.42	69.52±6.82	1.08 (1.04, 1.13)	<0.001*
Body weight (kg)	61.83±14.00	60.63±11.95	1.01 (0.98, 1.03)	0.523
Height (cm.)	157.66±9.87	157.14±6.96	1.01 (0.97, 1.05)	0.715
BMI (kg/m^2)	14.87±3.42	24.15±3.39	1.02 (0.95, 1.09)	0.623
Marital Status				
Single	9 (17.0)	36 (14.9)	ref.	
Married	27 (50.9)	137 (56.6)	1.06 (0.41, 2.70)	0.908
Widow	14 (26.4)	53 (21.9)	0.79 (0.34, 1.83)	0.578
Separated	3 (5.7)	16 (6.6)	0.75 (0.18, 3.14)	0.694
Educational level				
No education	4 (7.5)	4 (1.7)	6.60 (1.24, 35.23)	<0.05*
Primary school	37 (69.8)	129 (53.3)	1.89 (0.69, 5.19)	0.215
Secondary school	6 (11.3)	55 (22.7)	0.72 (0.21, 2.55)	0.610
Diploma	1 (1.9)	21 (8.7)	0.31 (0.03, 2.88)	0.306
BSC or Over	5 (9.4)	33 (13.7)	ref.	
Occupation				
Unemployed	21 (39.6)	82 (33.9)	ref.	
Retried	16 (30.2)	78 (32.2)	0.80 (0.39, 1.65)	0.546
Employed	8 (15.1)	44 (18.2)	0.71 (0.29, 1.73)	0.452
Trade	4 (7.5)	28 (11.6)	0.56 (0.18, 1.77)	0.321
Other	4 (7.5)	10 (4.1)	1.56 (0.45, 5.48)	0.486
Comorbidity				
Hypertension	43 (81.1)	175 (72.3)	1.65 (0.78, 3.46)	0.189
Diabetes	29 (54.7)	82 (33.9)	2.36 (1.29, 4.31)	<0.05*
DLP	30 (56.6)	129 (53.3)	1.14 (0.63, 2.08)	0.663
Drug adherence	49 (92.5)	215 (88.80	1.54 (0.52, 4.59)	0.441
Alcohol consumption				
Regularly	4 (7.5)	16 (6.6)	1.32 (0.42, 4.19)	0.636
Stopped	14 (26.4)	41 (16.9)	1.81 (0.89, 3.66)	0.101
Never	35 (66.0)	185 (76.4)	ref.	
Smoking				
Stopped	6 (11.3)	25 (10.3)	1.11 (0.43, 2.85)	0.831
Never	47 (88.7)	217 (89.7)	ref.	
Caffeine intake				
Regularly	30 (56.6)	146 (60.3)	0.76 (0.41, 1.40)	0.373
Stopped	1 (1.9)	15 (6.2)	0.25 (0.03, 1.96)	0.185
Never	22 (41.5)	81 (33.5)	ref.	

TABLE 3. The analysis for comparing the general information with dementia. (continue)

	Dementia presented (n=53)	Dementia absented (n=242)	Odds ratio (95%CI)	p-value
Substant				
Never	53 (100.0)	242 (100.0)	-	-
Exercise				
Regularly	20 (37.7)	99 (40.9)	ref.	
Sometime	33 (62.3)	143 (59.1)	1.14 (0.62, 2.11)	0.670
Television uses				
Regularly	40 (75.5)	200 (82.6)	ref.	
Sometime	13 (24.5)	42 (17.4)	1.55 (0.76, 3.14)	0.227
Mobile uses				
Never	18 (34.0)	29 (12.0)	9.19 (3.85, 21.92)	<0.001*
Classic version	25 (47.2)	65 (26.9)	5.69 (2.59, 12.53)	<0.001*
Smart phone	10 (18.9)	148 (61.2)	ref.	
Computer skill				
Yes	1 (1.9)	41 (16.9)	ref.	
No	52 (98.1)	201 (83.1)	10.61 (1.43, 78.93)	<0.05*
Internet skill				
Yes	9 (17.0)	111 (45.9)	ref.	
No	44 (83.0)	131 (54.1)	4.14 (1.94, 8.86)	<0.001*
Social Participation				
Regularly	33 (62.3)	188 (77.7)	ref.	
Sometime	20 (37.7)	54 (22.3)	2.11 (1.21, 3.97)	<0.05*
Family history of dementia				
Yes	0 (0.0)	18 (7.4)	ref.	
No	53 (100.0)	224 (92.6)	NA	NA
Participating in religious activities				
Normally	21 (39.6)	144 (59.5)	ref.	
Sometime	32 (60.4)	98 (40.5)	2.24 (1.22, 4.11)	<0.05*
Family Type				
Nuclear Family	30 (56.6)	134 (55.4)	1.62 (0.53, 4.96)	0.396
Extended Family	19 (35.8)	79 (32.6)	1.74 (0.55, 5.56)	0.347
Alone	4 (7.5)	29 (12.0)	ref.	
MMSE score	14.87±3.42	24.15±3.39	0.51 (0.42, 0.62)	<0.001*

* Significant level at 0.05 <NA: cannot present in Odds ratio because some variable n=0>

Nonthaburi Province. The multiple regression analysis (a stepwise method) is applied to analyze variables with the statistical significance at 0.05, calculated by the univariate analysis. As presented in Table 3, the predictor variables are gender, age, educational level, having diabetes as a chronic disease, social participations, having relatives who have a dementia and religious participations. From the results of the analysis, there are seven steps of prototypes. In a section of the study results, only the analysis results of the 7th step, or the last step in the stepwise method, will be demonstrated. (Table 4)

The illustration of the multiple linear regression between predictor variables and dementia from an assessment in MMSE-Thai 2002 in the last step (the 7th step). It is found that personal features, including a primary-school degree, non-graduate, an ability in using computers and internet, age and having relatives who have a dementia, are associated factors predicting of a dementia in the elderly who live in Bang Kruai Sub-District, Bang Kruai District, Nonthaburi Province (the statistical significance: $p < 0.05$). According to MMSE-Thai 2002, it is found that the most associated factor is a primary-school degree, following by non-graduate, an ability in using computers and internet, age and having relatives who have a dementia respectively. The regression coefficient (β) are -0.345, -0.288, 0.170, 0.131, 0.128, -0.114 and 0.095 respectively. By based on MMSE-Thai 2002, the factors, including a primary-school degree and an age, show negative correlations with having a dementia, while the other factors, including abilities in using computers, internet and mobile phones, age as well as having relatives who have a dementia show positive correlations with having a dementia. These seven factors show the regression coefficient at 0.659, and the statistical significance at 0.05 ($p=0.035$). The success of MMSE-Thai 2002 in predicting a dementia in the elderly is at 43.5 percent, and the predicting error is ±3.75. Meanwhile, the factors, including gender, social and religious participations do not statistically affect having a dementia in the elderly who live in Bang Kruai Sub-District, Bang Kruai District, Nonthaburi Province. (Table 5)

TABLE 4. The testing of relation between predictor factors and Dementia was evaluated by MMSE-Thai 2002.

Model	Sum of squares	df	Mean Square	F	p-value
Regression	3098.640	7	442.663	31.517	<0.001*
Residual	4031.008	287	14.045		
Total	7129.647	294			

* Significant level at 0.05

TABLE 5. The Relation between Predictor factors and Dementia was evaluated by MMSE-Thai 2002.

Model	Unstandardized B	Coefficients SE	Standardized coefficients Beta	t	p-value
Educational level					
Primary level	-3.422	.490	-.345	-6.986	<0.001*
No education	-8.720	1.389	-.288	-6.277	<0.001*
Internet skill	1.314	.540	.131	2.434	0.016*
Computer skill	2.393	.720	.170	3.324	0.001*
Mobile Phone	1.725	.652	.128	2.647	0.009*
Age	-0.082	.035	-.114	-2.354	0.019*
Family history of dementia	1.942	.919	.095	2.114	0.035*

$R = 0.659$, $R^2 = 0.435$, Adj. $R^2 = 0.421$, SE est = 3.748, F change 4.467, p-value = 0.035

*Significant level at 0.05

DISCUSSION

Prevalence of dementia

The prevalence of dementia is 18 percent, this corresponds with the study of Artithaya Suwan and Suttisri Trakulsittichok[6] indicated that the prevalence of dementia in the elderly is 18.6 percent. The prevalence of these two studies is similar owing to the similarity of the research design, the use of the same tools and the use of a primary medical center as a study area. The difference between the two researches is that this study is more active in accessing the participants. However, since both communities in the studies are urbanized, the access to medical centers, especially primary ones, is quite convenient. The prevalence of dementia in this study is also similar to those in Japan[9] and Brazil[10], where the prevalence was 15.7% and 16.9%, respectively. A key factor that may differentiate the prevalence of dementia with this study is the difference in social factors of each country, such as the educational status or the elderly participation in social activities.

Nevertheless, several studies show the considerable different results of the prevalence. The study in Lampang province[8] found the prevalence of dementia equal to 28 percent and the study in rural northeastern region[11] found the prevalence of dementia was 25.6 percent. According to the data, it is found that population in these studies are from the rural areas which have low educational level, so this lead to the higher prevalence.

In conclusion, from the literature review, it is found that the prevalence rate of dementia varies significantly due to the differences in methodology, population feature, sampling size, population's age, study area, and criteria and tools chosen for the diagnosis of a dementia.

Associated factors

Gender: from the study, it is found that the number of male participants who have dementia is significantly higher than the females. This does not correspond with other studies. After reviewing the study, it is found that most participants are female, and the proportion of male participants is only 21 percent. Due to the small data of male participants, this may result in some errors. **Age:** the study indicates that the average age of participants with dementia is higher than that of those who do not suffer from dementia. This corresponds with all other studies and the disease theory, as this disease results from the age degeneration. Those who are older, then, are more likely to have dementia. **Educational Level:** the study indicates that non-graduates and primary-degree holders are more likely to have dementia than those who obtain high school-degree or higher. This corresponds with the previous studies.[6,8,11,12] The results do not contradict with any studies, so it can be concluded that the lower educational levels might be a cause of dementia in the elderly. **Having diabetes as a chronic disease:** the study indicates that those with diabetes are more likely to have dementia than those without. This corresponds with the study of Lalita Panakorn et al.[7] The correspondence might be explained by the fact that patients with unwell-controlled diabetes tend to have serious complications, and this can cause them a state of confusion, which can be related to dementia. **The usage of mobile phones, computer and the internet:** the study indicates that those who are skilled at using mobile phones, computer and the internet are less likely to have dementia than those who are unskilled. However, since the results are unprecedented, the conclusion cannot be reached owing to a lack of data. Still, it cannot explain that technology can prevent people from having dementia owing to the study limitations. **Social and religious participations:** the study indicates that people who regularly participate in social and religious actives are less likely to have dementia than those who do not. This corresponds with the previous studies.[7,8,12] The results do not contradict with any studies, so it can be concluded that the infrequent social and religious participations might be a cause of dementia in the elderly. **The other factors** in the study do not seem to have a significant association with dementia. However, the results do not correspond with other studies, as this study shows no associations between Body Mass Index (BMI) and dementia. From Artithaya Suwan[6], it is found that lower BMI can be associated with dementia. After the literature is reviewed, the average of BMI of samples in this study is higher than the study of Artithaya Suwan and Suttisri Trakulsittichok, so this might lead to dissimilar results. In addition, this study shows no associations between regular exercise habits and dementia. From Artithaya Suwan[6], it is found that the absence of exercise can be associated with dementia. After reviewing literature, it is found that the participants of this study can choose whether they "exercise regularly" or not whereas "never exercise" and "rarely exercise" are the options that the participants in the study of Artithaya Suwan and Suttisri Trakulsittichok can also choose. This, consequently, might lead to dissimilar results. Additionally, this study shows no associations between smoking habits and dementia, and this does not correspond with the study of Lalita Panakorn et al.[7] After reviewing literature, it is found that none of participants in this study are a current smoker, so there is only a comparative study between non-smokers and ex-smokers. This might result

in the differences of the results. Furthermore, this study shows no associations between the employment and dementia. From Lalita Panakorn et al[7], it is found that those who are currently unemployed can be associated with dementia. After reviewing literature, the samples of this study are living in the urbanized areas, so it might be convenient for them to have social gatherings and activities frequently. Meanwhile, the samples of Lalita Panakorn et al's study[7] are living in the rural areas, so it might be more challenging for them to have social gatherings owing to the difficulties in commuting. This also might lead to the differences of the results.

One of the advantages of this study is that there is a use of active study to examine the elderly in the community. This, consequently, leads to an easy access towards participants. Since the educational levels of the residents in this community greatly vary, the tools in this study are divided into different educational categories. Also, the researcher assessed and interviewed all participants by herself to reduce differences of scoring criteria. However, one of the limitations of this study is that the sensitivity and specificity of assessment tools are different according to the educational levels. As most of the participants hold a primary school-degree, the sensitivity and specificity significantly decrease. Moreover, as this is a cross-sectional study, it is unable to identify risk factors, but it can only determine the connections between dementia and the associated factors.

CONCLUSION

Dementia is one of the most common condition in elderly. Therefore, primary care doctors are recommended to be concerned and implement a dementia screening in primary care unit because the evidence of study shows that dementia's prevalence is as high as 18% or approximately 1 of 5 in the elderly population.

In particular, screening in the elderly with the following characteristics: male sex, high age, low education level, diabetes mellitus, no mobile phone, no computer skill, no internet skill, rarely social participation and rarely religion participation. Because there are supporting data that these factors are significantly associated with dementia.

Suggestions

Dementia is one of the crucial public's health problems, especially in the community of elderly people since the number of patients with this disease consistently increases with the rise of the population's ages. This can cost an enormous amount of money in receiving medical service. Therefore, the efficiency of the disease prevention and the health promotion is significant as it can reduce the disease opportunities and assist in identifying a patient at an earlier stage. This could help patients to lead better lives and receive medical service as rapidly as possible. The findings indicate that the prevalence of dementia in the 60-year and older residents living in Bang Kruai Sub-District, Bang Kruai District, Nonthaburi Province is 18 percent. This demonstrates that the number of elderly with dementia in the community is considerable, and the medical officers should be aware of this disease, especially in those with extremely high ages, lower educational levels, health issues which may affect their social and religious participations, as well as difficulties in learning how to use technology. Moreover, it is advisable to encourage the elderly, who do not show a symptom of dementia, to regularly participate in social and religious gatherings, and they should be encouraged to learn how to use recent technology as well.

The limitation of this study is that the researcher is not able to unsupervised diagnose a dementia by using DSM IV criteria, so an assessment tool, such as MMSE Thai 2002, is applied instead. However, the sensitivity and specificity of this tool can decrease when the educational levels of participants are at a primary-school degree or lower. Thus, the use of more efficient tools can lead to a better study result. In addition, there might be an issue regarding recall bias or under report from the participants as the direct interview is applied in this study without any use of participant's previous medical records or data. This can result in errors deriving from wrong recollections or understanding of the researcher.

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REFERENCES

1. United Nations, Department of Economic and Social Affairs. World Population Ageing 2019: Highlights (ST/ESA/SER.A/430). New York: UN; 2019.
2. Karakade J. Thailand and Ageing Society [Internet]. 2019 [cited 2018 Mar 10]. Available from: https://il.mahidol.ac.th/upload/img/2019-05-15-052430.pdf
3. Alzheimer's Disease International, Alzheimer's Australia. Dementia in the Asia Pacific Region [Internet]. 2014 [cited

2017 Jun 8]. Available from: https://www.alzint.org/u/Dementia-Asia-Pacific-2014.pdf.
4. Muangpaisan W. Dementia: Prevention, Assessment and Care. Bangkok: Phaphpim Co., Ltd. 2016.
5. ICT of MOPH Thailand. Population Piramid of Health Region 4 Nontaburi Province Bangkruai Annual Year Report 2019 [internet]. 2019 [cited 2020 Jan 20]. Available from:https://hdcservice.moph.go.th/hdc/reports/report.php?source=populationpyramid.php&cat_id=ac4eed1bddb23d6130746d62d2538fd0&id=db4e8d42e1234a75bd03d430c31feb2f
6. Suwan A, Trakulsitthichock S. Prevalence and Factors Associated with Dementia among Elderly in Lukhok Sub-district, Mueang District, Pathumtani Province. APHEIT Journals 2016;2:21-32. [in Thai]
7. Panakorn L, Nanthamongkolchai S, Pitikultung S, Munsawaengsub C, Teachaboonsermsak P. Factors Influencing Dementia in Elderly Women in Lamphun Province. Journal of Public Health 2015;45:197-209.
8. Kawitu K, Siri S, Sujirarat D. Prevalence and Associated Factors with Dementia in Elderly; Lampang Province. In: Graduate School Khon Kaen University. The 34th National Graduate Research Conference; 2013 Mar 27; Khon Kaen University. Khon Kaen, Thailand; 2013.p.915-23.
9. Asada T. Prevalence of dementia in Japan: past, present and future. Clin Neurol 2012;52(11):962-4.
10. Pricila Cristina Correa Ribeiro, Claudia de Souza Lopes, Roberto Alves Lourenco. Prevalence of Dementia in Elderly Clients of a Private Health Care Plan: A Study of the FIBRA-RJ, Brazil. Dement Geriatr Cogn Disord 2013;35:77-86.
11. Sowanna A. Prevalence and Associated Factors of Dementia in Ederly : 3 Provinces in Northern Rural Area [dissertation]. Nakhon Pathom: Mahidol University; 1998.
12. Kungsanaruk A. Epidemiology of Dementia among Elderly: A study in community. The Journal of Thai Air Force Medical Gazette 1993;39:19-293.

The Effectiveness of Cognitive Flexibility Training Program on Cognitive Functions and Activities of Daily Living in Patients with Ischemic Stroke

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ABSTRACT

Objective: To evaluate the effectiveness of a cognitive flexibility training program on cognitive functions and activities of daily living (ADLs) in patients with ischemic stroke.

Methods: A single blind randomized controlled trial study was conducted in a stroke unit of a tertiary hospital in a Bangkok setting. The sample size was 80 participants of both genders, aged 18 – 80 years. The sample size was stratified by age. Randomization was generated by a computer program dividing 40 participants into the experiment and 40 into the control group. Eleven participants dropped out during data collection. Therefore, 34 participants in the experimental group received cognitive flexibility training four days a week for 30-40 minutes per day over a period of 4 weeks in addition to usual care. There were 35 participants in the control group who received diary recording and usual care. The study used various instruments for data collection, including a Thai version of the Montreal Cognitive Assessment and Barthel's Index of Activities of Daily Living. Data were analyzed by multivariate analysis of covariance (MANCOVA).

Results: The experimental group had higher cognitive functions and abilities in performing activities of daily living than the control group with statistical significance ($p < .05$).

Conclusion: The study suggested that the program can be used to increase both cognitive functions and activities of daily living. Nurses and healthcare staff should apply this program in patients with acute ischemic stroke for nervous system recovery.

Keywords: Ischemic stroke; cognitive flexibility training program; cognitive functions; activities of daily living (Siriraj Med J 2021; 73: 236-244)

INTRODUCTION

Stroke, or cerebrovascular disease, is a severe neurological disease that affects many aspects involving patients, families, economics and society. Stroke is also commonly found in adults and elderly around the world. According to a 2019 World Stroke Organization report, stroke is a major public health problem and the second leading cause of death in the world. There are 80 million stroke patients worldwide; an average of 13.7 million new patients are found per year and there are 5.5 million

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stroke-related deaths annually.[1] In Thailand, stroke is a disease with the second highest mortality rate and second leading burden of disease. In addition, stroke can cause disability-adjusted life years (DALYs) from death and premature deaths at higher rates than the burden of illness.[2]

Stroke is a leading cause of cognitive impairment due to decreased blood supply to the brain and oxygen deficiency resulting in degeneration of neurons in the brain. The incidence of cognitive impairment in stroke patients is between 20-60% from the first 24 hours to 6 months after the stroke occurs.[3] Approximately 50 - 70% of patients have mild to moderate cognitive impairment with significant impact on advanced cognitive skills, executive function and cognitive flexibility. Furthermore, 15 to 30% of stroke survivors live with disabilities including impaired physical and cognitive functions. Patients, therefore, require assistance in their daily activities and dependency within one year post-stroke.[4]

Cognitive flexibility is considered a hallmark of human cognition and intelligent behavior.[5] It is also considered a core executive function and can be conceptualized as a well-delimited ability of the cognitive system, namely, set-shifting and higher-order ability such as cognitive control, a measure for divergent thinking and planning and flexibility in problem-solving. The focus is on the introduction of nerve impulses and network connections in the brain working together as a dynamic.[6] Cognitive flexibility produces thinking processes and skills in a systematic way and connects basic concepts and skills in daily activities through the coordination of two hemispheres of the brain, modifying the structure and function of the brain and signalling the transmission of nerve impulses that are more effective, thereby resulting in rapid recovery of the nervous system. The optimal recovery period for the nervous system occurs within two to four weeks.[7] The recovery of the nervous system is evident within the first 30 days, and there is still another 90 days of recovery. From 90 days to 6 months, recovery continues to take place, but is not as noticeable as in the initial phase.[8] Therefore, cognitive flexibility training in the acute phase can help restore the cognitive skills and basic daily activities of stroke patients more efficiently.[9]

According to a literature review related to cognitive flexibility training abroad, most of them mainly focused on chronic phase after stroke to improve performance of several daily routines and cognitive recovery in memory and communication. The VR-based intervention involving a virtual simulation of a city tasks in the performance of daily routines in stroke patients underwent a twelve-session intervention over a period of 4-6 weeks, results showed statistical significance in global cognitive functioning, executive functions and ADL performance.[10] The findings correspond with the computer-based cognitive flexibility training consisting of 9 tasks in the domains of shifting ability, cognitive control, adaptation, memory and reasoning over a period of 12 weeks, all groups showed improvements in cognitive and executive functioning. Furthermore, these improvements remained stable at 4 weeks after training completion.[11] In addition, the PC-cognitive training consisting of the fives specific cognitive domains for 8 weeks may be a useful method for accelerating post-stroke cognitive recovery, particularly in memory and language communication.[12]

Most of the literature reviewed in relation to cognitive flexibility training in Thailand, involved cognitive training combined with executive function. Most programs included memory attention and diary recording for 4 weeks. The programs could be used to recover brain function and increase attention, memory and basic cognitive skills, not including advanced cognitive skills.[13] Moreover, executive training programs including games and calculations 3 times a week for 25 minutes/session for 6 weeks can be used to improve memory attention and executive functions in chronic phase after stroke.[14] Furthermore, comprehensive rehabilitation programs continued for 30 days could be used to increase both cognitive functions and ADLs in patients with traumatic brain injuries, but did not include cognitive flexibility skills.[15] Thus, the specialized practice of cognitive flexibility training in acute phase after stroke remains limited and may not be enough to create brain connections and adjust perceptions or adaptations in various different situations and effective problem-solving.[11] Training in initial phase would be benefits in promoting of neuroplasticity and resulting in rapid recovery of the nervous system than general training.[24]

For these reasons, the researcher gained an interest in the development of a cognitive flexibility training program in acute ischemic stroke patients, mainly focused on promoting both cognitive functions and ADLs abilities through learning a variety of cognitive flexibility skills over a period of 4 weeks. The program including diary recording, memorization, shopping at the market and bank scenarios, categorization, prioritization, divergent thinking, planning and flexibility problem-solving with activities to recover nervous system function through the mechanism of modifying the neurological structure and physiology of cognitive processes. Stimulating brain learning with a variety of activities allows the brain to send nerve impulses easily and promotes greater efficiency in neurological recovery.[16]

MATERIALS AND METHODS

Research design

The present study was a single blind randomized controlled study. It was a randomized controlled evaluator-blinded trial in a pre-test - post-test design which assessed by the research assistant who did not know which groups of participants (experimental or control group) to reduce detection bias. The study conducted at a stroke unit of a tertiary hospital in Bangkok, Thailand, from June 2019 to February 2020.

Participants

This study consisted of male and female patients aged between 18 - 80 years and first diagnosed with acute ischemic stroke who had passed the critical phase at least 24 hrs.

Inclusion Criteria

1. Moderate stroke severity or higher as determined by a physician.
2. No vision problems, blindness and visual field defects.
3. No hearing problems or hearing loss confirmed by medical records.
4. Presence of a caregiver with a smartphone, ability to use an application to send messages and availability to participate in the program for four weeks.

Exclusion Criteria

1. Patients diagnosed with aphasia and impaired language comprehension.
2. Patients diagnosed with severe diseases such as ESRD and cancer.
3. Patients with a history of psychiatric illnesses and Alzheimer's disease.
4. Patients with severe cognitive impairment (TMSE < 20 points).
5. Patients with depression (PHQ-9 ≥ 7 points).

Sample size calculation

The researchers used the effect size of a previous study based on cognitive function outcomes.[12] The calculation showed that "f" is 0.4, which is a good effect size. The sample size for the present study was derived though power analysis (alpha = 0.05 with 80% power). The G power program (version 3.1) determined that the total sample size should be 64 people. In this study, the researchers increased the sample size by 20% to account for the drop-out rate. Thus, 80 participants were subsequently and evenly divided into the experimental and control groups by random sampling and stratified by age (≤ 60, > 60 years). A computer-randomized block design randomized 40 participants each into the experimental and control groups.

Ethics

This study was approved by the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital at Mahidol University, Bangkok, Thailand (Si 240/2019). The protocol number is 032/2019(EC3), and all participants signed informed consent forms.

Recruitment

Patients were invited to participate in the study after the researcher gained access to the samples by enlisting the research assistants as research publicists. Then the objectives, durations and risks involved in the study were explained. Confidentiality issues were also addressed. The subjects who agreed to participate then voluntarily completed and signed the informed consent forms (Fig 1).

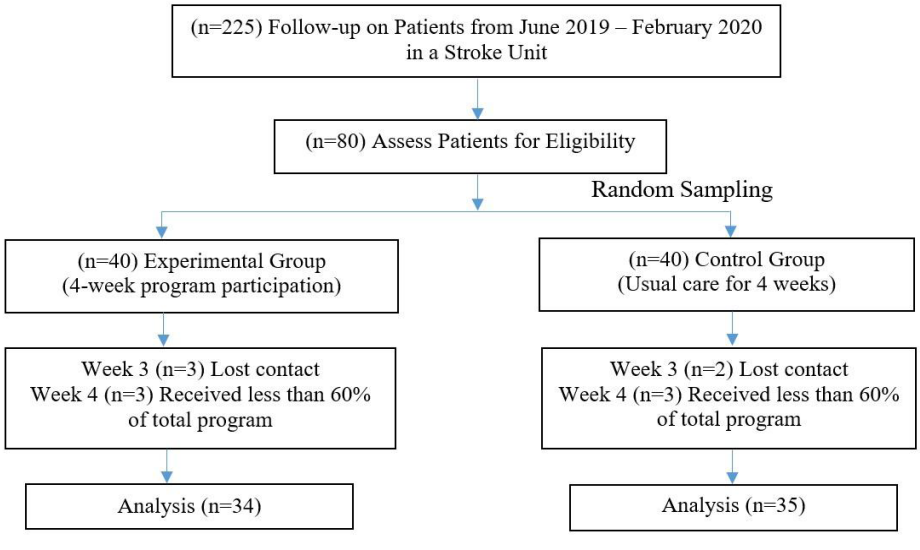

Fig 1. Flow Chart of the Research Process.

Intervention

Experimental Group

The cognitive flexibility training program, which was a set of activities developed by the literature review, included diary recording, memorization, shopping at the market, bank scenarios, categorization, prioritization, divergent thinking, planning and flexibility in problem-solving activities, which took 30 - 45 minutes/session for a total of 4 daily sessions, 4-week periods. The program required patients to do the exercises in the book handed out as a guide for patients to use in cognitive training while in the hospital and after discharge from hospital (Table 1).

Control Group

During the 4-week periods, patients received diary writing training which took 15 - 20 minutes a day and usual nursing care at a stroke unit of a tertiary hospital. The researcher telephoned to evaluate the problems and obstacles encountered in diary writing once a week, asked about general health conditions and encouraged continuous use of diary writing.

TABLE 1. Program activities.

Time period	Sessions	Activities
Week 1		
Day 1	1. Pretest assessment by research assistant. (15 minutes)	- Research assistant assessed cognitive function by using the MoCA-Thai and Barthel ADL Index to assess ADL performances before the experiment.
Day 2 – 5	2. Cognitive flexibility training program by the researcher. (45 minutes)	**Pre-training activities (15 minutes)** - Orientation time, place, person - Self-awareness training and brain exercises - Diary writing **Training activities (30 minutes)** - Working and recall memory training: spell the name, surname, months backwards, proverb telling activities - Set shifting training: 5 step sequences activities - Cognitive control training: beads sorting, magic character games, pattern block and categorization practice activities - Divergent thinking training: magic matchstick games, calculation activities, reasoning and decision-making activities - Planning and flexibility problem-solving training: shopping at the market and bank scenarios activities
Week 2-4	1. Cognitive flexibility training program by the researcher. (30 – 40 minutes) 2. Telephone follow-up calls by the researcher. (10 minutes)	- The researcher provided the guidelines and handbook for the cognitive flexibility training program to the subjects for training continuously at home. - Caregivers sent the exams' pictures to the researcher via an applications on smartphone. **Personal Follow-Up Telephone Calls (10 minutes)** - Evaluate the problems and obstacles encountered in training at home - Asked about general health conditions - Encouraged continuous use of the program
End of week 4	1. Post-test assessment by research assistant. (15 minutes)	- The research assistant assessed cognitive function by using the MoCA-Thai and Barthel ADL Index to assess ADL performance after the experiment. - To reduce detection bias, the research assistant was blind to which patients were in the control and experimental groups.

Measurements

1. Part 1: Demographic and Clinical Characteristic Data

Demographic information on age, gender, marital status, family role, occupation, education years and clinical characteristics including underlying diseases, lesions, stroke symptoms, interventions, severity of stroke, length of stay and onset of stroke in minutes were obtained from all of the participants.

2. Part 2: Cognitive Functions Measurement

The MoCA-Thai (Montreal Cognitive Assessment) was developed by Solaphat Hemrungrojn and the Faculty (2011).[22] The examination was used to assess various skills of cognition before and after receiving the training program and contained eight question categories including executive, naming, memory, attention, language, abstraction, delayed recall and orientation with a total score of 0 – 30 points. The results of test-retest reliability equalled 0.95.

3. Part 3: Activities of Daily Living (ADLs) Performance Measurement

Barthel's ADL index (Barthel's Index of Activities of Daily Living) was developed by Piyapata Detphratham and colleagues (2006).[23] The scoring criteria was 0, 5, 10 and 15 points. A full score of 0 – 100 points was assessed by observing the behaviour of the patients in 10 activities: feeding, transfer, grooming, toilet use, bathing, mobility, stairs, dressing, bowel movements and bladder continence. The results of inter-rater reliability equalled 0.99.

Statistical analysis

SPSS statistics software (Version 22) was used for data analysis. The significance level was set at .05. Demographic data and clinical characteristics were analyzed by distribution of frequency and percentage while comparisons of the differences in demographic characteristics were made by using chi-square, Fisher's exact test and independent t-test statistics.

Differences in the average pre-post test scores of cognitive function and ADLs in ischemic stroke patients in the experimental and control groups were analyzed by using mean, standard deviation, minimum-maximum and paired t-test statistics. Moreover, differences in the average post-test scores for cognitive function and ADLs between experimental and control groups were analyzed by using multivariate analysis of covariance (MANCOVA) statistics. The pre-test scores for cognitive function and ADLs were used as covariates.

RESULTS

Part 1: Demographic and Clinical Characteristic Data

Thirty-four subjects remained in the experimental group at the end of the study (attrition rate = 15%). Contact was lost with three persons, while three other persons received less than 60% of the total program. Thirty-five subjects remained in the control group (attrition rate = 12.5%). Contact was lost with two persons and three other persons received less than 60% of the total program. Overall, the total attrition rate was 13.75%.

The demographic information of both groups included 53.6% of the subjects who were aged over 60 years, an average age of 60.4 years (±13.72) for stroke survivors and an average age of 45.9 years (±11.93) for caregivers. Most of the samples were males (62.3%), married (75.4%), family members (58%), had average education for 9.4 years (±5.06) and were unemployed (34.8%). However, when personal characteristics were compared between the experimental and control groups, there were no statistically significant difference (Table 2).

According to the clinical characteristics of the research, the most common diseases found in both groups were hypertension at 66.7%, dyslipidemia at 36.2%, diabetes mellitus at 31.9% and atrial fibrillation at 21.7%. Approximately half of the patients presented with pathological lesions in the left brain at 52.2%, which resulted in right-side weakness. The symptoms of stroke included limb weakness at 52.2%, difficulty speaking at 78.3% and facial palsy at 72.5%. Moderate or greater severity of stroke was determined by average scores of 12.3 points (±5.77), while the time to hospital since the onset of stroke in minutes was 146.2 minutes (±94.14) and the average of length of stay was 7.7 days (±5.04). Furthermore, the majority of treatments were rt-PA 37.7% and rt-PA combined with mechanical thrombectomy (MT) 27.5%. However, when the clinical characteristics were compared between the two groups by using chi-square, Fisher's exact test and independent t–test were not significantly different (Table 3).

Part 2

The experimental group had cognitive function after training equal to 24.71 points (S.D. 2.11), which was higher than that of the control group with a score 22.40 points (S.D. 2.44). Furthermore, when tested with paired t-test statistics, the cognitive functions within the experimental group before and after training were significantly different (p-value < 0.05). In addition, the average ADLs abilities in the experimental group before training was 60.00 points (S.D. 13.93), while the control group had 65.29 points (S.D. 15.76). After training, the experimental group had a score of 83.38 points (S.D =

TABLE 2. Demographic data of the experimental and control groups.

Characteristics	Experimental Group n (%)	Control Group n (%)	*P*-value
Age			0.81[a]
≤ 60 years	15 (44.1)	17 (48.6)	
> 60 years	19 (55.9)	18 (51.4)	
Patients	$\underline{\chi}$ = 59.9, SD = 15.14	$\underline{\chi}$ = 61.0, SD = 12.30	0.75[c]
Caregivers	$\underline{\chi}$ = 43.9, SD = 12.47	$\underline{\chi}$ = 47.9, SD = 11.38	0.17[c]
Gender			1.0[a]
Male	21 (61.8)	22 (62.9)	
Female	13 (38.2)	13 (37.1)	
Marital Status			0.27[b]
Single/Widowed/Divorced	10 (29.4)	7 (20.0)	
Married	24 (70.6)	28 (80.0)	
Family Roles			1.0[a]
Family Head	14 (41.2)	15 (42.9)	
Family Member	20 (58.8)	20 (57.1)	
Occupations			0.90[b]
Unemployed	11 (32.4)	13 (37.1)	
Employed	8 (23.5)	5 (14.3)	
Business Owner	5 (14.7)	5 (14.3)	
Retirement/Civil Servant	10 (29.4)	12 (34.3)	
Education (years)	$\underline{\chi}$ = 9.5, SD = 5.29	$\underline{\chi}$ = 9.2, SD = 4.82	0.81[c]

[a] = Chi-square test, [b] = Fisher's exact test, [c] = Independent t-test

11.85), which was higher than the control group with an average of 67.86 points (S.D. 14.72). And when tested with paired t-test, the activities of daily living within the experimental group before and after training were significantly different (p-value < 0.05) (Table 4).

Part 3

When using the pre-test scores of cognitive function and ADLs as covariates with multivariate analysis of covariance (MANCOVA) statistics, the effectiveness of the cognitive flexibility training program on cognitive functions after the experiment was less than 0.05 (p-value < 0.05), and the ability to perform ADLs after the experiment was also less than .05 (p-value < 0.05). It has been stated that the cognitive function and ADLs of the experimental group who received the training program were different with statistical significance at .05. The findings demonstrate the effectiveness of the cognitive flexibility training program on increasing cognitive function and ADLs performance (Table 5).

DISCUSSION

According to the research findings on the effectiveness of the cognitive flexibility training program, the patients with ischemic stroke who received the training program had higher levels of cognitive functions and ADLs than who received usual nursing care only with statistical significance. Furthermore, the patients who received the program had higher levels of cognitive functions and ADLs than pre-training with statistical significance.

The above findings can be described as follows: The patients with acute ischemic stroke who received the cognitive flexibility training program had higher levels of cognitive function and ADLs. These may cause by the patients received longer intervention time in the experimental group. Furthermore, in developing

TABLE 3. Clinical characteristics of the experimental and control groups.

Characteristics	Experimental Group n (%)	Control Group n (%)	*P*-value
Underlying Diseases			0.43[b]
Hypertension	21 (61.8)	25 (71.4)	
Dyslipidemia	12 (35.3)	13 (37.1)	
Diabetes mellitus	11 (32.4)	11 (31.4)	
Atrial fibrillation	4 (11.8)	11 (31.4)	
Lesions			0.81[a]
Left side brain	17 (50.0)	19 (54.3)	
Right side brain	17 (50.0)	16 (45.7)	
Stroke symptoms			
Left side weakness	17 (50.0)	16 (45.7)	0.81[a]
Right side weakness	17 (50.0)	19 (54.3)	0.81[a]
Dysarthria	26 (76.5)	28 (80.0)	0.77[a]
Facial palsy	22 (64.7)	28 (80.0)	0.19[a]
Intervention			0.98[b]
None	10 (29.4)	10 (28.6)	
rt-PA	12 (35.3)	14 (40.0)	
MT	2 (5.9)	2 (5.7)	
rt-PA with MT	10 (29.4)	9 (25.7)	
Severity of Stroke	$\underline{\chi}$ = 12.9, SD = 5.12	$\underline{\chi}$ = 11.7, SD = 6.41	0.40[c]
Length of Stay (days)	$\underline{\chi}$ = 6.8, SD = 4.68	$\underline{\chi}$ = 8.6, SD = 5.40	0.14[c]
Onset of Stroke (minutes)	$\underline{\chi}$ = 156.4, SD = 104.0	$\underline{\chi}$ = 135.9, SD = 83.4	0.37[c]

[a] = Chi-square test, [b] = Fisher's exact test, [c] = Independent t-test

TABLE 4. The results on cognitive functions and activities of daily living (ADLs) abilities between the experimental and control groups at pre- and post-test.

Variables	Experimental Group mean (SD)	min - max	Control Group mean (SD)	min - max	*P*-value
Cognitive Functions					<0.001
Before Training	21.12 (2.33)	17 – 25	21.89 (2.69)	18 – 27	
After Training	24.71 (2.11)	20 – 28	22.40 (2.44)	18 – 27	
ADLs Performance					<0.001
Before Training	60.0 (13.93)	40 – 90	65.3 (15.76)	40 – 100	
After Training	83.3 (11.85)	60 – 100	67.8 (14.72)	40 – 100	

Paired *t*-test

TABLE 5. The results of the effectiveness of the cognitive flexibility training program on cognitive functions and activities of daily living between the experimental and control groups.

Source	Dependent Variables	Mean Square	F	*P*-value
Covariates				
MoCA (Pretest)	Cognitive Functions	210.35	386.469	<0.001
	Activities of Daily Living	143.80	4.488	.038
Barthel (Pretest)	Cognitive Functions	0.802	1.473	.229
	Activities of Daily Living	5973.4	186.447	<0.001
Effects of the intervention	Cognitive Functions	148.52	272.869	<0.001
	Activities of Daily Living	6659.7	207.869	<0.001

Box's M = 2.608, *P*-value < 0.05

Multivariate analysis of covariance (MANCOVA)

neuroplasticity, which is considered an important mechanism for recovering brain ability, the concept of neuroplasticity is the ability to change structure and function in the central nervous system, which can occur throughout life depending on the experience or activity of the stroke patient. It is an important mechanism for restoring the ability of the nervous system.[18] Neuroplasticity was mostly found to occur during Weeks 3 to 4 after the ischemic events and continued for three months after stroke.[24] This finding was consistent with the conceptual framework of the pathophysiological aspect of brain plasticity[17] and modulation of neural plasticity (experience-dependent plasticity),[18] which states that neuroplasticity is an important mechanism for restoring the ability of the nervous system with changes in the anatomical structure and nerve network in addition to increasing the dendrite branches and stimulated recovery of the nervous system through a cognitive process. Thus, the nerve cells sprout, become elongated or regenerate and, when continuously stimulated, have increased ability of nerve conduction and networking between brain hemispheres working together as a dynamic. As a result, the brain changes its structure and adjusts its function to replace injured nerve cells for increased in cognitive function. Moreover, dynamic linkage allows patients to perform more activities of daily living independently.

The findings correspond with findings of Faria and colleagues (2016)[10] who examined the effectiveness of a VR-based intervention. The results showed statistical significance in global cognitive functions, executive function and ADLs performance. Furthermore, the findings correspond with Van de ven and colleagues (2017)[11] who examined the effectiveness of computer-based cognitive flexibility training, all groups improved on cognitive and executive functioning. In addition, the findings also correspond with De Luca and colleagues (2018)[12] who examined the effectiveness of PC-cognitive flexibility training, the findings suggest that training may be a useful method for accelerating post-stroke cognitive recovery. However, the findings differ from the study of Aulwatthanasiri, P. (2012),[13] Khantee, R. (2016)[14] and Phancham, N. (2010).[15] This study took less training time and improved both cognitive functions and ADLs in patients through the stimulation of cognitive processes by various skills with statistical significance.

In the control group, cognitive functions and ADLs before and after training were significantly different. This finding can be explained in that there was a spontaneous recovery of the nervous system. The recovery is evident within the first 30 days followed by another 90 days. From 90 days to 6 months, recovery continues to take place, but is not as noticeable as in the initial phase.[8] During the first week, there is recovery from local factors, improved blood circulation and partial recovery of the brain cells. Later is the process of neuroplasticity, which requires rehabilitation and training activities. Therefore, cannot yet be concluded that all treatments will enable rapid rehabilitation for patients.

Limitations

The findings of present study show that the 4-week program is compatible with participants who routinely

come for follow up appointments at three to four weeks post-stroke. Moreover, this program should be given more training time in control group. In addition, to promote cognitive functions and ADLs performance, this program should be extended to interventions lasting at least 3-month based on the nervous system recovery theory.

CONCLUSION

According to the findings, the cognitive flexibility training program consisting of memory training and 4 domains of cognitive flexibility (set shifting, cognitive control, divergent thinking/planning and flexibility in problem-solving) can increase both cognitive functions and ADLs through the mechanism of modifying neurological structure and the physiology of cognitive processes. Thus, nurses and healthcare staff should apply this program in patients with acute ischemic stroke for nervous system recovery.

Conflicts of Interest: Authors report no conflicts of interest in this work.

REFERENCES

1. Lindsay MP, Norrving B, Sacco RL, Brainin M, Hacke W, Martins S, et al. Global Stroke Fact Sheet 2019. Int J Stroke 2019;14:806-17.
2. Strategy and Planning Division Office of the Permanent Secretary. Public Health Statistics A.D.2018. Nonthaburi: WVO Thai Printing; 2018.
3. Turunen KE, Laari SP, Kauranen TV, Uimonen J, Mustanoja S, Tatlisumak T, et al. Domain-specific cognitive recovery after first-ever stroke: a 2-year follow-up. J Int Neuropsychol Soc 2018;24:117-27
4. Pahlman U, Savborg M, Tarkowski E. Cognitive dysfunction and physical activity after stroke: The Gothenburg cognitive stroke study in the elderly. J Stroke Cerebrovasc Dis 2012;21: 652-8.
5. Rende B. Cognitive flexibility: Theory, assessment, and treatment. Semin Speech Lang 2000;21:121-53.
6. Ionescu T. Exploring the nature of cognitive flexibility. New Ideas Psychol 2012; 30:190-200.
7. Ward NS. Restoring brain function after stroke-bridging the gap between animals and humans. Nat Rev Neurol 2017;13:244-55.
8. Stinear CM, Petoe MA, Byblow WD. Primary motor cortex excitability during recovery after stroke. Brain Stimul 2015;8: 1183-90.
9. Zucchella C, Capone A, Codella V, Vecchione C, Buccino G, Sandrini G, et al. Assessing and restoring cognitive functions early after stroke. Funct Neurol 2014; 29:255.
10. Faria AL, Andrade A, Soares L, Badia SB. Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients. J Neuroeng Rehabil 2016;13:96.
11. Van de ven RM, Buitenweg JI, Schmand B, Veltman DJ, Aaronson JA, Nijboer TC, et al. Brain training improves recovery after stroke but waiting list improves equally: A multicenter randomized controlled trial of a computer-based cognitive flexibility training. PloS One 2017;12:e0172993.
12. De Luca R, Leonardi S, Spadaro L, Russo M, Aragona B, Torrisi M, et al. Improving cognitive function in patients with stroke: can computerized training be the future? J Stroke Cerebrovasc Dis 2018;27:1055-60.
13. Adulwattanasiri P, Puwarawuttipanit W, Saneha C, Nilanont Y. The effectiveness of brain training program on attention and memory in acute ischemic stroke patients. Proceedings of the 3rd Hatyai National & International Conference; 2012 May 10; Hatyai University.
14. Khanthee R, Dhippayom JP, Munkhetvit P. Effects of cognitive training program on cognitive abilities in stroke patients. J Assoc Med Sci 2016;49:298.
15. Phancham N, Jitpanya C. Effects of comprehensive rehabilitation program and brain exercise on cognitive functions and activities on daily living in patients with traumatic brain injury. JNSCU 2010;22:22-33.
16. Pajaree K. Modern Neurology. Bangkok: October print house; 2019.
17. Hebb DO. The organization of behavior: A neuropsychological theory. New York: Chapman & Hall; 1949.
18. Pekna M, Pekny M, Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. J Stroke 2012;43:2819-28.
19. Glass GV. Primary, secondary & meta-analysis of research. Educ Res 1976;5:3-8.
20. Train the Brain Forum Committee (Thailand). Thai Mental State Examination. Siriraj Hospital Gazette 1993;45:359-74.
21. Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC Psychiatry 2008;8:46-8.
22. Hemrungrojn S. Montreal Cognitive Assessment (MOCA) [Internet]. 2011 [cited 2018 Nov 25]. Available from: http://www.mocatest.org/pdf_files/test/MoCA-Test-Thai.pdf.
23. Dajpratham P, Meenaphant R, Junthon P, Pianmanakij S. The Inter-rater reliability of barthel index in stroke patients. J Rehabil Med 2006;16:1-9.
24. Cho DR, Lee SH. Effects of virtual reality immersive training with computerized cognitive training on cognitive function and activities of daily living performance in patients with acute stage stroke. Medicine 2020; 99:e20598.

Long-term Outcome of the Management of Otitis Media with Effusion in Children with and Without Cleft Palate Using the House-brand Polyethylene Ventilation Tube Insertion

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ABSTRACT

Objective: To study the long-term outcome of otitis media with effusion in children with and without cleft palate treated with the same protocol of ventilation tube insertion.

Materials and Methods: A retrospective cohort study was conducted in eighty-five children with cleft palate and 80 children without cleft palate who had otitis media with effusion and had follow-up between 2001 and 2019. Both groups were treated with ventilation tube insertion for longstanding middle ear effusion more than 90 days. The main outcome was the cumulative incidence of surgical management, time of the indwelling ventilation tubes, conditions of the tympanic membrane, and the hearing outcome.

Results: At 24 months old, 63.5% of children with cleft palate and 11.3% of children without cleft palate had their first ventilation tube insertion. Repeated surgery was done in 81.2% of children with cleft palate and 50% of children without cleft palate ($p < 0.001$). The median duration of the indwelling tube was 11.3 months in the children with cleft palate and 12.4 months in the non-cleft children ($p = 0.82$). At the end of the study, 63.7% of children without cleft palate and 43.5% of children with cleft palate had normal tympanic membrane ($p = 0.009$). The hearing outcomes of children with and without cleft palate were 20.7 dB and 19.3 dB, respectively.

Conclusion: Children with and without cleft palate were managed under the same guideline and the hearing outcome was favorable in both groups.

Keywords: Cleft palate; otitis media with effusion; ventilation tube (Siriraj Med J 2021; 73: 245-251)

INTRODUCTION

Cleft palate is an important underlying factor for otitis media in infants and children. The incidence of non-syndromic cleft palate without cleft lip is 1:2,000 live births.[1] Anatomical abnormalities of the eustachian tube in cleft palate include abnormal insertion of the levator veli palatini and tensor veli palatini muscle, a small paratubal muscle, greater cartilage cell density, less elastin in the hinge portion, and a smaller angle between the tensor veli palatini muscle and the eustachian tube.[2,3]

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Relocation of the levator veli palatini muscle during palatoplasty has been reported to have no effect on the eustachian tube function.[4] Da Silva et al.[5] found that the middle ear status had no correlation with velopharyngeal function after palatoplasty. Also, the type of cleft palate has been reported to have no association with the number of ventilation tube insertions.[6] Children with cleft palate are more prone to otitis media with effusion (OME) than children without cleft palate. Previous studies reported that children with cleft palate had an onset of OME in infancy with prolonged effusion, higher incidence of complications and hearing loss from chronic OME.[7,8]

Myringotomy and ventilation tube insertion are accepted as the most effective management for chronic middle ear effusion and hearing loss in children with cleft palate. The timing of the ventilation tube insertion and the management protocol in children with cleft palate are the main controversial issues and remain under extensive review.[9,10] Insertion of ventilation tubes in children with cleft palate can be done in a routine fashion or only when chronic effusion is present. There are no data in the literature to support early routine ventilation tube insertion in children with cleft palate in terms of the benefit of the outcome, especially when effusion is not found. From the clinical practice guideline ventilation tube insertion in at-risk children should be done in cases with persistent middle ear effusion longer than 90 days or effusion that is unlikely to resolve itself as demonstrated by a type-B (flat) tympanogram.[11] We present herein the results of a retrospective cohort study of OME in children with and without cleft palate. Both groups were treated with regular follow-up and ventilation tube insertion for longstanding middle ear effusion more than 90 days. The main outcome was the cumulative incidence of OME, age incidence and number of tympanostomy tube insertion, time of the indwelling tubes, age of resolution of OME, outcome of the tympanic membrane (TM), and the hearing outcome.

MATERIALS AND METHODS

This retrospective cohort study was conducted in children with and without cleft palate who had OME and had regular follow-up between January 2001 and May 2019. The research was approved by the institutional review board of our institute. Children with cleft palate or craniofacial anomalies were first seen by the plastic surgery service and they were referred to the Pediatric Otolaryngology clinic for ear evaluation. Children without cleft palate came to the Pediatric Otolaryngology clinic for ear problems, hearing problems, or for an evaluation of their speech and development. Children with congenital syndromic and non-syndromic sensorineural hearing loss were excluded from the study. Data gathering included the demographic data, physical examination, diagnosis, and hearing test results. Diagnosis of OME was done by pneumatic otoscopy. Pneumatic oto-endoscopy was done in some cases with difficult diagnosis to add extra visualization of the TM and the middle ear. All ear examinations were done in the outpatient department. Ear events during the follow-up period were recorded. The definition of acute otitis media (AOM) was an acute inflammation of the middle ear, with bulging of the TM and middle ear effusion. Otitis media with effusion (OME) was defined as middle ear effusion without symptoms and signs of acute inflammation. A hearing test was done as early as possible after the first visit. In young infants, Auditory brain stem response (ABR) and auditory steady state response (ASSR) tests were done. Hearing tests were done periodically according to the ear events and after each surgery. Pure tone audiometry was done when the child was old enough to be able to co-operate.

The indication of myringotomy with ventilation tube insertion was the presence of longstanding middle ear fluid for more than 90 days with or without hearing loss. Type-B tympanogram was not included in the routine investigations because tympanometry might not be reliable in very young children. If chronic middle ear fluid was found near the date of the scheduled palatoplasty, the first myringotomy and ventilation tube insertion were done in the same setting. After surgery, the patients had regular follow-up every 8–12 weeks until their ear conditions were resolved. In patients with ventilation tubes, the condition of the TM and ventilation tubes were recorded until the tubes fell out. The duration time of the indwelling tubes were recorded.

Middle ear fluid culture was done in patients who had myringotomy and ventilation tube insertion. Middle ear fluid samples were aseptically collected and sent to the microbiology laboratory within 30 minutes for Gram staining and culture. The specimen was inoculated onto chocolate agar, 5% sheep blood agar, and MacConkey agar plates for the cultivation of aerobic and facultative anaerobic bacteria and were then examined after 24, 48, and 72 hours of incubation. The results of the middle ear fluid culture were recorded.

All children with cleft palate were scheduled for regular follow-up until no more recurrence of OME was found. Children without cleft palate were re-evaluated for their ear events at intervals until the middle ear effusion or abnormalities of the TM were no longer present. The outcome of the treatment was recorded at the last follow-up by ear examination and hearing test.

A favorable outcome was defined as a normal TM with no middle ear effusion and a normal hearing threshold less than or equal to 20 decibels (dB).

Descriptive statistics were used for the demographic and other descriptive data. Univariate analysis was done for comparisons between the data of the children with and without cleft palate using chi-square, T-test, or non-parametric statistics. The cumulative incidence of first ventilation tube insertion for OME and the resolution of OME with a normal TM were plotted between the events and the age of the patients. A Kaplan–Meier life table plot was used for the duration of the indwelling ventilation tubes. Statistical analysis was done by using SPSS version 22.

RESULTS

The data of 165 pediatric patients with OME were included in the analysis, comprising 85 children with cleft palate and 80 children without cleft palate. The children's demographic data are shown in Table 1. The children with cleft palate had an associated cleft lip in 48 cases (56.5%). There was a significant difference in age at first contact for the children with and children without cleft palate. Most of the children with cleft palate (72.9%) were referred to the Pediatric Otolaryngology clinic when they were younger than 24 months old, while children without cleft palate were seen in the clinic at the median age of 4 years old.

Ear events in this series consisted of acute otitis media (AOM), otitis media with effusion (OME), and otorrhea through ventilation tube. The rate of AOM was 1.96±5.1 per year in children with cleft palate and 1±3.2 per year in children without cleft palate ($p = 0.147$). The rate of otorrhea in children with cleft palate was 7.2 per year and 0.73 per year in children without cleft palate ($p = 0.003$). There was no cholesteatoma and no other suppurative complications of otitis media in this series.

All of the patients in this series had chronic OME requiring myringotomy and ventilation tube insertion. The cumulative percentage of patients who had first myringotomy and ventilation tube insertion according to age is shown in Fig 1. The cumulative incidence of OME that met the criteria for myringotomy and ventilation tube insertion was significantly higher in children with cleft palate, especially in the first 5 years of life. At 24 months old, 63.5% of the children with cleft palate had their first myringotomy compared to 11.3% of the children without cleft palate. Most of the children without cleft palate had their first myringotomy between 24 to 72 months old. Repeated ventilation tube insertion was done in 69 cases (81.2%) of children with cleft palate and in 40 cases (50%) of children without cleft palate ($p < 0.001$). The mean number of myringotomy and ventilation tube insertions throughout the cohort was 2.7 in the children with cleft palate and 1.9 in the children without cleft palate ($p = 0.002$).

TABLE 1. Demographic data of the children with and without cleft palate.

	Cleft	Non-cleft	P-value
Number of patients	**85**	**80**	
Gender			
Male	48 (56.5%)	44 (55%)	0.85
Female	37 (43.5%)	36 (45%)	
Age (months)			
first contact	8 (25)*	49.5 (55)*	< 0.001**
first myringotomy	17 (50)*	51 (51)*	< 0.001**
last contact	95.5±62.3	115.8±57.2	0.03
Follow-up duration (months)	73.7±49.3	57.8±38.8	0.02

*median and interquartile range.

** non-parametric statistics.

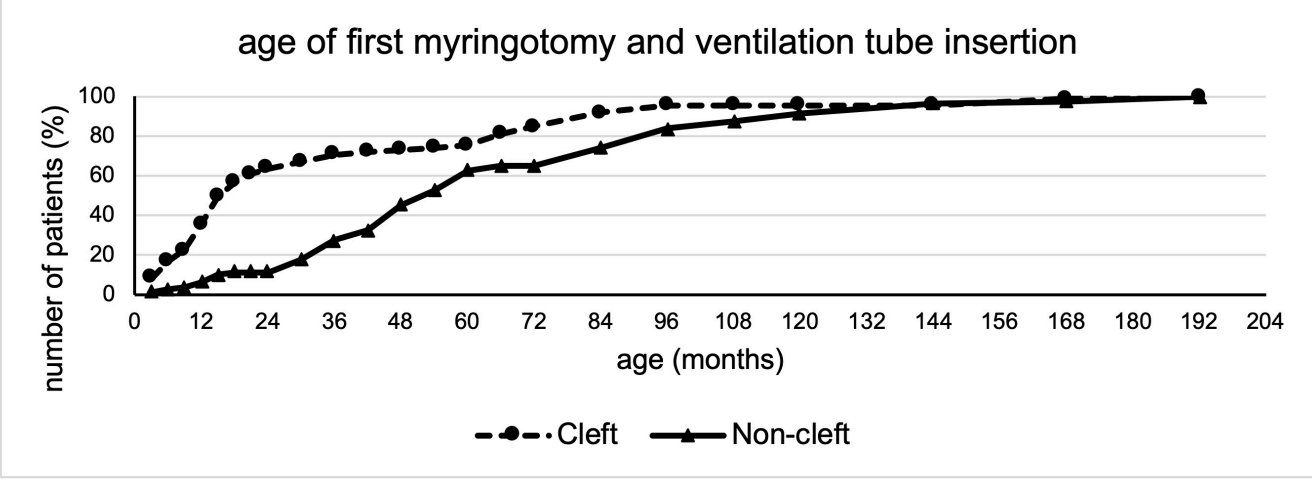


Fig 1. Cumulative percentage of patients who had first myringotomy and ventilation tube insertion for OME according to age
OME = otitis media with effusion.

The duration of the indwelling ventilation tubes was compared between 72 children with cleft palate and 62 children without cleft palate who used a house-brand ventilation tube, which was made from a polyethylene tube and shaped like a bobbin. Our study cohort included patients who used other tubes, such as the modified Armstrong tube, Shepard tube, T-tube, and Shah tube, but the sample size was too small for comparison. The duration times of the indwelling tubes in children with and without cleft palate are shown in Fig 2. The median duration time of the indwelling tube was 11.3 months (95% confidence interval = 9.2,13.4) in the children with cleft palate and 12.4 months (95% confidence interval = 9.5,15.3) in the children without cleft palate (p = 0.82). The mean total follow-up time until resolution of OME was 73.7±49.3 months in cleft children and 57.8 ± 38.8 months in non-cleft children.

Bacterial culture of the middle ear fluid from the first myringotomy was done. From the specimens of the 165 patients, 156 bacterial isolates were found. No growth was found in 76 cases. The prevalence of bacteria in the middle ear fluid was similar in the children with and without cleft palate. Coagulase-negative Staphylococcus was the most common bacteria found in both groups, followed by *Staphylococcus aureus* and *Haemophilus influenzae*.

The outcomes of the management of OME are shown in Table 2. The children without cleft palate had more intact TM than the children with cleft palate with statistical significance (p = 0.009). The mean age at the last contact with a bilateral intact TM was 98.7 months old in the children with cleft palate and 118.4 months old in the children without cleft palate (p = 0.14). The rate of TM perforation was not different between the children with cleft palate and the children without cleft palate.

The hearing threshold at the first contact and subsequent hearing evaluation were obtained by ABR, ASSR, speech reception threshold or pure tone audiometry according to the patient's age and co-operation. Visual reinforcement audiometry (VRA), otoacoustic emission and tympanogram were not done routinely but they were used in selected cases. The hearing threshold was shown in Table 2. At the end of the study, 66.2% of the children with cleft palate and 69.6% of the children without cleft palate had normal hearing. The average hearing threshold was 20.7 dB in cleft children and 19.3 dB in non-cleft children.

The cumulative rate of resolution of OME in children with cleft palate is shown in Fig 3. The earliest resolution of OME was found in one case at 3 years old, but the peak incidence of resolution occurred between 5 to 8 years old. At 10 years old, the resolution rate of OME in the children with cleft palate was 83.8%. Fifty-one percent of the children with cleft palate had normal hearing at 7 years old and 80.4% of the children had normal hearing at 10 years old.

DISCUSSION

Children with cleft palate are identified as "at-risk" children for OME.[12] Hearing loss from OME may add more severity to any speech defect that already exists from cleft palate. In our previous study,[13] we found that the cumulative incidence of OME in children with cleft palate was 53.7% at 12 months of age and 81.1% when the children reached 24 months old. Chronic middle

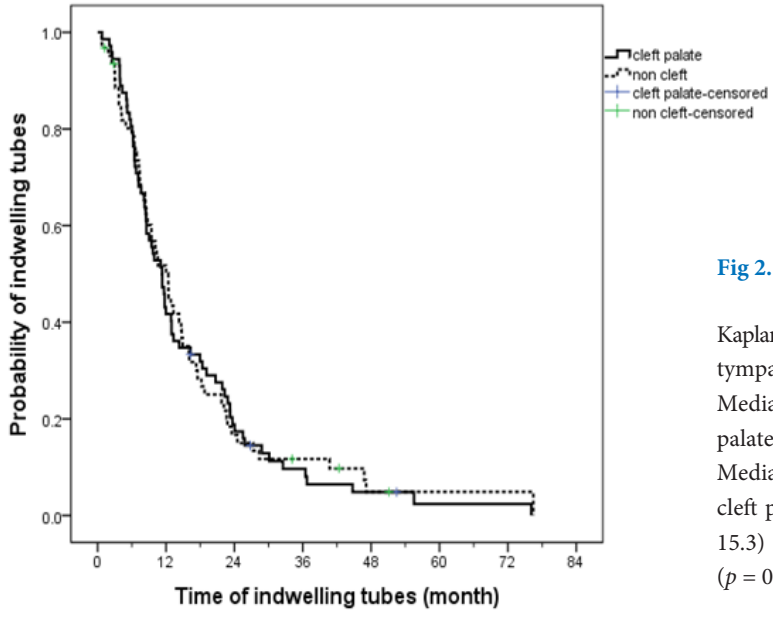


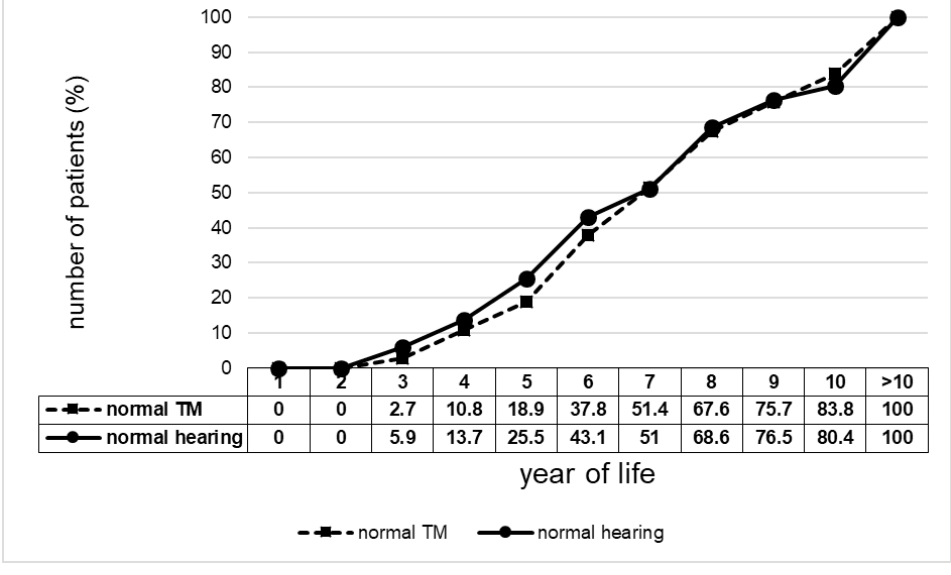
Fig 2. Time in place of the indwelling tubes

Kaplan–Meier curves showing the time in place of the indwelling tympanostomy tube
Median time of the indwelling tube in the children with cleft palate = 11.3 months (95% confidence interval = 9.2, 13.4)
Median time of the indwelling tube in the children without cleft palate = 12.4 months (95% confidence interval = 9.5, 15.3)
(p = 0.82)

TABLE 2. Outcome of the management of otitis media with effusion in the children with and without cleft palate.

	Cleft	Non-cleft	P-value
TM and middle ear			
Intact (bilateral)	37/85 (43.5%)	51/80 (63.7%)	0.009*
Perforation (at least one side)	9/85 (10.6%)	5/80 (6.2%)	0.318
Tube in place (at least one side)	31/85 (36.5%)	14/80 (17.5%)	0.006*
Residual effusion (at least one side)	8/85 (9.4%)	9/80 (11.2%)	0.698
Residual retraction	0	1 (1.2%)	-
Total	85	80	
Hearing threshold (dB)			
First hearing	40.2	42.6	0.40
Last hearing	20.7	19.3	0.52

TM = tympanic membrane.



	1	2	3	4	5	6	7	8	9	10	>10
normal TM	0	0	2.7	10.8	18.9	37.8	51.4	67.6	75.7	83.8	100
normal hearing	0	0	5.9	13.7	25.5	43.1	51	68.6	76.5	80.4	100

Fig 3. Cumulative percentage of the children with cleft palate who had a resolution of OME with a normal tympanic membrane/ normal hearing according to age
OME = otitis media with effusion.

ear effusion and frequent recurrences are characteristic of OME in children with cleft palate. Ear and hearing evaluation should be done as early as possible because OME in children with cleft palate usually presents when they are young infants. Regular ear examination should be done to detect the recurrence or longstanding middle ear effusion justifying ventilation tube insertion. There is no clinical evidence to support early prophylactic ventilation tubes in terms of speech and language development.[9] Smillie et al.[14] concluded from their study that the same guideline should be used for ventilation tube insertion in children with and without cleft palate as the complication rate was not higher in children with cleft palate.

Children with cleft palate had their first myringotomy at a younger age when compared to children without cleft palate. In the systematic review by Felton et al[15], there were some studies that children with cleft palate who had early placement of tympanostomy tubes at the time of cleft lip repair (at 3-4 months old) had achieved normal hearing and speech comparable to the non-cleft children. However, this group of infants had higher rate of otorrhea than older children.[15] Most of the children with cleft palate in our study had their tympanostomy tube insertion at the time of palatoplasty. In our study, 70% of the children with cleft palate had their first myringotomy before they were 3 years old, while 62.5% of the children without cleft palate had their first ventilation tubes within their first 5 years. From the study of Huang et al.,[16] the mean age at first myringotomy in children with cleft palate was 1.3 years old, which was about the same age as in our study. The age of the first myringotomy had no effect on the long-term hearing outcome.[17]

The median time of the indwelling tubes remaining in the children with cleft palate was 11.3 months, which was a little shorter than in the children without cleft palate, but without significant difference. The indwelling duration of our house-brand ventilation tube was the same as for the commercial short-term tube, which was 10-18 months. Ahn et al.[18] found that repeated insertion was associated with a shorter indwelling time of the tube.

Middle ear effusion causes mild to moderate hearing loss. In our study, the mean hearing threshold in the children with and without cleft palate with OME before ventilation tube insertion was around 40 dB. The first hearing test in young infants was done by auditory brain stem response (ABR) and auditory steady state response (ASSR). Subsequent pure tone audiometry confirmed that the hearing loss was conductive. The children without cleft palate in this study were older than the children with cleft palate when they entered the study and some of their first hearing tests were done by pure tone audiometry. Sundman et al.[19] reported an ABR threshold of 41.4 dB in infants with OME and 40.1 dB in infants with cleft lip and cleft palate. The median neonatal ABR threshold in infants with cleft palate in the study of Tengroth et al.[20] was 35 dB (range, 20-45 dB). Kim et al.[17] studied the rate of hearing loss and TM perforation in children with cleft palate at 10 years old and found that the rate of hearing loss (>25 dB) was 38.8%. In this study, the mean hearing threshold after the management was normal in both groups without significant difference.

The detection of OME requires regular ear examination as the disease is asymptomatic. Children with OME who are not at risk require regular follow-up every 3-6 months until the fluid disappears to prevent complications, such as retraction or cholesteatoma.[12] At the end of this study, the number of children with cleft palate who still had ventilation tubes in place was greater than in the non-cleft group, so the children with cleft palate would be expected to be followed for a longer period. Regular follow-up with hearing evaluation in children with cleft palate should be continued until the resolution of OME is found and the hearing is stabilized.

The main limitation of this study was related to the retrospective nature of the data. Also, the children without cleft palate could not be considered as a true control because they did not undergo the same surveillance as the children with cleft palate, rather they came in as patients with ear or hearing-related problems. We did not compare the resolution rate of OME and the time to normal hearing between the children with and without cleft palate because the results could not be generalized. Finally, the choice of tympanostomy tube was made according to the patient's reimbursement scheme and the surgeon's preference.

On the other hand, information on the children with cleft palate was collected from the first day that they entered the craniofacial clinic and were placed under surveillance for ear diseases throughout the study. The results of this study should be useful as a description of OME in children with cleft palate in the aspect of the long-term outcome. From this study, a strategy involving careful observation and ventilation tube insertion when the middle ear effusion did not resolve in due course could be useful for children with cleft palate as well as for children without cleft palate. The outcome was comparable in terms of the children achieving a normal hearing threshold, the low rate of TM perforation and no severe complications.

CONCLUSION

The children with cleft palate had their first ventilation tube insertion at a younger age than the children without cleft palate. The children with cleft palate had a greater number of ventilation tubes and more episodes of otorrhea. The duration time of the indwelling tubes was not different in both groups. At the last follow-up, there were more children with cleft palate who still had a ventilation tube in place. Children without cleft palate had a greater number of normal TM than the cleft palate group. The rate of TM perforation was lower in the children without cleft palate, but with no statistical significance. The children with and without cleft palate who had OME were managed with the same guideline and the hearing outcome was favorable in both groups. The children with cleft palate were expected to have a longer period of follow-up.

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REFERENCES

1. Deleyiannis FWB, Maguire RC. Congenital malformations of the mouth and pharynx: orofacial cleft and related syndromes. In: Bluestone CD, Healy GB, Simons JP, editors. Pediatric Otolaryngology. 2. 5th ed. Shelton: People's Medical Publishing House-USA; 2014.p.1879-84.
2. Takasaki K, Sando I, Balaban CD, Ishijima K. Postnatal development of eustachian tube cartilage. A study of normal and cleft palate cases. Int J Pediatr Otorhinolaryngol 2000;52: 31-6.
3. Heidsieck DS, Smarius BJ, Oomen KP, Breugem CC. The role of the tensor veli palatini muscle in the development of cleft palate-associated middle ear problems. Clin Oral Investig 2016; 20:1389-401.
4. Kobayashi H, Sakuma T, Terao H, Sanbe T, Suzaki H, Ohkubo F. Palatoplasty and growth of the temporal bone mastoid air cells. Cleft Palate Craniofac J 2012;49:541-5.
5. da Silva DP, Collares MV, da Costa SS. Effects of velopharyngeal dysfunction on middle ear of repaired cleft palate patients. Cleft Palate Craniofac J 2010;47:225-33.
6. Garcia-Vaquero C, Mir C, Graterol D, Ortiz N, Rochera-Villach MI, ME LL, et al. Otologic, audiometric and speech findings in patients undergoing surgery for cleft palate. BMC Pediatr 2018;18:350.
7. Kobayashi H, Sakuma T, Yamada N, Suzaki H. Clinical outcomes of ventilation tube placement in children with cleft palate. Int J Pediatr Otorhinolaryngol 2012;76:718-21.
8. Skinner ML, Tunkel DE. Primary care of infants and children with cleft palate. In: Bluestone CD, Healy GB, Simons JP, editors. Pediatric Otolaryngology. 2. 5th ed. Shelton: People's Medical Publishing House-USA; 2014.p.1879-84.
9. Ponduri S, Bradley R, Ellis PE, Brookes ST, Sandy JR, Ness AR. The management of otitis media with early routine insertion of grommets in children with cleft palate -- a systematic review. Cleft Palate Craniofac J 2009;46:30-38.
10. Karanth TK, Whittemore KR. Middle-ear disease in children with cleft palate. Auris Nasus Larynx 2018;45:1143-51.
11. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, et al. Clinical practice guideline: Tympanostomy tubes in children. Otolaryngol Head Neck Surg 2013;149(1 Suppl):S1-35.
12. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical Practice Guideline: Otitis Media with Effusion (Update). Otolaryngol Head Neck Surg 2016;154 (1 Suppl):S1-S41.
13. Ungkanont K, Boonyabut P, Komoltri C, Tanphaichitr A, Vathanophas V. Surveillance of Otitis Media With Effusion in Thai Children With Cleft Palate: Cumulative Incidence and Outcome of the Management. Cleft Palate Craniofac J 2018;55: 590-5.
14. Smillie I, Robertson S, Yule A, Wynne DM, Russell CJ. Complications of ventilation tube insertion in children with and without cleft palate: a nested case-control comparison. JAMA Otolaryngol Head Neck Surg 2014;140:940-3.
15. Felton M, Lee JW, Balumuka DD, Arneja JS, Chadha NK. Early Placement of Ventilation Tubes in Infants with Cleft Lip and Palate: A Systematic Review. Otolaryngol Head Neck Surg 2018;158:459-64.
16. Huang CY, Wu CS, Tang CH, Wang MC, Kuo TY, Tu TY. Palatoplasty decreases the re-insertion rate of middle ear ventilation tube in cleft palate children - A population-based birth cohort study. Acta Otolaryngol 2016;136:768-74.
17. Kim E, Kanack MD, Dang-Vu MD, Carvalho D, Jones MC, Gosman AA. Evaluation of Ventilation Tube Placement and Long-term Audiologic Outcome in Children With Cleft Palate. Cleft Palate Craniofac J 2017;54:650-5.
18. Ahn JH, Kang WS, Kim JH, Koh KS, Yoon TH. Clinical manifestation and risk factors of children with cleft palate receiving repeated ventilating tube insertions for treatment of recurrent otitis media with effusion. Acta Otolaryngol 2012;132: 702-7.
19. Sundman H, Flynn T, Tengroth B, Lohmander A. ABR thresholds in infants born with CLP and OME and infants with OME. Int J Pediatr Otorhinolaryngol 2016;81:21-5.
20. Tengroth B, Lohmander A, Hederstierna C. Hearing Thresholds in Young Children With Otitis Media With Effusion With and Without Cleft Palate. Cleft Palate Craniofac J 2020;57:616-23.

Change in Corneal Endothelial Cell Density after Baerveldt Shunt Implantation in Glaucoma Patients

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ABSTRACT

Objective: To evaluate changes in corneal endothelial cells density (EDC) at 1 one, six, and twelve months after Baerveldt shunt implantation.

Materials and Methods: This prospective study included 24 patients who underwent Baerveldt shunt implantation for refractory glaucoma, and who had one full year of post-surgical follow-up. Best corrected visual acuity (BCVA), intraocular pressure (IOP), number of glaucoma medications, central corneal thickness (CCT), corneal endothelial cell density (EDC), and morphology in central, inferior, and superotemporal (stEDC) areas were recorded at baseline, and 1, 6, and 12 months after surgery. Distance between the tip of tube to corneal endothelium (TTC) was measured using optical coherence tomography at one month after surgery.

Results: Twenty-four eyes from 24 patients were analyzed. Sixty-two percent were primary open-angle glaucoma, and 73.1% of patients had previous trabeculectomy. Mean BCVA was not significantly changed. The mean IOP at six months (12.2±4.35 mmHg) and at one year (11.1±4.31 mmHg) was significantly lower than baseline (20.1±9.24 mmHg) (p<0.001 and p<0.001 respectively). Median (min, max) number of anti-glaucoma medications significantly decreased from 4 (1, 6) at baseline to 1 (0, 3) and 1 (0, 3) at six months and one year after surgery (p<0.001 and p<0.001, respectively). Mean baseline stEDC was 1,527±644 cells/mm^2. From linear mixed model, stEDC showed the most significantly decreasing slope (y=1365.54 – 18.6125t, p=0.014), and CCT showed a significant increase over time (y=533.65 + 1.8853t). Pearson's correlation coefficient between TTC and stEDC change at one year was not statistically significant (-0.403, p=0.172).

Conclusion: After Baerveldt shunt implantation, EDC loss over time was found in the area closest to where the tube was placed in addition to increasing CCT. Distance from tip of tube to cornea is not the only factor that can cause EDC loss after shunt implantation. Additional study to identify other possible mechanisms is warranted.

Keywords: Corneal endothelial cells; Baerveldt shunt implantation; glaucoma; Thailand (Siriraj Med J 2021; 73: 252-258)

INTRODUCTION

Drainage implant surgery is one of the most effective treatments for refractory glaucoma.[1] Compared to conventional trabeculectomy, drainage implant surgery was shown to have a higher success rate for controlling intraocular pressure (IOP) during 5 years of follow-up in patients who had previous trabeculectomy and/or cataract extraction.[1] Many types of shunts have been introduced since Molteno introduced his first glaucoma drainage devices.[2] Baerveldt shunt is one of the contemporary drainage devices that was shown to achieve satisfactory pressure reduction in many studies.[1,3,4] Many studies

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have compared the efficacy and complications of widely used devices. Among those, a randomized controlled trial compared the Baerveldt shunt with the Ahmed shunt. The results of that study revealed a higher success rate in the Baerveldt group; however, the Baerveldt shunt requires a greater number of interventions than the Ahmed shunt.[4]

Although glaucoma drainage implantation has demonstrated good efficacy in refractory glaucoma cases, this intervention can result in endothelial cell density (EDC) loss with severe adverse effect in some cases.[5-12] Various mechanisms of EDC loss have been proposed. One hypothesis is that mechanical trauma caused by introduction of a silicone tube into the anterior chamber could effectuate EDC loss. The result from a two-year prospective study of 41 eyes after superotemporal Ahmed implantation found endothelial cell loss compared to control eyes, and cell loss was greatest in the superotemporal cornea where the tube was placed.[8] Another theory suggests that change in flow or composition of aqueous humor after glaucoma surgery could be a cause of EDC loss. This hypothesis arose after EDC loss was observed in eyes whose anterior chamber had not been penetrated by a silicone tube.[13,14]

The primary aim of this prospective study was to evaluate changes in EDC after Baerveldt shunt implantation by comparing post-surgical EDC parameters at one, six, and twelve months to baseline. Due to the uncertain mechanism of EDC loss, our secondary aim was to investigate whether tube and endothelial distance correlate with endothelial cell change.

MATERIALS AND METHODS

This prospective study enrolled patients under the care of one of the authors (N.R.) who was scheduled for Baerveldt shunt implantation at the Department of Ophthalmology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during July 2010 to July 2017. The indication for surgery were secondary glaucoma and any cases with uncontrolled intraocular pressure after conventional trabeculectomy. The exclusion criteria were patients with corneal opacity or lesion that could obscure corneal endothelial cell count examination such as Haab striae in congenital glaucoma and pseudophakic bullous keratopathy. Any patient that developed serious complication or who required additional intraocular surgery was withdrawn from the study. Only patients with at least one full year of postoperative follow-up were included in the final analysis. Eventually, 24 eyes from 24 patients were enrolled, and written informed consent was obtained from all participants. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (Si 676/2010).

Age at surgery, gender, type of glaucoma, history of previous laser or intraocular surgery, other ocular disease, and anti-glaucoma drugs were recorded. Best corrected visual acuity (BCVA), a thorough eye examination using slit-lamp biomicroscope, and IOP using a Goldmann applanation tonometer were obtained at every visit. Postoperatively, any surgical complication and number of anti-glaucoma medications were recorded. After shunt operation, anti-glaucoma medication was initiated to maintain individual target IOP.

Corneal endothelial cell density (EDC) and central corneal thickness (CCT)

EDC and CCT were measured at baseline, and at 1, 6, and 12 months after surgery. EDC was measured in 3 different areas of the cornea, including central, superotemporal, and inferior by one experienced technician (PC) using a Nidek-CS4 confocal microscope (Nidek Co. Ltd, Japan). Only the manual center dot method was used. CCT was measured by optical coherence tomography (Visante; Carl Zeiss Meditec, Germany).

Distance from tip of the tube to corneal endothelium (TTC)

Tip of tube to corneal endothelium distance perpendicular to posterior cornea was measured using optical coherence tomography (Visante; Carl Zeiss Meditec) at one month after surgery by the same technician. Patients were asked to look at the internal fixation light and the scanning axis was placed along the tube. The technician took special care not to apply pressure to the eye.

Surgical details

All cases were implanted with the same Baerveldt shunt model (model BG101-350, which has a surface area of 350 mm^2; Abbott Medical Optics, Inc., Santa Ana, CA, USA) at the superotemporal region. Using the standard technique, all shunts was inserted by a single surgeon (NR). A 7-0 traction suture was placed at the superotemporal cornea to expose the superotemporal conjunctiva. A conjunctival flap was made by 12-14 mm length conjunctival incision that was made parallel to and 8 mm posterior to the limbus. Muscle hooks were used to identify the superior and lateral rectus muscles. The superior rectus was isolated and retracted from the globe with a muscle hook. A second muscle hook was inserted under the belly of the muscle more posteriorly to aid in elevation and retraction. Both implant wings were placed under the superior and medial rectus muscles.

The implant was then sutured to the sclera with 8-0 virgin silk suture through the suture holes. The suture knots were rotated into the suture hole eyelets. Scissors were used to cut the tube so that approximately 1-2 mm of tube length would be inside the eye with an upward-facing bevel. The tube was then ligated within a few millimeters of the implant flange with 6-0 Vicryl. The tube was checked for complete occlusion by inserting a 30-gauge cannula at the cut end, and an attempt was made to flush saline. A clear cornea paracentesis was made at 9 o'clock using a 15-degree blade. The anterior chamber at the intended area for needle track internal opening was deepened with viscoelastic. A 23-gauge needle was used to create a track aim for the tube parallel to the iris plane. The tube was then inserted through the track. Once it was in proper position, the tube was sutured to the episclera with 10-0 nylon. Early filtration was aided by piercing the tube anterior to the ligation using a 15-degree blade (Sherwood's method). The tube was then covered with scleral graft with interrupted 10-0 nylon anchoring sutures. Tenon along with conjunctiva were sutured using 8-0 virgin silk and 10-0 nylon running suture. The wound was tested for water tightness. Dexamethasone (4 mg/ml) 0.5 ml was injected subconjunctivally into the inferior quadrant.

After the operation, a 1% prednisolone acetate eye drop was given every 2 hours during the first few weeks, with a tapered decrease to discontinuation by the 3-month postoperative time point. A 0.5% levofloxacin eye drop was given 4 times daily, and a 0.3% tobramycin and 0.1% dexamethasone eye ointment was given once before bedtime for several months according to wound healing and inflammation. Anti-glaucoma drugs were managed according to the target IOP level.

Statistical analysis

All data analyses were performed using SPSS software version 18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize patient demographic and clinical characteristics, and those results are reported as number and percentage, mean plus/minus standard deviation, or median (minimum, maximum). Wilcoxon signed-rank test was used to compare non-normally distributed continuous data, while paired *t*-test was used to compare normally distributed continuous data. Random intercept mixed model was used to create the equation to evaluate EDC and CCT change over time. Pearson's correlation coefficient was used to determine the correlation between TTC and EDC loss. A *p*-value less than 0.05 was considered statistically significant for all tests.

RESULTS

There were 31 patients (31 eyes) who underwent uneventful Baerveldt shunt implantation at Siriraj Hospital by a single experienced surgeon (NR) during June 2010 to July 2017. Two eyes were withdrawn from the study due to conjunctival wound leak with hypotony and recurrent granulomatous anterior uveitis. Five eyes were excluded from analysis due to ≤ 2 postoperative EDC measurements. All 24 patients completed one full year of follow-up, and all patients had baseline EDC measurement and at least 3 postoperative EDC measurements. P demographic and clinical data is summarized in Table 1. The mean preoperative stEDC was 1,527±644 cell/mm^2.

Mean visual acuity was not significantly changed between before and after surgery; however, mean IOP and the median number of anti-glaucoma medications were significant lower compared to baseline (Table 2). Table 3 showed mean EDC in particular regions at baseline and post-operative time points. Table 4 showed mean CCT at baseline and post-operative time points. According to the results of mixed model analysis (Table 5), EDC decreased over time during the one-year period after Baerveldt shunt implantation, with the greatest rate of decrease in the superotemporal region, and CCT was observed to have increased. Endothelial cell loss at 1 year was 18.07%, 8.79%, and 9.18% at the superotemporal, central, and inferior cornea, respectively. The mean CCT at baseline, and at 1, 6, and 12 months is shown in Fig 1.

Pearson's correlation coefficient revealed no statistically significant correlations between TTC and EDC change for any region (Table 6).

DISCUSSION

In this study, we investigated whether there is EDC loss after Baerveldt shunt implantation, and whether TTC correlates with EDC loss.

We found EDC loss, which is supported by the result from linear mixed model (Table 3). The greatest negative multiplier with time of stEDC emphasized the greatest EDC loss rate in that region.

The percentage of EDC loss at one year was consistent with previous studies.[15,16] One retrospective study showed 10.7% of endothelial cell loss at one year, which is comparable to our findings (8.79%). We measured EDC loss at the superotemporal cornea, whereas the previous study made their measurement at the central cornea. Other studies reported EDC loss to be greatest at the cornea quadrant where the tube was placed.[11,16,17] Iwasaki and associates found 13.1% EDC loss, which is lower than our findings. This difference may have resulted from their greater

TABLE 1. Patient characteristics.

Characteristics	N
Number of patients, n	24
Age, median (min, max), years	65 (29,80)
Gender, n (%)	
Male	15 (62.5%)
Type of glaucoma, n (%)	
POAG	15 (62.5%)
PACG	3 (12.5%)
JOAG	1 (4.2%)
Secondary glaucoma	5 (20.8%)
Uveitis	3
Steroid induced glaucoma	1
Lens subluxation	1
Lens status	
Pseudophakia	23 (92%)
Aphakia	1 (8%)
Previous trabeculectomy, n (%)	19 (73.1%)
Number of previous intraocular surgery, n (min, max)	1.76 (1,3)
Baseline stEDC	1527 ± 644
Distance between tip of the tube to endothelium	1.4 ± 0.6

Abbreviations: JOAG, juvenile open angle glaucoma; PACG, primary angle closure glaucoma; POAG, primary open angle glaucoma; SD, standard deviation; VKH; stEDC, superotemporal endothelial cell density.

TABLE 2. IOP and number of anti-glaucoma medications before and after Baerveldt shunt implantation.

Parameters	N	Value	p-value
IOP, mean ± SD, mmHg			
Baseline	26	20.12 ± 9.24	
1 month	26	17.73 ± 8.12	0.288*
6 months	26	12.15 ± 4.35	<0.001*
12 months	24	11.08 ± 4.31	<0.001*
Number of anti-glaucoma medications, median (min,max)			
Baseline	26	4 (1,6)	
1 month	26	1 (0,5)	<0.001 †
6 months	26	1 (0,3)	<0.001 †
12 months	24	1 (0,3)	<0.001 †

Notes: * Paired T-test, † Wilcoxon signed-rank test
p-value < 0.05 was considered statistical significance.
Abbreviations: IOP, intraocular pressure; SD, standard deviation.

TABLE 3. Mean EDC before and after Baerveldt shunt implantation.

Region	Baseline after operation	1 month after operation	6 months after operation	12 months
stEDC (mean ± SD)	1526.6±644.29	1420.8± 558.85	1364.8± 625.9	1289.3± 594.24
cEDC (mean ± SD)	1504.9±486.21	1588.2±534.10	1545.5±534.82	1476.2±542.51
iEDC (mean ± SD)	1406.3±497.01	1387.8±474.42	1401.7±482.72	1319.6±528.67

Abbreviations: stEDC, superotemporal endothelial cell density; cEDC, central endothelial cell density; iEDC, inferior endothelial cell density

TABLE 4. The correlation between distance from tip of the tube to corneal endothelium and EDC change.

Time	CCT (micron) Mean ± SD
Baseline	529.61±29.919
1 month after operation	521.55±39.946
6 months after operation	525.20±29.169
12 months after operation	535.80±25.548

Abbreviation: CCT, Central corneal thickness

TABLE 5. Linear mixed model equations for EDC and CCT change over time.

Parameters	Equation (mixed model)	p-value t, t^2
stEDC	y=1365.54-18.6125t	0.0144
cEDC	y=1518.44-5.2495t	0.1775
iEDC	y=1373.54-6.0106t	0.2210
CCT	y=533.65 + 1.8853t	0.0137

t = month

Abbreviations: stEDC, superotemporal endothelial cell density; cEDC, central endothelial cell density; iEDC, inferior endothelial cell density

TABLE 6. The correlation between distance from tip of the tube to corneal endothelium and EDC change.

Time	Site	Pearson correlation	p-value
6 months	stEDC	-0.340	0.112
	iEDC	0.172	0.382
	cEDC	0.130	0.510
12 months	stEDC	-0.403	0.172
	iEDC	-0.049	0.869
	cEDC	0.165	0.541

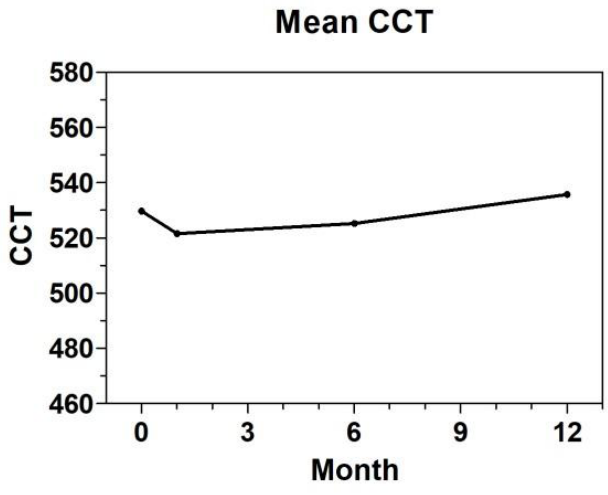

Fig 1. Mean Central corneal thickness after baerveldt shunt implantation

baseline EDC compared to our patients (2,107±625 cells/mm^2 *vs.* 1,527±644 cells/mm^2, respectively) since the lower EDC cornea is more susceptible to any cause of damage. There was one prospective study that found a rate of EDC loss of 7.43% per year, which is comparable to our study.[17]

From linear mixed model - stEDC, which was the quadrant closest to the tube in the anterior chamber, was found to be the most affected region of the 3 evaluated regions (Table 5). The local effect of EDC loss is comparable to previous reports.[11,15,17] Moreover, from the model we found increased CCT, which might represent early sign that could lead to corneal decompensation. Corneal decompensation after glaucoma drainage device implantation has been reported previously.[9,18] In the present study, we found increased CCT and decreased stEDC, which is comparable to Koo and colleagues who found an inverse correlation between CCT and superotemporal endothelial cell count in patients with EDC less than 1,000 cells/mm^2.[11]

Even though we found local EDC loss at the cornea quadrant where the tube was placed, we did not find TTC to be significantly correlated with EDC loss. In contrast, Iwasaki and colleagues reported that tube to cornea angle negatively correlated with EDC loss (Pearson's correlation -0.55, p=0.0013).[16] In the present study, we used a different tube to cornea parameter that may not be comparable. A cross-sectional study reported TTC to be the only significant predictor of EDC loss at superotemporal cornea compared to inferior cornea.[11] The lack of baseline and longitudinal data is the limitation of the study mentioned. Apart from that, the mean tube to cornea distance in the previous study was 1.1±0.8 mm compared to 1.4±0.6 mm in our study. The closer the tube is to cornea might result in greater damage to endothelium.

Many theories have been proposed to explain corneal endothelial cell loss after shunt surgery. Mechanical trauma could be caused by tube motility. Tan and associates found greater EDC loss in the 'Free' tube in the anterior chamber subgroup compared to 'Transiridial' tube, which may suggest that the tube is more stable with transiridial technique. There was no significant difference between those two subgroups relative to TTC (1.7±0.5 mm and 1.6±0.7 mm for 'Free' tube and 'Transiridial' tube, respectively). Another possible mechanism is a change in composition and/or flow of aqueous humor. Cytokines that are released due to a foreign body reaction to the plate could flow from bleb to the anterior chamber via the tube.[19] Instead of flowing symmetrically through the trabecular meshwork, aqueous humor flow to the tube could alter the environment with resulting adverse impact to endothelial cells.[19,20] In the future, study of how aqueous humor change in composition and flow could affect EDC after glaucoma shunt implantation should be conducted.

There are several limitations in this study. First, the tube parameter was TTC at 1-month post-operation, which may have been too early to determine whether or not tube migration occurred during follow-up time. There were 12 eyes from 24 eyes that had tube distance measured at 1st and 6th to 12th months. The mean difference in tube distance between 1st and 6th to 12th month was 0.08±0.189 mm closure to cornea (range: 0.53 mm closer to cornea to 0.14 mm away from cornea). This represents a small change in tube distance.

Second, tube to cornea angle, tube motility, and tube length were not measured, and one, two, or all three of these factors could influence EDC loss. Third, we included primary and secondary glaucoma, which could result in corneal endothelial cell loss. However, 79.2% of patients were primary glaucoma with no history of acute angle closure that could result in dramatic endothelial cell loss. Comparing secondary and primary glaucoma, there is no statistically significant difference in the mean EDC and stEDC at every time point. The effect of previous surgeries cannot be totally eliminated since in clinical practice, shunt surgery is reserved for refractory glaucoma cases. In this study, all cases had undergone cataract surgery. We found that after shunt surgery, endothelial cell loss (8.79%) is greater compared to a previous report of corneal endothelial cell loss in cataract surgery alone (2.06%)[21]. Therefore, the observed endothelial cell loss resulted from shunt surgery rather than cataract surgery.The only previous glaucoma surgery was trabeculectomy with mitomycin-C, which was performed in 69.2% of patients. Moreover, all of

those operations were performed more than 6 months before shunt operation. In trabeculectomy, endothelial cell loss was found during the immediate postoperative period, which is less than 3 months post-operation. Our patients had trabeculectomy performed longer than 6 months; therefore, the effect from trabeculectomy should be considered minimal at best. Lastly, we did not measure the level of inflammation or cytokine release before and after shunt implantation. Further study designed to investigate or account for these factors about these possible factors will yield more information about tube-induced EDC loss.

The present study emphasizes that the tube can induce local EDC loss in the cornea quadrant nearest to the tube after Baerveldt shunt implantation. The mechanism is still unclear, but other mechanisms apart from the distance from tip of tube to cornea should be studied.

CONCLUSION

After Baerveldt shunt implantation, EDC loss over time was found in the area closest to where the tube was placed in addition to increasing CCT. Distance from tip of tube to cornea is not the only factor that can cause EDC loss after shunt implantation. Additional study to identify other possible mechanisms is warranted.

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REFERENCES

1. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 2012;153:789-803.e2.
2. Lim KS, Allan BD, Lloyd AW, Muir A, Khaw PT. Glaucoma drainage devices; past, present, and future. British journal of ophthalmology, Br J Ophthalmol 1998;82:1083-9.
3. Seah SKL, Gazzard G, Aung T. Intermediate-term outcome of Baerveldt glaucoma implants in Asian eyes. Ophthalmology 2003;110:888-94.
4. Christakis PG, Kalenak JW, Zurakowski D, Tsai JC, Kammer JA, Harasymowycz PJ, et al. The Ahmed Versus Baerveldt study: one-year treatment outcomes. Ophthalmology 2011;118:2180-9.
5. Hau S, Barton K. Corneal complications of glaucoma surgery. Curr Opin Ophthalmol 2009;20:131-6.
6. Hollander DA, Giaconi JA, Holland GN, Yu F, Caprioli J, Aldave AJ, et al. Graft failure after penetrating keratoplasty in eyes with Ahmed valves. Am J Ophthalmol 2010;150:169-78.
7. Casini G, Loiudice P, Pellegrini M, Sframeli AT, Martinelli P, Passani A , et al. Trabeculectomy Versus EX-PRESS Shunt Versus Ahmed Valve Implant: Short-term Effects on Corneal Endothelial Cells. Am J Ophthalmol 2015;160(6):1185-90.e1.
8. Lee E-K, Yun Y-J, Lee J-E, Yim J-H, Kim C-S. Changes in corneal endothelial cells after Ahmed glaucoma valve implantation: 2-year follow-up. Am J Ophthalmol 2009;148:361-7.
9. McDermott ML, Swendris RP, Shin DH, Juzych MS, Cowden JW. Corneal endothelial cell counts after Molteno implantation. Am J Ophthalmol 1993;115:93-96.
10. Hau S, Scott A, Bunce C, Barton K. Corneal endothelial morphology in eyes implanted with anterior chamber aqueous shunts. Cornea 2011;30:50-55.
11. Koo EB, Hou J, Han Y, Keenan JD, Stamper RL, Jeng BH, et al., Effect of glaucoma tube shunt parameters on cornea endothelial cells in patients with Ahmed valve implants. Cornea 2015;34:37-41.
12. Koo EB, Hou J, Keenan JD, Stamper RL, Jeng BH, Han Y.Effects of Glaucoma Tube Surgery on Corneal Endothelial Cells: A Review. Eye Contact Lens 2016;42:221-4.
13. Rososinski A, Wechsler D, Grigg J. Retrospective review of pars plana versus anterior chamber placement of Baerveldt glaucoma drainage device. J Glaucoma 2015;24:95-99.
14. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol 2012;153:789-803.e2.
15. Kim CS, Yim JH, Lee EK, Lee NH. Changes in corneal endothelial cell density and morphology after Ahmed glaucoma valve implantation during the first year of follow up. Clin Exp Ophthalmol 2008;36:142-7.
16. Iwasaki K, Arimura S, Takihara Y, Takamura Y, Inatani M. Prospective cohort study of corneal endothelial cell loss after Baerveldt glaucoma implantation. PLoS One 2018;13:e0201342.
17. Tan AN, Webers CAB, Berendschot TTJM, Brabander J, Witte PM, Nuijts RMMA, et al. Corneal endothelial cell loss after Baerveldt glaucoma drainage device implantation in the anterior chamber. Acta Ophthalmol 2017;95:91-96.
18. Kim KN, Lee SB, Lee YH, Lee JJ, Lim HB, Kim CS. Changes in corneal endothelial cell density and the cumulative risk of corneal decompensation after Ahmed glaucoma valve implantation. Br J Ophthalmol 2016;100:933-8.
19. Freedman J, Iserovich P. Pro-inflammatory cytokines in glaucomatous aqueous and encysted Molteno implant blebs and their relationship to pressure. Invest Ophthalmol Vis Sci 2013;54:4851-5.
20. Tuulonen A, Risteli J, Risteli L, Välimäki J, Airaksinen PJ. Collagen synthesis activity in the aqueous humour of eyes with glaucoma surgery: a pilot study. Br J Ophthalmol 1996;80:74-77.
21. Choi JY, Han YK. Long-term (≥10 years) results of corneal endothelial cell loss after cataract surgery. Can J Ophthalmol 2019;54:438-44.

Costs per DALYs Averted of Quadrivalent Influenza Vaccine versus Trivalent Influenza Vaccine in Elderly Population in Thailand

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ABSTRACT

Objective: Influenza is an infection of the respiratory system with a high annual incident rate. Influenza vaccine can reduce the severity of influenza and prevent transmission of the virus. Influenza vaccines in Thailand are the Trivalent Influenza Vaccine (TIV) and the Quadrivalent Influenza Vaccine (QIV). The cost and the effectiveness of the QIV in preventing transmission of the virus are greater than the TIV. Until now, no studies have been conducted to compare the economic impact of using QIV or TIV. This study aimed to evaluate the economic effects of using QIV versus TIV in Thai populations age 60 years and over.

Materials and Methods: The study was carried out from a societal perspective for cost per DALYs averted. A decision tree model was used to analyse the costs and DALYs averted of Thais after they received the vaccine.

Results: In a period of one year, it was found that in Thais age 60 years and over, the total cost of TIV was 2,445.19 baht with 0.0094 DALYs and total cost of the QIV was 2,629.28 baht with 0.0082 DALYs and the incremental cost-effectiveness ratio (ICER) of the QIV was 158,489.24 baht per DALYs averted. The acceptability curves demonstrated that the probability of QIV being cost-effective was 95% of the willingness to pay, being 1.2 times the Thai gross national income per capita.

Conclusion: Therefore, in Thai people age over 60 years and over, QIV is more cost-effective than TIV. The results of this study can be used by policymakers to help inform their decisions about which influenza vaccine is more cost-effective.

Keywords: Cost-effectiveness; DALYs averted; Influenza vaccine; Influenza; Trivalent Influenza Vaccine; Quadrivalent Influenza Vaccine (Siriraj Med J 2021; 73: 259-267)

INTRODUCTION

Influenza is a respiratory infection caused by the influenza virus.[1] There are three types of viruses that cause influenza in humans: A, B, and C. Influenza A has been a cause of worldwide pandemics (subtypes H1N1 and H3N2). Whereas influenza B has contributed to regional outbreaks only and influenza C is even less common.[1,2] Overall influenza occurs globally with an incidence rate of 5–10% in adults and 20–30% in children.[3]

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The World Health Organization (WHO) estimated that there are up to 650,000 deaths associated with influenza each year.[4] In Thailand in 2019, there were 390,733 cases with 27 leading to death. The mortality rate was 6.91 per 100,000 population.[5]

Vaccination is the most effective strategy to protect against influenza infection and to reduce its severity.[2] Each year WHO announces three virus strains that will be used in the manufacture for the trivalent influenza vaccine (TIV). Based on recommendations from WHO, Trivalent influenza vaccines contain two strains of A subtypes (H1N1 and H3N2) and one influenza B lineage from either the Yamagata or the Victoria lineage.[6,7] TIV effectiveness against A/H1N1 A/H3N2 and B/Yamagata lineage were 65%, 24%, and 49%[8], respectively. TIV needs to be evaluated annually to see whether its composition needs to be adjusted. This evaluation is based on the influenza strains that are expected to be in circulation during the upcoming influenza season. In Thailand from 2007 to 2012, there was a mismatch of 50% between the influenza B component of TIV and the result was a suboptimal vaccine. This mismatch led to the development of the Quadruple Influenza Vaccine (QIV). QIV contains two strains of influenza A and both B lineages (Yamagata and Victoria). QIV provides coverage and protection against the TIV-mismatched influenza B lineage.[9] Currently, the United States, Canada, Australia and the United Kingdom recommend QIV.[10] The efficacy of QIV (immune response) is 70% and TIV is 59%.[11,12] QIV would prevent influenza B 16% more than TIV.[11] These studies have shown that QIV is more effective than TIV.

From a systematic review, the influenza vaccine was not cost-effective in the population ages 18-59 years from a societal perspective.[13-15] So the influenza vaccination depends on each need. However some studies show the influenza vaccine was cost-effective in the population 60 years and over from a societal perspective.[16-25] The influenza vaccine is part of the health policy in Thailand and many other countries.[26,27] In Thailand, QIV is recommended as an alternative to TIV, but is more costly.[9] Also, hitherto now, a study had not been conducted comparing the cost-effectiveness of QIV and TIV. This study evaluated the cost-effectiveness between QIV and TIV from a societal perspective in Thai people ages 60 and over. Furthermore, the purpose of this study was to evaluate the economic outcomes between QIV and TIV and to develop a health policy for influenza vaccination.

MATERIALS AND METHODS

Study design

This study was a model-based economic evaluation in health technology assessment. A decision tree model was developed to compare the cost-effectiveness analysis from a societal perspective.

Intervention

There are 2 types of influenza vaccines in Thailand which are TIV and QIV. TIV includes influenza A (H1N1), influenza A (H3N2) and one lineage of influenza B which is based on recommendations from WHO, while QIV contains the same lineage as TIV and has another B lineage. The influenza vaccine is administered by an intramuscular injection of 0.5 ml once a year, due to the change in circulatory disseminated strains every year.

Decision Model

The decision tree model[28] was used to perform decision analysis. The study population was divided into two groups, those who received QIV and those who received TIV. Afterwards, when any of the population bacame infected by influenza and received treatment in a hospital, they were divided into an inpatient or an outpatient group, which had different levels of severity for symptoms and expenses. The model is presented in Fig 1 and was developed and validated by two experts with M.D. and Ph.D. degrees.

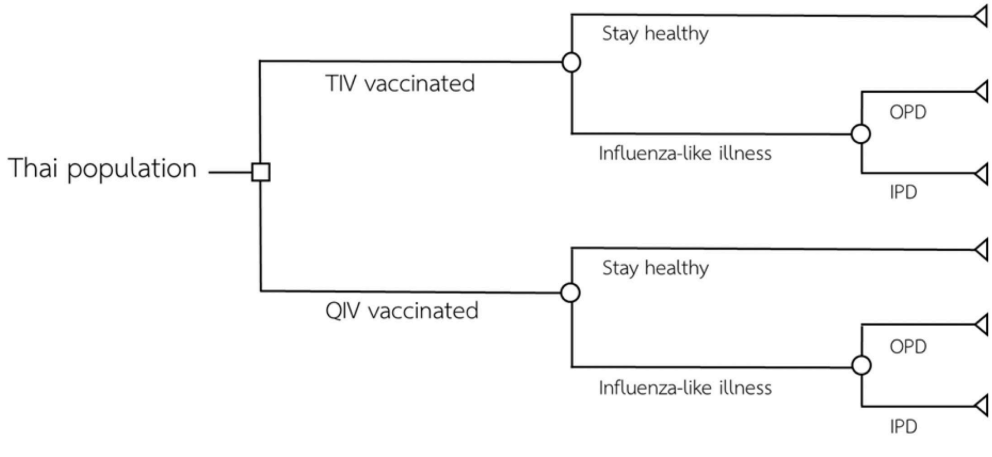

Fig 1. The decision tree model

Assumptions of the model

1. The study population is Thais ages 60 years and over.
2. The population in this model received the vaccination once a year.[29]
3. This model does not consider the occurrence of adverse reactions caused by receiving 3 species of TIV and 4 species of QIV.[29-32]
4. This model does not consider the very rare Guillain-Barré syndrome.[33]
5. This model does not consider the immunity.
6. The patients with symptoms of influenza infection received outpatient and inpatient treatment.
7. The coverage of influenza vaccination was 66%.[33]

Time Frame

The economic evaluation was considered by using a 1 year study framework to track the results of receiving TIV and QIV, since the influenza vaccine can prevent influenza in the first year of the outbreak.

Probability of clinical outcomes

A systematic search was conducted in PubMed, Cochrane Library, Scopus and Science Direct. The keywords were "Thailand", "Quadrivalent influenza vaccine", "Trivalent influenza vaccine" and "effectiveness". Two independent reviewers surveyed titles, abstracts, and articles based on the study eligibility criteria. The studies were identified as eligible for inclusion if they were published as full text and in the English language. All probabilities were obtained from the study which was included (i) randomized control trial, systematic review, or meta-analysis. If none of these were available an observational study was included instead and comprised (ii) a comparison of efficacy between QIV and TIV (iii) and injectable influenza vaccine (iv) through 2019. The studies were excluded if they met any of the following exclusion criteria: (i) non-English language and (ii) no full text. All probabilities are shown in Table 1.

Costs

All costs were expressed in Thai baht and are shown in Table 2. Cost of Quadrivalent Influenza Vaccine (per dose) was derived from the Hospital for Tropical Disease[34] and cost of TIV (per dose) was derived from the health technology assessment program.[33] All direct non-medical costs such as cost of transportation to the hospital, food, outpatient and inpatient treatment and productivity loss were obtained from the standard cost lists for health technology assessment in Thailand.[33]

All costs were adjusted to 2020 values using the consumer price index from the Bureau of Trade and Economic Indices, The Ministry of Commerce, Thailand.

Disability weight

Disability weight was used to measure outcomes. The humanistic outcomes were measured in disability weight for different health states after Thais received the vaccination. The average life expectancy in Thai people age 60 years and over was 14.49 years.[36] Disability weights were obtained from health technology assessment programme[33] and are shown in Table 3.

Sensitivity analysis

The one-way sensitivity analysis was performed by Microsoft Excel 2016. The parameter values were changed one by one, usually to a low and a high value. The results are presented by a tornado diagram. A Monte Carlo Simulation was used for probabilistic sensitivity analyses by Microsoft Excel 2016. All variables were randomized 1,000 times by probability distribution and the ICER estimated. The result is presented as a cost-effectiveness plane.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis was conducted from a societal perspective. It analysed the cost-effectiveness of the TIV and QIV vaccination in Thai population 60 years of age and over. The result shows that the total cost of TIV was 2,445.19 baht with 0.0094 DALYs while the total cost of the QIV was 2,629.28 baht with 0.0082 DALYs, and the incremental cost-effectiveness ratio (ICER) of the QIV was 158,489.24 baht per DALYs averted.

Sensitivity analysis

The one-way sensitivity analysis in Fig 2 was presented by a tornado diagram. The results showed that probability of illness from TIV was the variable with the most impact on the ICER.

The probabilistic sensitivity analysis in Fig 3 presented the incremental costs and DALYs averted for QIV compared with TIV as a cost-effectiveness plane. Each variable was randomized 1,000 times by the Monte Carlo simulations. The base-case ICER was presented in a yellow point and falls below the willingness to pay 160,000 baht. This revealed a probability of 95% that QIV was more cost-effective than TIV as shown in Fig 4.

TABLE 1. All parameters used in the decision tree model.

Probability parameters	Distribution	Mean	SE	References
Transitional probabilities				
Trivalent influenza vaccine (TIV)				
Probability of remaining healthy	Beta	0.5900	0.0408	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection	Beta	0.410	0.0408	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an outpatient treatment	Beta	0.969	0.000172	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an inpatient treatment	Beta	0.031	0.000172	Health Intervention and Technology Assessment Program[33]
Quadrivalent influenza vaccine (QIV)				
Probability of remaining healthy	Beta	0.616	0.0419	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection	Beta	0.394	0.0419	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an outpatient treatment	Beta	0.970	0.000169	Health Intervention and Technology Assessment Program[33]
Probability of changing health state from healthy to influenza infection with received an inpatient treatment	Beta	0.030	0.000169	Health Intervention and Technology Assessment Program[33]

TABLE 2. Cost parameters used in the decision tree model.

Parameters	Distribution	Mean	SE	References
Cost parameters (baht)				
Cost of Trivalent influenza vaccine (per dose)	Gamma	208.08	20.81	Health Intervention and Technology Assessment Program[33]
Cost of Quadrivalent influenza vaccine (per dose)	Gamma	437.00	43.70	Hospital for tropical disease[34]
Vaccination fee (per dose)	Gamma	79.52	7.95	Health Intervention and Technology Assessment Program[35]
Cost of transportation to hospital (round-trip)	Gamma	209.52	20.95	Health Intervention and Technology Assessment Program[33]
Cost of food (per meal)	Gamma	36.34	3.63	Health Intervention and Technology Assessment Program[33]
Cost of productivity loss due to getting vaccination (per day)	Gamma	384.07	38.41	Health Intervention and Technology Assessment Program[33]
Cost of an outpatient treatment	Gamma	386.136	38.61	Health Intervention and Technology Assessment Program[33]
Cost of care giver's productivity loss (per day)	Gamma	384.07	38.41	Health Intervention and Technology Assessment Program[33]
Cost of an inpatient treatment	Gamma	9,221.71	922.17	Health Intervention and Technology Assessment Program[33]
Cost of care giver's food (per meal)	Gamma	36.34	3.63	Health Intervention and Technology Assessment Program[33]

TABLE 3. Disability weights used in the decision tree model.

Parameter	Distribution	Mean	SE	References
Health state				
Disability weight of symptomatic influenza infection	Beta	0.005	0.0018	Health Intervention and Technology Assessment Program[33]
Disability weight of influenza infection with out patient treatment	Beta	0.0078	0.0073	Health Intervention and Technology Assessment Program[33]
Diability weight of influenza infection with inpatient treatment	Beta	0.0217	0.0203	Health Intervention and Technology Assessment Program[33]

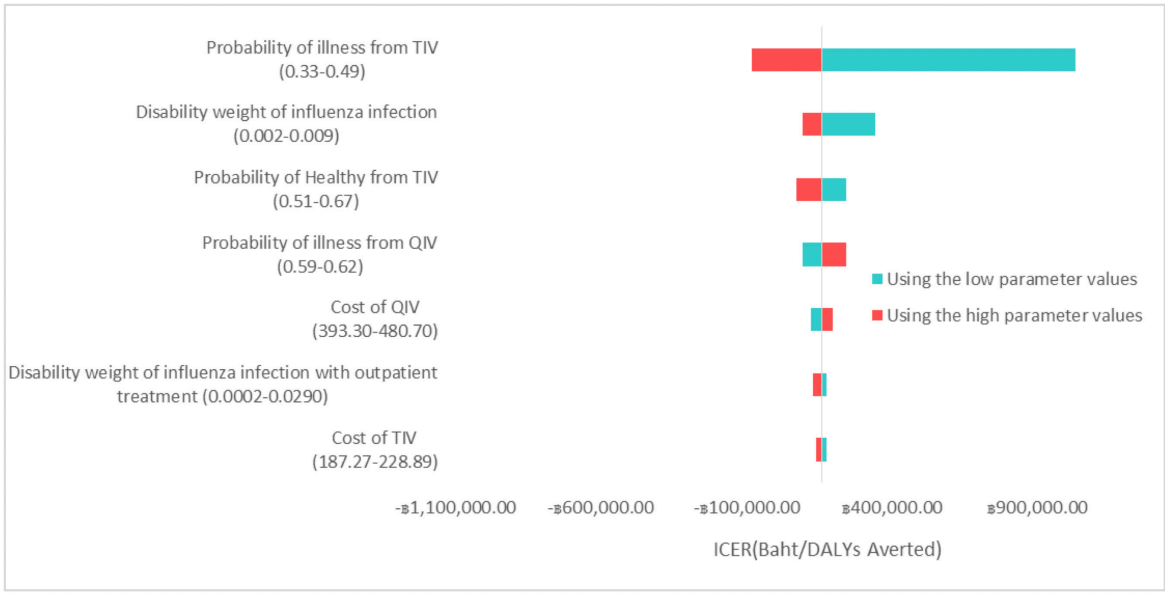

Fig 2. Tornado diagram showing the results of one-way sensitivity analysis

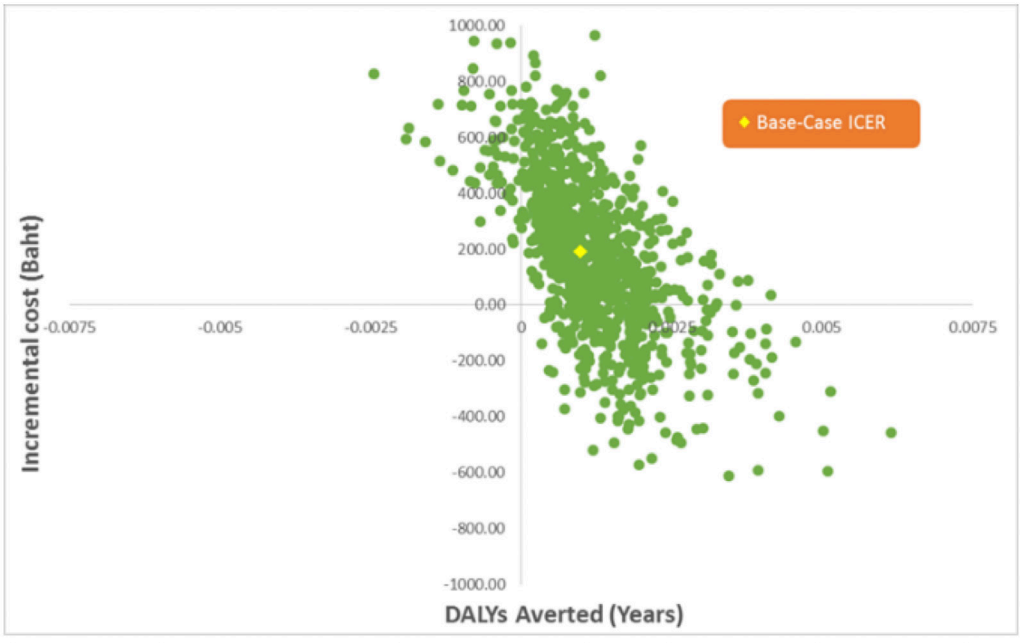

Fig 3. The cost-effectiveness plane between QIV and TIV

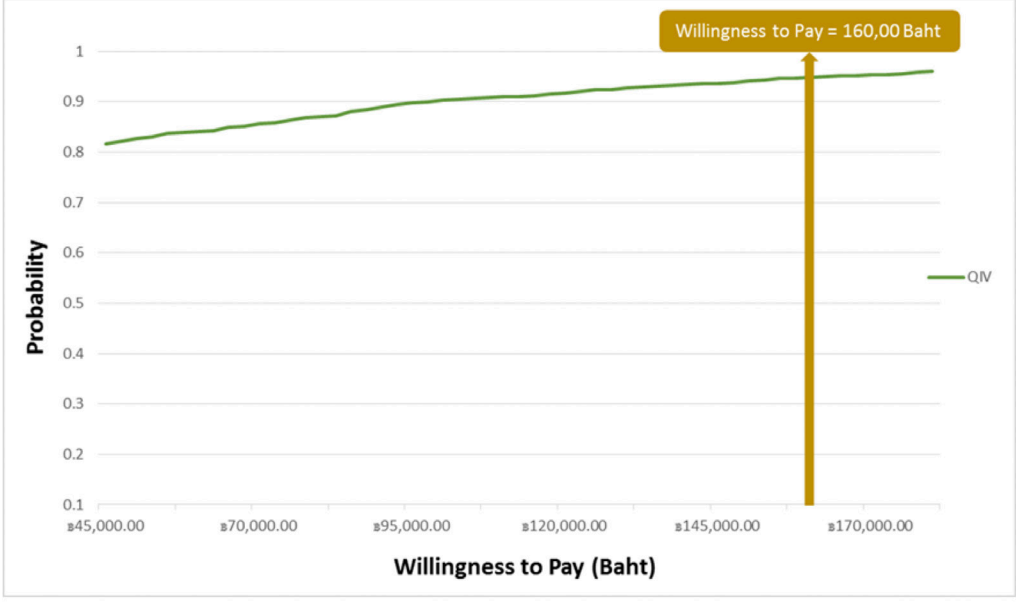

Fig 4. Acceptability curve

DISCUSSION

The cost effectiveness of the TIV and the QIV vaccination was analysed in this study. The study consists of a societal perspective, which was done in the Thai population 60 years and over. This cost effectiveness analysis was conducted to facilitate decision making regarding the selection of a vaccine. According to the Health Intervention and Technology Assessment Program (HITAP) recommendation of willingness to pay, the threshold for Thailand is 1.2 times of the gross national income (GNI) which equals 160,000 baht.[37] The results showed that QIV was more cost-effective than TIV with a probability of 95%.

Although TIV is a more attractive strategy for Thai's children, it has yet to be determined that this is so for Thai's elderly population.[7] Therefore, this study which used detailed accounting for the elderly on such metrics as life expectancy and cost, should help to clarify the current situation. This finding finds support from a corroboration of other results from previous studies from Finland[38], Germany[39] Vietnam[13] and China[40] that indicates the QIV is more cost-effective than the TIV.

According to the literature review, the effectiveness of QIV from studies in Italy, Canada, the USA, Taiwan, and Hong Kong were calculated from TIV.[41-46] Previous studies did not provide an effective report of the QIV in the Thais. However, similar analyses on the effectiveness of QIV data were collected from Kittikraisak W, et al.[9] and other studies from numerous countries. These data declare that the different rate of effectiveness between QIV and TIV is 0.16-4.6%.[9,17,41,43,47,48] However, vaccine effectiveness may be lower in Southeast Asia, and much lower in mass immunization campaign than in randomized trials.[49] In this study, the probabilistic sensitivity analysis (PSA) was done to reduce of an absence of reliable data.

Data was not only gathered on the effectiveness from many studies in years with and without an influenza epidemic, but also through the use of sensitivity analysis to predict the likelihood of an epidemic. Thus, this result may be used to consider annual vaccination in a year with and without an influenza epidemic. Limitations of this study but should not affect the conclusion. This study neglected mortality rate unrelated to influenza because it was analysed over a 1 year period only. Even though the study showed that influenza vaccination was less effective in the elderly who, at times, had to boost their dose or receive a double dose, some studies demonstrated that effectiveness did not improve.[50] Thus, this analysis did not focus on double doses or boosters. However, recent evidence reported that a high dose of influenza vaccination was more effective.[51] The analysis of the cost-effectiveness of a high-dose of TIV or QIV is recommended for further study.

This study is exempt from Human Ethics Committee (No. 60/2561) and did not receive any specific grant from funding agencies in the public or commercial domains.

CONCLUSION

Quadrivalent Influenza Vaccine is more cost-effective than Trivalent Influenza Vaccine in the prevention of influenza infection in the Thai population ages 60 years and over from a societal perspective. The results of this study could contribute to informed decision making by policymakers.

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REFERENCES

1. Bureau of Epidemiology. Influenza [cited 2018 8 November]. Available from: http://www.boe.moph.go.th/fact/Influenza.htm.
2. World Health Organization. Influenza (Seasonal) [cited 2018 8 November]. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
3. World Health Organization. Vaccines against influenza. WHO position paper November 2012. 2012.
4. World Health Organization. Up to 650 000 people die of respiratory diseases linked to seasonal flu each year 2017 [cited 2018 8 November]. Available from: https://www.who.int/news-room/detail/14-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year.
5. Department of disease control. Department of disease control warns Thai people to beware influenza infection in this winter. 2020. Available from: https://ddc.moph.go.th/brc/news.php?news=10965&deptcode=brc&news_views=1382.
6. National Institute of Health of Thailand, Department of Medical Sciences, Ministry of Public Health, Thailand. Recommended composition of influenza virus vaccines for use in the 2018 southern hemisphere influenza season, 2017.
7. Meeyai A, Praditsitthikorn N, Kotirum S, Kulpeng W, Putthasri W, Cooper BS, et al. Seasonal Influenza Vaccination for Children inThailand: A Cost-Effectiveness Analysis. PLoS Med 2015;12: 1-25.
8. Flannery B, Chung JR, Belongia EA, McLean HQ, Gaglani M, Murthy K, et al. Interim Estimates of 2017–18 Seasonal Influenza Vaccine Effectiveness — United States, February 2018. MMWR Morb Mortal Wkly Rep 2018. 2018.p.180–5.
9. Kittikraisak W, Chittaganpitch M, Gregory CJ, Laosiritaworn Y, Thantithaveewat T, Dawood FS, et al. Assessment of potential public health impact of a quadrivalent inactivated influenza vaccine in Thailand. Influenza Other Resp 2016;10:211-9.
10. de Boer PT, van Maanen BM, Damm O, Ultsch B, Dolk FCK, Crépey P, et al. A systematic review of the health economic consequences of quadrivalent influenza vaccination. Expert

Rev Pharm Out 2017;17:249-65.
11. Tisa V, Barberis I, Faccio V, Paganino C, Trucchi C, Martini M, et al. Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg 2016;57:E28-33.
12. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36-44.
13. de Boer PT, Kelso JK, Halder N, Nguyen T-P-L, Moyes J, Cohen C, et al. The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia. Vaccine 2018;36:997-1007.
14. Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. Am J Med2005;118:68-77.
15. Bridges CB, Thompson WW, Meltzer MI, Reeve GR, Talamonti WJ, Cox NJ, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA 2000;284:1655-63.
16. Patterson BW, Khare RK, Courtney DM, Lee TA, Kyriacou DN. Cost-effectiveness of influenza vaccination of older adults in the ED setting. Am J Emerg Med 2012;30:1072-9.
17. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the U.K. J Med Econ 2015; 18:746-61.
18. Maciosek MV, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Influenza vaccination health impact and cost effectiveness among adults aged 50 to 64 and 65 and older. Am J Prev Med 2006;31:72-79.
19. Brydak L, Roiz J, Faivre P, Reygrobellet C. Implementing an Influenza Vaccination Programme for Adults Aged ≥ 65 Years in Poland. Clin Drug Invest 2012;32:73-85.
20. Shields GE, Elvidge J, Davies LM. A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union. BMJ Open 2017;7: e014847.
21. Baio G, Pammolli F, Baldo V, Trivello R. Object-oriented influence diagram for cost-effectiveness analysis of influenza vaccination in the Italian elderly population. Expert Rev Pharmacoecon Outcomes Res 2006;6:293-301.
22. Lugnér AK, van Boven M, de Vries R, Postma MJ, Wallinga J. Cost effectiveness of vaccination against pandemic influenza in European countries: mathematical modelling analysis. Brit Med J 2012;345:e4445.
23. Postma MJ, Bos JM, van Gennep M, Jager JC, Baltussen R, Sprenger MJ. Economic evaluation of influenza vaccination. Assessment for The Netherlands. Pharmacoeconomics 1999;16 Suppl 1:33-40.
24. Scuffham PA, West PA. Economic evaluation of strategies for the control and management of influenza in Europe. Vaccine 2002;20:2562-78.
25. Department of Epidemiology and Department of International health policy development Moph, Thailand. Cost-effectiveness of influenza vaccine in population age over 60 years and over with chronic diseases in Thailand in 2008, 2011.
26. Centers for Disease Control and Prevention. International Influenza Report FY 2016–2017. Atlanta: US Department of Health and Human Services.
27. National Health Security Office (NHSO) T. Influenza vaccination in high risk population 2018. Available from: https://www.nhso.go.th/frontend/NewsInformationDetail.aspx?newsid=MjM0NQ==.
28. Dilokthornsakul P, Chaiyakunapruk N. Decision analysis model I: Decision tree model. Center for Continuing Pharmaceutical Education, 2016.p.1-16.
29. Infectious Disease Association of Thailand. Recommended Adult and Elderly Immunization Schedule 2018. Available from: https://www.idthai.org/Contents/Views/?d=qwzJ!17!4!!390!fb86LuPe.
30. Greenberg DP, Robertson CA, Noss MJ, Blatter MM, Biedenbender R, Decker MD. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults. Vaccine 2013;31:770-6.
31. Song JY, Lee J, Woo HJ, Wie SH, Lee JS, Kim SW, et al. Immunogenicity and safety of an egg-based inactivated quadrivalent influenza vaccine (GC3110A) versus two inactivated trivalent influenza vaccines with alternate B strains: A phase III randomized clinical trial in adults. Hum Vaccin Immunother 2019;15:710-6.
32. Trombetta CM, Gianchecchi E, Montomoli E. Influenza vaccines: Evaluation of the safety profile. Hum Vaccin Immunother 2018;14:657-70.
33. Health Intervention and Technology Assessment Program (HITAP), Department of Health, Ministry of Public Health. Cost-utility analysis of seasonal influenza vaccine among school children in Thailand, 2013.
34. Hospital for Tropical Diseases. Vaccine Price List 2020. Available from: https://www.thaitravelclinic.com/th/cost-th.html.
35. Health Intervention and Technology Assessment Program (HITAP). Standard Cost List For Health Technology Assessment 2009. Available from: http://costingmenu.hitap.net/.
36. Health Information System Development Office. Life Expectancy of Thai population. Available from: https://www.hiso.or.th/hiso/visualize/Index.php?links=v1.
37. The Subcommittee of National List of Essential Medicines Development. The Manual of Health Technology Assessment in Thailand Volume 2. Nonthaburi, Thailand: Watcharin Printing Co., Ltd, 2013.
38. Nagy L, Heikkinen T, Sackeyfio A, Pitman R. The Clinical Impact and Cost Effectiveness of Quadrivalent Versus Trivalent Influenza Vaccination in Finland. Pharmacoeconomics 2016;34:939-51.
39. Dolk C, Eichner M, Welte R, Anastassopoulou A, Van Bellinghen LA, Poulsen Nautrup B, et al. Cost-Utility of Quadrivalent Versus Trivalent Influenza Vaccine in Germany, Using an Individual-Based Dynamic Transmission Model. Pharmacoeconomics 2016;34: 1299-308.
40. Jiang M, Li P, Wang W, Zhao M, Atif N, Zhu S, et al. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine for elderly population in China. Vaccine 2020;38:1057-64.
41. Capri S, Barbieri M, de Waure C, Boccalini S, Panatto D. Cost-effectiveness analysis of different seasonal influenza vaccines in the elderly Italian population. Hum Vaccin Immunother 2018; 14:1331-41.
42. Mennini FS, Bini C, Marcellusi A, Rinaldi A, Franco E. Cost-effectiveness of switching from trivalent to quadrivalent inactivated influenza vaccines for the at-risk population in Italy. Hum Vaccin Immunother 2018;14:1867-73.
43. Thommes EW, Ismaila A, Chit A, Meier G, Bauch CT. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. Bmc Infect Dis 2015;15:465.

44. de Boer PT, Crépey P, Pitman RJ, Macabeo B, Chit A, Postma MJ. Cost-Effectiveness of Quadrivalent versus Trivalent Influenza Vaccine in the United States. Value Health 2016;19:964-75.
45. Yang MC, Tan EC, Su JJ. Cost-effectiveness analysis of quadrivalent versus trivalent influenza vaccine in Taiwan: A lifetime multi-cohort model. Hum Vaccin Immunother 2017;13:81-9.
46. You JH, Ming WK, Chan PK. Cost-effectiveness of quadrivalent influenza vaccine in Hong Kong - A decision analysis. Hum Vaccin Immunother 2015;11:564-71.
47. Chit A, Roiz J, Briquet B, Greenberg DP. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. Vaccine 2015;33:734-41.
48. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: a lifetime multi-cohort model. PloS One 2014;9:e98437.
49. Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, et al. The global circulation of seasonal influenza A (H3N2) viruses. Science 2008;320:340-6.
50. Roos-Van Eijndhoven DG, Cools HJ, Westendorp RG, Ten Cate-Hoek AJ, Knook DL, Remarque EJ. Randomized controlled trial of seroresponses to double dose and booster influenza vaccination in frail elderly subjects. J Med Virol 2001;63:293-8.
51. Saade E, Canaday DH, Davidson HE, Han LF, Gravenstein S. Chapter 3 - Special Considerations for Vaccines and the Elderly. In: Poland GA, editor. Vaccinations: Elsevier; 2019.p.35-53.

Validity and Reliability of Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF) Thai Version

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ABSTRACT

Objective: The study objective is to adapt the Lymphoedema functioning, disability and health questionnaire (Lymph-ICF) for use in the Thai language and to investigate the validity and reliability of the Thai version.

Materials and Methods: This study was done in 5 stages in line with established guidelines for cross-cultural adaptation of self-report measures; 1) Initial translation 2) Synthesis of the translations 3) Back translation 4) Expert committee review and 5) Test of the prefinal version. The face validity was assessed by interview content experts. In the assessment of the validity of the construct, the Spearman correlation coefficient was used to examine the correlations between the scores of the Thai Lymph-ICF and the scores of the Thai EQ-5D-5L. The intraclass correlation coefficient (ICC) was used to establish test-retest reliability while Cronbach's alpha was used to determine the internal consistency of the whole questionnaire and of each domain.

Results: Fifty participants were evaluated for validity and reliability. Face validity was supported. Construct validity showed strong correlations between the scores of the Thai Lymph-ICF and the scores of the Thai EQ-5D-5L. Internal consistency and test-retest reliability were both excellent.

Conclusion: The Lymph-ICF Thai version was shown to be both valid and reliable for evaluating the quality of life of patients with breast cancer-related lymphoedema.

Keywords: Breast cancer; lymphoedema; lymphoedema questionnaire; quality of life; reliability; Thai; validity (Siriraj Med J 2021; 73: 268-274)

INTRODUCTION

The study of cancer in 184 countries worldwide shows breast cancer to be the most common type of cancer in women.[1] From cancer registry data in Thailand in 2010-2012[2], breast cancer has the highest incidence among other cancers in the Thai female population, which is as high as 28.6 cases per 100,000 people.

After the successful breast cancer treatment, the survival rate is 89% at the 5th year, 83% at the 10th year and 78% at 15th year.[3] But despite the high survival rate, some patients still continue to suffer substantial adverse effects. One of the most important and most common complications is lymphoedema, which potentially affects the patient's quality of life. Although no studies

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on Thailand's incidence or prevalence of lymphedema following cancer-related breast surgery exists, a systematic review and meta-analysis found that the incidence of arm lymphedema after breast cancer treatment is 21.4%.[4] From this data, we can infer that approximately one in five Thai women will eventually develop arm lymphoedema post breast cancer treatment. Affected women can experience pain, swelling, tightness, and heaviness of the arm. All of these limit the patient's ability to perform their daily life activities. Furthermore, it leads to cosmetic embarrassment and potential compromises quality of life and social participation.

As the breast cancer related lymphoedema (BCRL) affects the patient's life in many ways, the quality of life assessment, therefore, has to include every related aspect. The Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF), which was published in 2011, is the current tool to assess the quality of life of patients with lymphoedema. The study was from 2006-2007, included 60 patients and resulted in good validity and reliability.[5]

The Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF) is more context-specific for patients suffering from BCRL when compared to other quality of life assessment tools which cover a wide range of aspects of life that can be adversely affected by ill-health. For example, Patients with BCRL don't normally have trouble with mobility and ambulation. However, other quality of life assessment tools always consist of these unnecessary domains. The Lymph-ICF encompasses all aspects of functioning and health in this group of patients including 1) physical function (heavy, stiff, swollen, lost strength, tingle, hurt, tensed skin), 2) mental function (feel sad, feel discouraged, lack of self-confidence, feel stressed), 3) household activities (clean, cook, iron, garden), 4) mobility activities (tasks with elevated arm, lift heavy objects, sleep on effected side, work on computer, sunbathe, drive a car, walk more than 2 km, cycle), and 5) life and social activities (go on vacation, perform hobbies, practice sports, wear clothes of choice, do a job, do social activities). Each of the 29 questions corresponds to a score on Visual Analogue Scale (VAS) from 0 to 100 mm. The total score and scores on each domain of the Lymph-ICF is the sum of the scores on the questions divided by the total number of answered questions. Thus, the total score on the Lymph-ICF and the scores on the 5 domains range between 0 and 100. The questionnaire has been translated and tested for the validity and reliability in many languages. The Turkish and Danish versions showed good validity and reliability and demonstrated that Lymph-CF was an effective tool to assess the quality of life of lymphoedema patients.[6,7]

With no Thai version available, this study was carried out to develop one, as well as to determine if this Thai version would be effective for assessing the quality of life in every aspect for patients with BCRL.

MATERIALS AND METHODS

The Siriraj Institutional Review Board approved this study - certificate of approval number (Si 610/2017). Participation information was read to each subject and informed consent obtained prior to participation.

Inclusion criteria were: 1) Age 18 - 80 years, 2) Diagnosed with unilateral breast cancer related Lymphoedema and 3) Ability to communicate and reply to instructions in Thai. Exclusion criteria were: 1) Lymphoedema from another cause or unknown cause 2) infection or ulcer in affected upper extremity or 3) still receiving cancer treatment.

This study was done in 5 stages in line with established guidelines for cross-cultural adaptation of self-report measures; 1) Initial translation 2) Synthesis of the translations 3) Back translation 4) Expert committee review and 5) Test of the prefinal version.[8] In stage 1, the Lymph-ICF English version was independently forward-translated into Thai by 2 Thai native physiatrists who were fluent in English. In stage 2, two translators and experts synthesized the translation into one. In stage 3, the Thai translation Lymph-ICF was translated back into English by two bilingual Thai-English speakers, neither of whom had prior knowledge of Lymph-ICF. In stage 4, an expert committee comprising medical personnel who specialized in breast cancer related lymphoedema (one physiatrist, one plastic surgeon, one occupational therapist and one physiotherapist) and translators reviewed the back-translation and developed the prefinal version. In stage 5, the prefinal version was tested on 5 patients with breast cancer related lymphoedema for their understanding of each item in the questionnaire. After completing the questionnaire, the participants were asked questions related to content validity[5]: 1) Is each question easy to understand? 2) Is the scoring system easy to use? 3) Does the questionnaire include all the complaints related to your lymphoedema, and 4) any suggestions for this questionnaire? All the participants gave positive answers (yes) for questions 1 to 3. One participant suggested that some open questions would be helpful for patients to give detail of their complaint.

Sample size calculation

According to the previous validity study using physical functioning domain of SF36 for quality-of-life

assessment with physical function domain of Lymph-ICF the correlation coefficient is -0.498.[6] Instead of SF36 our study used EQ-5D-5L for quality-of-life measurement, we imply that the correlation coefficient (r) is equal to -0.5. After adding all the information into the nQuery Advisor® Version 7.0 (Statistical Solutions Ltd., Cork, Ireland) software, we found that 38 participants would be enough for this study (power of 90% with a significant level of 0.05). On the other hand, for the reliability test (test-retest reliability), from previous study we found that the intraclass correlation coefficient of Lymph-ICF total score is equal to 0.9 with a 95 percent confidence interval width of 0.2. The sample size approximation is 19.[6] For the primary outcomes of validity and reliability of Lymph-ICF Thai version, we initially estimated that 38 participants would be needed. Assuming a 30% withdrawal rate, the final calculated sample size was a total sample of 50 participants.

Evaluation of psychometric property of the Thai version Lymph-ICF

The validity and reliability of the final Thai version was evaluated by 50 patients with unilateral BCRL. All participants did the questionnaire twice at least 2 hours apart, with all domains shuffled when they did it the second time to determine test-retest reliability. The first time, patients completed the demographic data, the Lymph-ICF questionnaire Thai version, and the EQ-5D-5L questionnaire at the outpatient rehabilitation department. Two hours later, they did the Lymph-ICF questionnaire again but with the domains shuffled.

The Lymph-ICF questionnaire has 29 questions and 5 domains: 1) physical function, 2) mental function, 3) household activities, 4) mobility activities, and 5) life and social activities. The questionnaire would take about five minutes to complete. Each of the 29 questions is rated on an 11-point Likert scale between 0 and 10. The total score of the questionnaire is the sum of the score from each question divided by the total number of answers and multiplied by 10. Each of the five domains is scored by adding the score from each question, divided by the total number of answers and multiplied by 10. The total score of the questionnaire and of the 5 domains would be between 0 and 100.

The EQ-5D-5L, a self-assessed, health related, quality of life questionnaire, measures the quality of life on a 5-component scale: 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Each component has a 5-level classification system. The EQ-5D-5L also has an overall health scale to describe the condition of the rater's health, where 0 indicates the worst imaginable condition and 100 the best imaginable condition. Convergent validity was demonstrated by a correlation between EQ-5D-5L and the dimensions of WHO 5, ($r=0.43$, $P<0.001$).[9] The EuroQol approach is reliable, average test-re-test reliability using inter-class coefficients with mean of 0.78 and 0.73.[10]

Data analysis

PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) were used for all statistical analyses, with a p-value < 0.05 considered to be statistically significant. Descriptive statistics were also performed. Continuous variables were reported using mean ± standard deviation (SD) for normally distributed data and median (interquartile range; IQR) for non-normally distributed data (Kolmogorov-Smirnov and Shapiro-Wilk tests). Categorical variables were presented as a number (percentage).

Assessment of validity: Face validity was investigated. One physiatrist, one plastic surgeon, one physical therapist, one occupational therapist and a breast cancer related lymphedema patient were asked to be content experts. All of these health care professionals worked in their field more than 10 years. All the experts agreed that all items in the Thai version of Lymph-ICF had face validity; they appeared to measure quality of life in BCRL patients. To establish construct validity, correlations between the scores of the Lymph-ICF and the scores of the EQ-5D-5L were examined using Pearson correlation coefficient for normally distributed score or Spearman correlation coefficient for non-normally distributed score. Correlation coefficients were rated with ≤ 0.3 indicates poor correlation, 0.31 to 0.6 indicates moderate correlation, and > 0.6 indicates strong correlation.[11] A p-value less than 0.05 was considered statistically significant.

Assessment of reliability: An intraclass correlation coefficient (ICC) was used to determine the test-retest reliability of the total score and of the scores of the 5 domains of the Lymph-ICF.[12] An ICC < 0.5 indicates poor reliability, 0.5 to 0.75 indicates moderate reliability, 0.75 to 0.9 indicates good reliability, and > 0.9 indicates excellent reliability.[13] To determine the internal consistency of the whole questionnaire and of each domain, Cronbach's alpha were used, with a value of > 0.7 indicating a reliable internal consistency.[14]

RESULTS

Fifty female participants with unilateral BCRL, aged 40-76 years (mean age 59.7±9.3 years), participated in the study; no participant dropped out. Their demographic data and clinical characteristics were shown in Table 1.

TABLE 1. Demographic data and clinical characteristics of the participants.

	Mean ± SD, n (%)	Range
Age (years)	59.7±9.3	40 - 76
Gender Female:Male	50:0 (100.0%:0.0%)	
Body Mass Index (kg/m^2)	26.6±4.4	18.1- 38.9
Education		
None	1 (2.0%)	
Primary school	24 (48.0%)	
Secondary school	6 (12.0%)	
Vocational Certificate/ High Vocational Certificate/ Diploma	3 (6.0%)	
Bachelor's degree	12 (24.0%)	
Master's degree and above	4 (8.0%)	
Dominant side (Right:Left)	42:8 (84.0%:16.0%)	
Affected side (Right:Left)	25:25 (50.0%:50.0%)	
Affected on dominant side (Yes:No)	25:25 (50.0%:50.0%)	
Region of lymphoedema		
Above elbow	50 (100.0%)	
Below elbow	48 (96.0%)	
Hand	33 (66.0%)	
Circumference of affected side		
Dorsum of hand	19.1 ± 2.6	16.5 – 32.0
Wrist	17.7 ± 2.7	13.5 – 29.0
Below elbow 10 cm	28.1 ± 5.6	20.0 – 44.0
Elbow	29.0 ± 5.1	15.0 – 38.0
Above elbow 10 cm	34.8 ± 5.9	25.0 – 47.0
Circumference of normal side		
Dorsum of hand	18.1 ± 0.8	16.5 – 20.0
Wrist	15.8 ± 2.5	7.0 – 26.0
Below elbow 10 cm	22.8 ± 2.6	17.5 – 30.0
Elbow	23.9 ± 2.9	16.0 – 29.0
Above elbow 10 cm	28.3 ± 5.7	15.0 – 42.0
Mean duration of lymphoedema (months)	55.9 ± 60.1	1 - 240
Time interval since surgery (months)	133.0 ± 95.8	1.0 – 432.0
Surgical type		
Lumpectomy	22 (44.0%)	
Mastectomy	28 (56.0%)	
Others	0 (0.0%)	
Radiation therapy	48 (96.0%)	
Chemotherapy	47 (94.0%)	
On pressure garment	42 (84.0%)	
Physical therapy program for lymphedema	37 (74.0%)	

Abbreviations: SD = standard deviation, n = number

Assessment of reliability: For the test-retest reliability of the Lymph-ICF total score and each domain using intraclass correlation coefficient (ICC), the ICC ranged from 0.76 to 0.96 indicating good to excellent reliability. The internal consistency of the whole questionnaire and of each domain using Cronbach's alpha ranged from 0.89 to 0.97, which indicates a reliable internal consistency. (Table 2)

The construct validity analysis was shown in Table 3. There were significant correlations between the scores of the Lymph-ICF and the scores of the EQ-5D-5L in all aspects except mobility. The correlation in the mental function was strong.

TABLE 2. Test retest reliability and internal consistency of Thai version of Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF).

Outcome	First assessment Median (IQR25, IQR75)	Second assessment Median (IQR25, IQR75)	Intraclass Correlation Coefficient (ICC)	95 % Confidence Interval for ICC	Cronbach's alpha
Lymph ICF total score	25.4 (7.2, 44.8)	26.0 (5.3, 44.2)	0.96	0.94 – 0.98	0.97
Physical function score	23.6 (9.6, 47.5)	24.3 (5.7, 41.8)	0.90	0.83 – 0.94	0.91
Mental function score	6.3 (0.0, 33.8)	3.8 (0.0, 26.3)	0.96	0.92 – 0.98	0.93
Household activities score	22.5 (0.0, 50.0)	25.0 (0.0, 50.0)	0.87	0.78 – 0.92	0.89
Mobility activities score	31.7 (9.4, 54.4)	30.0 (5.4, 51.3)	0.92	0.86 – 0.95	0.91
Life and social activities score	18.3 (1.7, 46.3)	16.7 (1.7, 40.8)	0.76	0.62 – 0.86	0.91

Abbreviations: IQR25 = Inter Quartile Ranges 25, IQR75 = Inter Quartile Ranges 75, ICC = Intraclass Correlation Coefficient

TABLE 3. Construct validity: correlation analysis of the Thai versions of the Lymph-ICF and EQ-5D-5L questionnaire.

Lymph ICF	Physical function		Mental function		Household activities		Mobility activities		Life and social activities	
EQ-5D-5L	r_s	p-value	r_s	p-value	r_s	p-value	r_s	p-value	r_s	p-value
Mobility	0.282	0.048	0.231	0.107	0.320*	0.025	0.247	0.087	0.321*	0.023
Self-care	0.491*	<0.001	0.464*	0.001	0.424*	0.002	0.305*	0.033	0.364*	0.009
Usual activities	0.532*	<0.001	0.543*	<0.001	0.435*	0.002	0.470*	0.001	0.473*	0.001
Pain/ discomfort	0.431*	0.002	0.384*	0.006	0.430*	0.002	0.387*	0.006	0.401*	0.004
Anxiety/ depression	0.455*	0.001	0.649**	<0.001	0.338*	0.006	0.331*	0.020	0.402*	0.004

*Moderate correlation **Strong correlation

r_s = Spearman rank correlation coefficient

DISCUSSION

This study demonstrated the Lymph-ICF Thai version to be valid and reliable for evaluating the quality of life in BCRL patients.

Baseline characteristics of our study are quite similar to the English (original)[5] and Danish versions[7] of Lymph-ICF. Mean age and body mass index (BMI) of patients in our study were 59.7±9.3 years and 26.6±4.4 kg/m^2, compared with 61.2±10 years and 27±6.2 kg/m^2 in the original English version, and 61±12.4 years and 27.7±5.4 kg/m^2 in the Danish version. Participants in the Turkish version[6] were younger and more obese compared with our study with mean age 53.8±5.8 years and BMI 30.4±4.1 kg/m^2. The age and BMI in the Turkish version, although differed from those of the other three versions, reflected age and BMI of the general Turkish population. According to data from World Health Organization, the average BMI in female in Turkey is 28.5 kg/m^2 which is substantially higher than in Thai (24.6 kg/m^2), Belgium (24.7 kg/m^2), and Denmark (24.5 kg/m^2).[15]

The original English version and the Turkish version use the Visual Analogue Scale (VAS) from 0 to100 mm while the Danish version uses the Numerical Rating Scale (NRS) from 0 to 10. A systematic review comparing the NRS, VAS, and/or Verbal Rating Scale (VRS) for unidimensional self-reporting of pain intensity found that NRS produced better compliance rates, higher responsiveness, greater ease of use, and better applicability relative to VAS and was the recommended tool in 11 studies[16], therefore, we chose NRS from 0 to 10 in this study. All three versions (English, Danish and Turkish) use the same range of final score (0 to100) for both the total score of the Lymph-ICF and each of the 5 domains.

The English and Turkish Lymph-ICF used SF-36 as the quality-of-life questionnaire to investigate correlation with Lymph-ICF. This study used EQ-5D-5L as it is the shortest and easiest questionnaire and its impletion was as good as SF-36.[17]

The construct validity analysis showed that there was a significant correlation between the scores of the Lymph-ICF and the scores of the EQ-5D-5L in all aspects except mobility. This might be due to the Lymph-ICF and the EQ-5D-5L questionnaire investigate mobility in different functions. The majority of mobility score of the Lymph-ICF (tasks with elevated arm, lift heavy objects, sleep on affected side, work on computer, sunbathe, drive a car, walk more than 2 km and cycle) investigates the upper extremities mobility whereas the mobility score of the EQ-5D-5L (walking) investigates the lower extremities mobility.

Comparing test-retest reliability of the Thai version with the other three versions (original English, Turkish and Danish), it was found that the Thai, Turkish and Danish versions had excellent reliability in the total score with ICC values > 0.9 and good to excellent reliability in scores on the 5 domains of the Lymph-ICF with ICC values > 0.75 ranging from 0.76 to 0.96, 0.80 to 0.98 and 0.84 to 0.95, respectively. The original English version had moderate reliability in life and social activities domain with ICC 0.65 and good to excellent reliability in the total score and scores on other 4 domains of the Lymph-ICF with ICC values ranging from 0.87 to 0.93.

Comparing internal consistency of the Thai version with the other three versions (original English, Turkish and Danish), it was found that all versions (Thai, original English, Turkish and Danish) had good internal consistency with Cronbach's alpha values of > 0.7 ranging from 0.89 to 0.97, 0.72 to 0.92, 0.89 to 0.99 and 0.92 to 0.98, respectively.

Study limitations

First, the follow-up period was relatively short (only 2 hours apart), however all domains of the questionnaire were shuffled the second time. Second, Lymph-ICF was a self-report questionnaire with no cognitive test for participants before their inclusion in the study. Nevertheless, ability to communicate and reply to instructions in Thai were assessed before recruitment. Third, our study compared quality of life of patients between the Thai version of Lymph-ICF scores and the Thai version EQ-5D-5L scores which differed from the previous study using SF-36, hence it cannot truly compare the outcome with the previous study. Fourth, all participants in this study were outpatients. These are patients with uncomplicated lymphedema. No Patients with complications from lymphedema participated in this study. Lastly, only unilateral breast cancer related lymphoedema (BCRL) patients were enrolled in this study so the study results cannot be applied to patients with bilateral BCRL and other causes of upper limb lymphoedema.

CONCLUSION

This study demonstrated that the Thai version of Lymph-ICF is a valid and reliable questionnaire for evaluating quality of life in BCRL patients and can be used in clinical practice and research for unilateral BCRL patients.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Cancer Registry Unit NCIT. Cancer in Thailand Vol VIII, 2010-2012. W. Imsamran AC, S. Wiangnon, D. Pongnikorn, K. Suwanrungrung, S. Sangrajrang, R. Buasom, editor. 202 Soi Charoenkrung 57, Yannawa, Sathorn, Bangkok 10120 Thailand: New Thammada Press (Thailand) Co., Ltd.; 2015.
3. Society AC. Breast Cancer Facts & Figures 2015-2016. Atlanta: American Cancer Society, Inc. 2015. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf.
4. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013;14:500-15.
5. Devoogdt N, Van Kampen M, Geraerts I, Coremans T, Christiaens MR. Lymphoedema Functioning, Disability and Health questionnaire (Lymph-ICF): reliability and validity. Phys Ther 2011;91:944-57.
6. Kostanoglu A, Hosbay Z, Tarakci E. Lymphoedema functioning, disability and health questionnaire Turkish version: translation, cross-cultural adaptation and validation. J Phys Ther Sci 2016; 28:1728-32.
7. Grarup KR, Devoogdt N, Strand LI. The Danish version of Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF) for breast cancer survivors: Translation and cultural adaptation followed by validity and reliability testing. Physiother Theory Pract 2019;35:327-40.
8. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine 2000;25:3186-91.
9. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717-27.
10. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72.
11. Post MW. What to Do With "Moderate" Reliability and Validity Coefficients? Arch Phys Med Rehabil 2016;97:1051-2.
12. Lexell JE, Downham DY. How to assess the reliability of measurements in rehabilitation. Am J Phys Med Rehabil 2005; 84:719-23.
13. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016;15:155-63.
14. Cicchetti DV. Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instrument in Psychology. Psychological Assessment 1994;6:284-90.
15. World Health Organization. Global status report on noncommunicable diseases 2014. Switzerland: World Health Organization; 2014.
16. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073-93.
17. Quercioli C, Messina G, Barbini E, Carriero G, Fani M, Nante N. Importance of sociodemographic and morbidity aspects in measuring health-related quality of life: performances of three tools: comparison of three questionnaire scores. Eur J Health Econ 2009;10:389-97.

Validity, Reliability and Responsiveness of the Thai Version of Patient-Rated Wrist Evaluation (Th-PRWE) in Distal Radius Fracture Patients

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ABSTRACT

Objective: Patient-Rated Wrist Evaluation (PRWE) is a specific tool for the assessment of wrist function and has been validated and translated into many languages. This study aimed to translate the PRWE into the Thai language and to evaluate its validity, reliability, and responsiveness in operatively treated distal radius fracture patients.

Materials and Methods: PRWE was translated into the Thai language according to a linguistic validation protocol by a forward–backward translation process. In total, 53 distal radius fracture patients who underwent volar locking plate fixation were included in the present study. However, 8 patients were excluded due to multiple injuries, leaving 45 patients who were prospectively enrolled and evaluated with the Thai version of the PRWE (Th-PRWE) and Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire within 2 weeks of their surgery. Reliability of the Th-PRWE was assessed by the test–retest reliability and internal consistency. The content, concurrent, and criterion validity of the Th-PRWE were measured. At 3 months after the operation, patients were re-assessed with Th-PRWE and DASH. The standardized response mean (SRM) and effect size (ES) were assessed to identify the responsiveness to a change of the tool.

Results: Most of the patients were female (64%) with average age of 55 years old and had sustained distal radius fractures. The intraclass correlation for the test–retest reliability of the Th-PRWE was 0.9. The internal consistency of the Th-PRWE was acceptable (Cronbach's alpha = 0.93). Th-PRWE had a high content validity (Item-objective congruence index = 0.8) and excellent correlation with DASH (Spearman's rank correlation = 0.81; $p < 0.001$). Its responsiveness was also considered excellent (SRM = 1.12, ES = 1.28).

Conclusion: Th-PRWE is valid, reliable, and responsive for the evaluation of distal radius fracture patients.

Keywords: Psychometric; patient outcome assessment; wrist injury; radius fracture (Siriraj Med J 2021; 73: 275-281)

INTRODUCTION

Distal radius fracture is a common fracture in all age groups, especially in the elderly.[1] Nowadays, there is an increasing number of elderly in the population as well as an increasing incidence of fractures. Such an injury represents not only a physical problem, but also a psychological and socioeconomic problem. Moreover, patients may have difficulty with self-care and in performing the activities of daily living after the injury. Surgical treatment tends to yield superior outcomes, in terms of

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a faster return to the pre-injury status and functional outcomes, compared to conservative treatment, especially in active, independent patients.

Operative treatment with volar locking plate fixation of the distal radius fracture is increasingly performed to allow an early range of motion of the wrist and a faster recovery toward being able to perform daily activities. There are several outcome measurements for the hand and wrist, such as the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire, Boston Carpal Tunnel Questionnaire, Jebsen-Taylor Hand Function Test, and Michigan Hand Outcomes Questionnaire.[2] However, the wrist joint has many specific functions and should be evaluated separately from other joints of the upper extremity. The Patient-Rated Wrist Evaluation (PRWE) was developed as a specific tool for assessment of the wrist functions.[2-6] PRWE is a simple self-reported outcome measurement carried out by the patients in the form of a questionnaire that can take them only a few minutes to complete. This disease-specific questionnaire had been translated into many languages.[7-14] However, the questionnaire had never been translated into Thai language before.

Consequently, this study is aimed to develop a Thai version of the PRWE (Th-PRWE) and to evaluate its validity, reliability, and responsiveness for operatively treated distal radius fracture patients.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of Siriraj Hospital and registered in the Thai Clinical Trials Registry (TCTR20180930002) (www.clinicaltrials.in.th).

The original English version of PRWE was translated into the Thai language according to the linguistic validation protocol by a forward-backward translation process. In this way, the final Thai language translation of PRWE was achieved. Three orthopedic surgeons and 2 orthopedic residents evaluated the content validity of the Th-PRWE by using an item-objective congruent index. The study prospectively enrolled distal radius fracture patients aged more than 18 years old who had been operatively treated with volar locking plate at a tertiary care hospital from July 2017 to April 2019. Patients with pathological fracture, concomitant neurovascular injury, impaired cognitive function, a known history of upper extremity disability, and multiple injuries were excluded from the study.

All the eligible participants were well-informed and consented to the study protocol before their participation. Participants completed the Th-PRWE and DASH questionnaire at 2 weeks after the operation and 1 week thereafter for evaluation of the test–retest reliability. At 3 months after the operation, the participants re-evaluated the Th-PRWE and DASH questionnaire to identify the responsiveness to a change of the tool.

Ethical approval: Ethical approval for this study was obtained from the Siriraj Institutional Review Board (Si 394/2017).

Outcome Measurements

Patient-Rated Wrist Evaluation (PRWE)[3]

The PRWE was developed by MacDermid et al. to assess pain and functional difficulties in the activities of daily living resulting from injuries to the wrist joint.

The PRWE comprises a 15-item patient-reported questionnaire, subcategorized into 2 subscales; a pain subscale and function subscale. The pain subscale has 5 items related to pain of the affected wrist at rest and during specific activities. The function subscale has 10 items, which rate a patient's difficulty in performing activities, which are further divided into 6 items corresponding to specific activities and 4 items corresponding to usual activities. Each item has a numeric rating scale, ranging from 0 to 10. The pain subscale has a maximum total score of 50 and the function subscale has a maximum total score of 100. A higher score reflects more pain or greater difficulty in performing the activities. The total score for the PRWE is obtained from a summation of the total pain subscale and half of the total function subscale. Therefore, the minimum score for the total PRWE that reflects the best outcome is 0, and the maximum score that reflects the worst outcome is 100.

$$Total\ score = Pain\ subscale + \frac{Function\ subscale}{2}$$

Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire[15]

The DASH questionnaire was developed by a joint effort by the American Academy of Orthopedic Surgeons, the Council of Musculoskeletal Specialty Societies, and the Institute for Work and Health in Toronto. The questionnaire aims to assess the region-specific disability of an upper extremity. It is widely utilized for upper extremity difficulty measurement for various disorders. The DASH questionnaire has been validated and translated into many languages, including Thai.

The DASH questionnaire is a self-administered questionnaire and is composed of 2 sections: a required

section and an optional additional section. The required section has 30 items, with the score ranging from 1 to 5 for each item, where a higher score reflects increasing difficulty in performing activities. The score for the required section is calculated by summing all the scores for the responded items and then dividing by the number of responded items, followed by subtracting 1 and multiplying by 25. The total score for the required section ranges from 0 to 100, where a higher score reflects a greater difficulty in performing activities of the upper extremity. The optional section has an additional 8 questions for specific activities, including a work module and sports/performing art module. The scoring for the optional module is calculated in the same way as for the required section and the score ranges from 0 to 100.

Statistical analysis

Data analysis was performed using SPSS version 16.0 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Demographic data are shown by the range, mean, and percentage of the outcomes. Content validity was determined by using the index of the item-objective congruence. Construct validity was evaluated by comparing Th-PRWE with the Thai version of the DASH questionnaire and by calculating the Spearman's rank correlation coefficient. To determine the test–retest reliability and internal consistency, Spearman's rank correlation and Cronbach's alpha were calculated, respectively. Floor and ceiling effects more than 15% were considered significant. The effect size (ES) and standardized response mean (SRM) were calculated to detect the responsiveness to a change of the tool. ES and SRM values of more than 0.8 were considered large.

RESULTS

In total, 53 patients were screened for eligibility, but 8 patients were excluded from the study due to having multiple injuries. Consequently, 45 patients were consecutively enrolled into the study, comprising 16 males (36%) and 29 females (64%), with an average age of 55 years old. Forty-two percent of the patients had injuries to their dominant hand. The patients' demographic data are shown in Table 1.

At 2 weeks follow-up, the total mean score of the Th-PRWE was 43.5 (SD 21.1) and the total mean score of the Thai version of DASH was 48.9 (SD 21.5); while at 3 months, the total mean scores of the Th-PRWE and of the Thai version of DASH were significantly decreased to 16.5 (SD 13.5) and 18.0 (SD 15.3), respectively. (Table 2)

Validity

All 15 items on the Th-PRWE had good content validity, as demonstrated by the item-objective congruence (IOC) index. Only 4 items (pain when doing a task with repeated wrist movement in the pain subscale, fastening buttons on my shirt, carrying a 10-pound object in my affected hand, and recreational activities in the function subscale) had an IOC index of 0.8, while the other items had an IOC index of 1.

TABLE 1. Demographic data of the study participants.

Demographic data	Statistics (n = 45)
Gender	
Male	16 (36%)
Female	29 (64%)
Age (years) *	55 (13)
Injury to the dominant hand	19 (42%)
AO Classification	
23-A	11 (24.4%)
23-B	20 (44.4%)
23-C	14 (31.1%)

*Data presented as the mean (SD)

TABLE 2. Th-PRWE and Thai version of DASH outcomes.

Outcomes	Total mean score (SD)
Th-PRWE	
Baseline at 2 weeks	43.5 (21.1)
1 week after baseline	43.1 (21.1)
3 months	16.5 (13.5)
Thai version DASH	
Baseline at 2 weeks	48.9 (21.5)
3 months	18.0 (15.3)

The construct validity of the function subscale and the total score of the Th-PRWE revealed excellent correlation with the Thai version of DASH, as shown in Table 3. The Spearman's rank correlation between the function subscale of the Th-PRWE and the Thai version of DASH was 0.87, and the correlation between the total score of the Th-PRWE and of the Thai version of DASH was 0.81; $p < 0.001$. However, the pain subscale of Th-PRWE had only a moderate correlation with the total score of the Thai version of DASH (Spearman's rank correlation 0.39; $p = 0.008$).

Reliability

The reliability results for Th-PRWE are presented in Table 4. The intraclass correlation for the test-retest reliability of the total score for Th-PRWE was 0.90. Each item in the pain subscale had a high intraclass correlation (ICC) ranging from 0.64 to 0.85. Similarly, the function subscale also had an excellent ICC, ranging from 0.64 to 0.95. The internal consistency for Th-PRWE was considered excellent, as indicated by its Cronbach's alpha of 0.93. The questionnaire also had an acceptable floor and ceiling effect at 2 weeks follow-up. Only 2.2% of the patients had a floor effect on the pain subscale and 4.4% of the patients had a ceiling effect on the function subscale. None of the patients had a ceiling and floor effect on the total score.

Responsiveness to change

The standardized response mean (SRM) and effect size (ES) of Th-PRWE were considered to be high, as shown in Table 5. The standardized response mean of the pain subscale was 0.78, while it was 1.1 for the function subscale and 1.12 for the total score. The effect size of the pain subscale was 0.89, while it was 1.26 for the function subscale and 1.28 for the total score. These data demonstrated the significant clinical improvement of the patients from 2 weeks to 3 months after the operation.

DISCUSSION

Specific-disease functional outcomes are becoming increasingly important for monitoring a patient's recovery. PRWE is one of the outcome measurements for the evaluation of pain and function of the wrist. We translated this tool from English language into Thai language for use in Thailand. All the items in the questionnaire could be easily understood and it took about 5 to 10 minutes to complete the questionnaire. We converted the unit of measurement from 10 pounds to 5 kilograms in the "carrying an object" item, due to kilograms being more commonly used in Thailand than pounds. This modified item has also been applied and validated in other countries that use the International System of Units for measurements.

The study results revealed that Th-PRWE had excellent construct validity. However, only the pain subscale of Th-PRWE had a moderate correlation with the Thai version of the DASH questionnaire. The pain subscale contributed to a half of the PRWE score, while DASH, which specifically focuses on the disability of the upper extremity, has only 2 pain-related questions. Thus, the correlation between the pain subscale and the DASH was lower compared to for the function subscale.

The internal consistency and test–retest reliability of the Th-PRWE were excellent and comparable to other versions, suggesting that the Th-PRWE is easy to understand. However, two of the five items in the pain subscale demonstrated a moderate ICC (0.64–0.66). The moderate reliability of the pain subscale reflects the typical course of pain, which tends to be more responsive in the early period after distal radius fracture fixation. The one-week-apart period before testing the reliability

TABLE 3. Construct validity of the Th-PRWE relative to the Thai version of DASH.

Th-PRWE	Thai version of DASH Spearman's rank correlation	95% CI	p-value
Pain subscale	0.39	0.06–0.64	0.008
Function subscale	0.87	0.77–0.92	< 0.001
Total score	0.81	0.67–0.87	< 0.001

TABLE 4. Reliability test of the Th-PRWE.

Th-PRWE items	Test–retest ICC	95% CI
Pain at rest	0.78	0.64–0.88
Pain during repeated wrist movement	0.66	0.45–0.80
Pain during lifting a heavy object	0.64	0.43–0.79
Pain at its worst	0.84	0.73–0.91
Pain frequency	0.85	0.74–0.91
Turning a doorknob	0.90	0.83–0.94
Using a knife	0.64	0.43–0.78
Fastening buttons	0.89	0.80–0.94
Pushing up from a chair	0.82	0.69–0.90
Carrying a 5 kg object	0.95	0.92–0.97
Using bathroom tissue	0.91	0.84–0.98
Personal care activities	0.84	0.73–0.91
Household work	0.85	0.73–0.91
Usual everyday work	0.80	0.66–0.89
Recreational activities	0.87	0.78–0.93
Total score	**0.90**	**0.83–0.95**

TABLE 5. Responsiveness to change of the Th-PRWE.

Th-PRWE	SRM	ES
Pain subscale	0.78	0.89
Function subscale	1.10	1.26
Total score	1.12	1.28

Abbreviations: SRM = standardized response mean; ES = effect size.

of the tool might have affected the clinical difference in these patients. Some patients were externally immobilized with a slab for 2 weeks after fracture fixation, while others were allowed to move their wrist immediately. The rehabilitation program for the wrist is generally initiated after removal of any external immobilization, which might affect the pain during the third week. At 2 weeks after the operation, some of the patients were externally immobilized; therefore, they might have experienced only mild pain compared to a week later, at which time a range of motion exercises was advocated. Additionally, we observed a discrepancy in one item in the function section of the PRWE, namely, "cut meat using a knife with my affected hand", as reflected by its lower ICC (0.64) compared to the other items. This was possibly due to cultural differences in that most Thai people rarely use a knife to eat food. This discrepancy has also been demonstrated in other Asian versions of the PRWE, some of which modified the question; for instance, into "cut food using knife with my affected hand" in the Korean version[10] and "cut vegetables using knife with my affected hand" in the Hindi version.[11]

The responsiveness to change of the Th-PRWE between 2 weeks follow-up and 3 months follow-up were large (SRM = 1.12). We observed a higher minimum detectable change (MDC = 15.5) than the Korean version of the PRWE. They reported an MDC of 4.4 at 3 and 6 months in 63 patients with distal radius fractures treated by open reduction and locking plate fixation.[10] This difference could partly explain the higher ICC in their study and the different timing of the responsiveness evaluation. In a previous study by MacDermid et al., the highest responsive of the PRWE in distal radius cases was during the 0- to 3-months period. A lower responsiveness was found during the recovery period at 3- to 6-months, as the SRM in the first 3 months was 2.27 and then decreased to 0.74 in the next 3 months.[4] The SRM of our study was 1.12, suggesting that the Th-PRWE has a large responsiveness to change for distal radius fracture evaluation. Although, our study found an MDC of 15.5, indicating that the score must change by 15.5% to ensure the recovery of the patients. The change of Th-PRWE mean score between postoperative 2 weeks and 3 months was more than 20%; therefore, the Th-PRWE is an appropriate and effective tool to detect responsiveness after distal end radius fracture treatment.

There were some limitations to note, such as the study was performed in a short-term period for distal radius fracture; therefore, longer-term evaluation should be performed to identify any possibility of floor and ceiling effects in longer follow-up periods. The study showed that this tool has excellent responsiveness to change. Thus, it can monitor a patient's outcome and detect unfavorable results after the treatment. Another limitation is that the outcomes in this study only apply to operatively treated distal radius fracture patients. Future studies should be performed on other wrist disorders for assessing the generalizability of the tool.

CONCLUSION

The Th-PRWE provided excellent validity, reliability, and responsiveness to change. This disease-specific measurement can effectively be used for the outcome measurement of operatively treated distal radius fracture patients.

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REFERENCES

1. Nellans KW, Kowalski E, Chung KC. The epidemiology of distal radius fractures. Hand Clin 2012;28:113-25.
2. Smith MV, Calfee RP, Baumgarten KM, Brophy RH, Wright RW. Upper extremity-specific measures of disability and outcomes in orthopaedic surgery. J Bone Joint Surg Am 2012; 94:277-85.
3. MacDermid JC. Development of a scale for patient rating of wrist pain and disability. J Hand Ther 1996;9:178-83.
4. MacDermid JC, Richards RS, Donner A, Bellamy N, Roth JH. Responsiveness of the short form-36, disability of the arm, shoulder, and hand questionnaire, patient-rated wrist evaluation, and physical impairment measurements in evaluating recovery after a distal radius fracture. J Hand Surg Am 2000;25:330-40.
5. MacDermid JC, Tottenham V. Responsiveness of the disability of the arm, shoulder, and hand (DASH) and patient-rated wrist/hand evaluation (PRWHE) in evaluating change after hand therapy. J Hand Ther 2004;17:18-23.
6. Mehta SP, MacDermid JC, Richardson J, MacIntyre NJ, Grewal R. A systematic review of the measurement properties of the patient-rated wrist evaluation. J Orthop Sports Phys Ther 2015;45:289-98.
7. Hemelaers L, Angst F, Drerup S, Simmen BR, Wood-Dauphinee S. Reliability and validity of the German version of "the Patient-rated Wrist Evaluation (PRWE)" as an outcome measure of wrist pain and disability in patients with acute distal radius fractures. J Hand Ther 2008;21:366-76.
8. Imaeda T, Uchiyama S, Wada T, Okinaga S, Sawaizumi T, Omokawa S, et al. Reliability, validity, and responsiveness of the Japanese version of the Patient-Rated Wrist Evaluation. J Orthop Sci 2010;15:509-17.

9. John M, Angst F, Awiszus F, Pap G, Macdermid JC, Simmen BR. The patient-rated wrist evaluation (PRWE): cross-cultural adaptation into German and evaluation of its psychometric properties. Clin Exp Rheumatol 2008;26:1047-58.
10. Kim JK, Kang JS. Evaluation of the Korean version of the patient-rated wrist evaluation. J Hand Ther 2013;26:238-43.
11. Mehta SP, Mhatre B, MacDermid JC, Mehta A. Cross-cultural adaptation and psychometric testing of the Hindi version of the patient-rated wrist evaluation. J Hand Ther 2012;25:65-77.
12. Mellstrand Navarro C, Ponzer S, Tornkvist H, Ahrengart L, Bergstrom G. Measuring outcome after wrist injury: translation and validation of the Swedish version of the patient-rated wrist evaluation (PRWE-Swe). BMC Musculoskelet Disord 2011;12: 171.
13. Ozturk O, Sari Z, Ozgul B, Tasyikan L. Validity and reliability of the Turkish "Patient-Rated Wrist Evaluation" questionnaire. Acta Orthop Traumatol Turc 2015;49:120-5.
14. Wah JW, Wang MK, Ping CL. Construct validity of the Chinese version of the Patient-rated Wrist Evaluation Questionnaire (PRWE-Hong Kong Version). J Hand Ther 2006;19: 18-26.
15. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29 602-8.

The First Endoscopic Sleeve Gastroplasty and Transoral Outlet Reduction in Thailand: Case Report and Literature Review

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ABSTRACT

Obesity is becoming a universal healthcare problem. The role of endoscopic bariatric and metabolic therapies is emerging in the management of obesity and its related conditions. The endoscopic treatment can be used as a primary weight loss procedure and a revision procedure after bariatric surgery. While the prevalence of obesity has been rising over the past two decades in Thailand, the treatment options have been limited to diet and exercise, pharmacological treatment, and bariatric surgery until recently. In 2020, an endoscopic full-thickness suturing device was introduced to Thailand, leading to successful endoscopic bariatric therapy using a suturing device in Thai patients. This article intends to report the first successful endoscopic sleeve gastroplasty and transoral outlet reduction in Thailand with a mini-review focusing on these two procedures' outcomes.

Keywords: Endoscopic sleeve gastroplasty; transoral outlet reduction; bariatric endoscopy; bariatric surgery; obesity; endoscopy (Siriraj Med J 2021; 73: 282-288)

INTRODUCTION

Obesity is a significant health problem affecting over 700 million people globally, with an increased prevalence by nearly triple since 1975. In 2011, Thailand became the country with the second-highest prevalence of obesity in Southeast Asia (second to Malaysia).[1] The treatment options include lifestyle modification, medications, endoscopic bariatric therapy (EBT), and bariatric surgery. Lifestyle modification and medical treatment fail to attain long-term weight loss in a substantial proportion of the patients. Bariatric surgery is the most effective treatment for patients with morbid obesity. Still, under 2% of suitable patients undergo surgical treatment due to the risk of complications, the procedure's irreversible nature, limited budget, and access to surgery.[2,3] The EBT has gained more interest as a primary weight loss procedure (endoscopic sleeve gastroplasty, ESG) and revision procedures, including transoral outlet reduction (TORe) and endoscopic sleeve revision, as it offers a minimally invasive option to achieve weight loss. Despite

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the increasing incidence of obesity-related medical conditions in Thai people, the treatment options for obesity were limited to medical treatment and bariatric surgery until 2020, when the endoscopic suturing device (Apollo Endosurgery, Austin, TX) successfully obtained regulatory approval and became commercially available in Thailand.

Herein, we report first ESG and TORe cases in Thailand using the full-thickness endoscopic suturing system with a single-channel endoscope.

Case 1:

A 55-year-old woman with class I obesity, hypertension, dyslipidemia, and severe obstructive sleep apnea treated with AutoPAP ranging from 5-15 cmH_2O presented for the treatment of obesity. Her body weight (BW) was 85 kg, with a body mass index (BMI) of 34.9 kg/m^2. She was unable to achieve sustained clinically significant weight loss with lifestyle modification and medical treatment, including topiramate 100 mg daily, which was discontinued due to severe dizziness. After discussing the treatment options, she decided to undergo ESG. Pre-operative evaluation, including cardiac and pulmonary assessment, psychological evaluation, abdominal ultrasound, and duplex ultrasound for deep vein thrombosis (DVT) screening, were unremarkable. Her physical status was compatible with the American Society of Anesthesiologists (ASA) class II. She also underwent colonoscopy, pelvic examination, and mammography for cancer screening before the endoscopic procedure. Her pre-procedural BW was 78 kg, and her BMI was 32.05 kg/m^2.

The following items have been prepared; 1) The suturing device (OverStitch Sx™; Apollo Endosurgery Inc., Austin, Texas, U.S.) connected to a 9.8 mm diameter gastroscope (GIF-H180; Olympus, Tokyo, Japan). The endoscopic suturing device has an external catheter sheath, consisting of two separate working channels allowing the anchor exchange and the OverStitch Sx™ accessories to operate independently of the scope channel. The needle driver handle is attached to the control section of the endoscope, and the needle endcap is attached to the distal tip of the endoscope, 2) Intravenous prophylactic antibiotics with 2 grams of ceftriaxone and 500 mg of metronidazole, 3) Carbon dioxide for insufflation. The procedure was performed under general anesthesia with the patient placed in the left lateral position. Enhanced recovery after surgery (ERAS) principles were applied, including short-acting anesthetic drugs, short-acting opioid, thromboprophylaxis, postoperative nausea and vomiting (PONV) prophylaxis and ventilator setting with lung protective strategy. A thorough gastric examination was done during the upper endoscopy before performing gastroplasty.

After the suturing device was advanced into the stomach, suturing was started from the level of incisura angularis. A running suture pattern, composed of 5 full-thickness bites, was started from the anterior wall, greater curvature, and posterior wall. The helix was used to grasp the tissue and pull it into the suturing device's jaws to facilitate a full-thickness bite. Upon finishing the running suture pattern, the needle was released to function as a tissue anchor, followed by removal of the anchor exchange catheter. The cinching catheter was inserted over the suture, which was tightened by applying intermittent and incremental tension before cinching. The suture was secured and cut by deploying a cinch. The following sutures were made in a "U" suture pattern alternating with an interrupted reinforcement suture. Each "U" was made of 8-12 stitches starting from the anterior wall, greater curvature, and posterior wall and then reverse pattern from the posterior wall more proximally, greater curvature and anterior wall. This pattern was then repeated following interrupted reinforcement with the next suture placed within 1 cm proximal to the previous set. In total, seven sutures were placed along the greater curvature in the distal to proximal direction, producing a sleeve-shaped gastric tube (Fig 1). The gastric fundus was not sutured, so that the patient had a pouch and accommodation capability. The procedure was successfully performed with a total procedure time of 120 minutes without adverse events. The patient was discharged two days after the procedure. A 3-day course of antibiotics and a 1-month course of daily proton pump inhibitor were prescribed. She was kept on full liquid diet for two weeks, followed by four weeks of soft diet and subsequently regular diet. The patient did well and her weight went from 78 kg to 67.7 kg at a three-month follow-up, representing a 13.2% total weight loss (TWL).

DISCUSSION

ESG is a primary endoscopic bariatric procedure using a suturing system that allows placement of full-thickness stitches through a minimally invasive method. This procedure was performed for the first time in 2012 by Thompson and Hawes using the Apollo Overstitch™ endoscopic suturing system.[4] The application of OverStitch™ requires a dual-channel therapeutic endoscope, and thus compatible with the Olympus GIF-2TH180 and GIF-2T160 scopes. Since then, several studies have demonstrated the technical feasibility, safety, and efficacy of ESG for weight loss and co-morbidity improvement using this

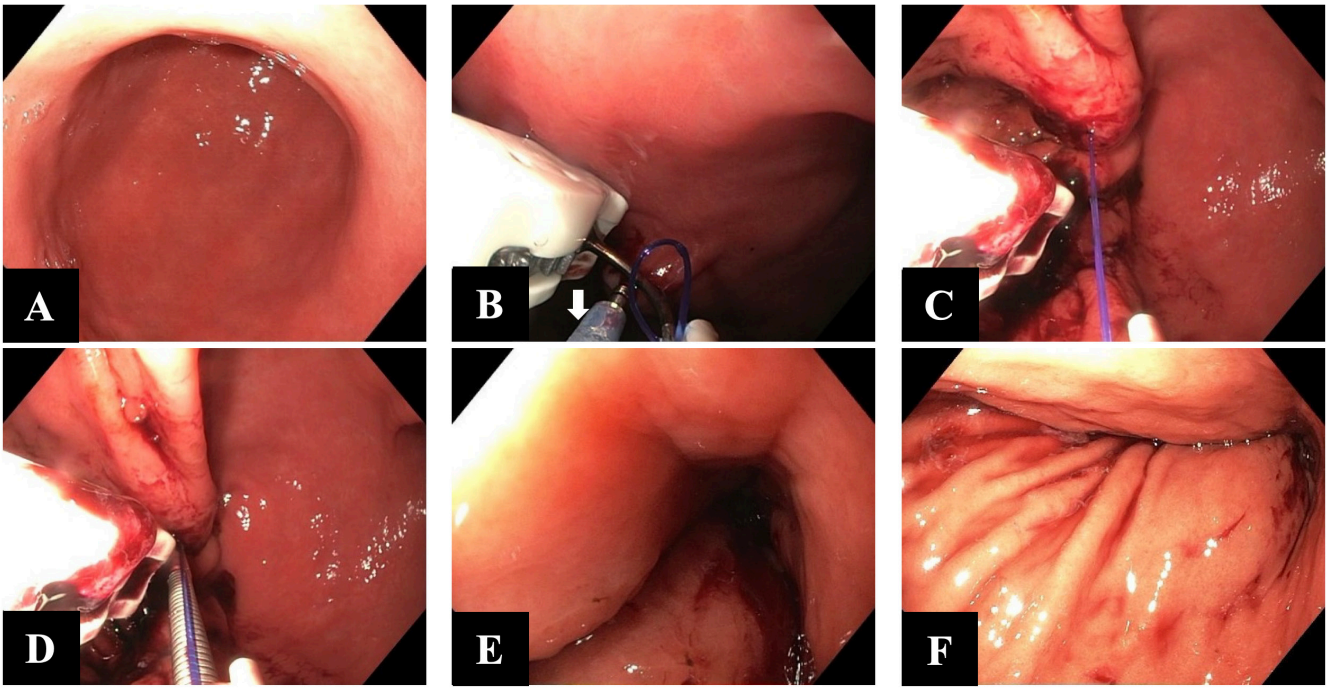

Fig 1. (A) Endoscopic image of the stomach. **(B)** The tissue helix (white arrow) is used to grasp tissue facilitating full-thickness bites. **(C)** The anchor is deployed, and the anchor exchanged device is removed after the last bite. **(D)** Cinching is performed to tighten the suture by applying intermittent and incremental pressure until adequate tissue approximation. **(E, F)** Endoscopic view demonstrating gastric sleeve on completion of the procedure.

device. Recently, Apollo Endosurgery released a newly developed suturing device, the OverStitch Sx™, which is compatible with single-channel flexible endoscopes. The OverStitch Sx™ keeps the needle (tissue anchor) and the needle driver in a secured cap on the end of the endoscope. The tissue helix can be inserted through a separate working channel.

Our first case of ESG was successfully performed using the OverStitch Sx™. The "U stitch" suture pattern with reinforcing stitches was used. The OverStitch Sx™ was capable of placing different suture patterns, including running and interrupted without difficulties. There were no adverse events during or after the procedure and no morbidity and mortality within the 90-day postoperative period. The percent of total weight loss (%TWL) and percent of excess weight loss (%EWL) was 13.2% and 38.1%, respectively, at the three-month follow-up. These results were similar to the outcomes of ESG reported in other studies.

Literature review

The principle of ESG is to create a restrictive gastric tube by placing transmural sutures along the greater curvature of the gastric body starting from the level of incisura angularis to the proximal body resulting in a gastric sleeve with an approximate 70% reduction in volume with likely delayed gastric emptying. A study has been conducted to compare gut hormone changes at six months after ESG vs. laparoscopic sleeve gastrectomy (LSG). The data demonstrated a significant decrease of the leptin level without significant changes of ghrelin, GLP-1, and PYY after ESG. In comparison, LSG resulted in a significant decline of ghrelin and a significant increase in GLP-1 and PYY level after six months. It is hypothesized that ESG does not affect the Ghrelin level because the fundus, where ghrelin is produced, is preserved after the procedure. In contrast, the fundus is excised, and the greater curvature is removed during LSG, which may decrease the ghrelin level. Therefore, the mechanism of weight loss after ESG is mainly related to early satiety by volume reduction and delayed gastric emptying.[5]

Different suture patterns and numbers of sutures have been reported, including "Z," "W", "U", and triangular or interrupted patterns.[6-10] Serial U suture patterns are performed starting on the anterior wall, the greater curvature, followed by the posterior wall, and moving proximally to the greater curvature concluding on the anterior wall proximal to the first bite. This procedure's primary focus is placing a running suture along the greater curvature, resulting in gastric shortening while concurrently narrowing the gastric lumen.[11] Another crucial point is the use of reinforcement sutures, which

may protect and help minimize U stitch tension.[12] To achieve efficiency in maneuvering the overstitch devices, at least 35 cases are required.[7,13]

The largest prospective study assessing the outcomes of ESG in 1000 patients showed that the mean %TWL at 6, 12, and 18 months was 13.7%, 15.0%, and 14.8%, respectively, and the mean %EWL at 6, 12, and 18 months was 64.3%, 67.5%, and 64.7%, respectively.[14] These outcomes were confirmed by three large meta-analyses, including over 1,500 patients in each study. The pooled analysis showed that the mean %TWL at 6, 12, and 24 months was 14.5%, 16%, and 17-20%, respectively. The pooled mean %EWL at 6, 12, and 24 months was approximately 53-57%, 60%, and 60%, respectively.[15-17] The weight loss following ESG appeared to plateau after 1 year, which is similar to that of bariatric surgery.[17] In terms of metabolic outcomes, a significant reduction in hemoglobin A1c, systolic blood pressure, waist circumference, alanine aminotransferase, and serum triglyceride has been reported at 12 months after ESG. The hypoglycemic agents were discontinued in 11% of the patients with pre-existing type 2 diabetes mellitus.[7] By far, ESG appeared to be an effective non-invasive method for weight reduction in those between a BMI of 30-40 kg/m^2.[18] Compared to intragastric balloon (IGB), ESG is superior in regards to %EWL and durability. A meta-analysis showed that ESG offered more %EWL at one year than IGB (60.51% vs. 29.65%). Also, weight loss after ESG is more durable than the IGB. The study showed that %EWL after IGB dropped from 34.83% at six months to 23.88% at 18 months, indicating weight regain after device removal. In contrast, %EWL after ESG remained above 50% at 18-24 months after the procedure.[19]

Nonetheless, ESG appears to have less effect in weight reduction than laparoscopic sleeve gastrectomy (LSG). A non-matched cohort study demonstrated that %TWL after ESG was significantly lower compared to LSG both at 6 months (14.4% vs. 23.5%, p <0.001) and 12 months (17.6% vs. 29.3%, p <0.001) after the procedures.[18] A case-matched retrospective study also showed that %TWL in the patients post ESG was lower than those with LSG (17.1% vs. 23.6%, p <0.01). However, a subgroup analysis demonstrated that %TWL of the patients receiving ESG was significantly lower than LSG in those with BMI >40 kg/m^2, but the difference was not statistically significant in those with BMI <40 kg/m^2. In contrast, the rate of adverse events after ESG was significantly lower compared to LSG (5.2% vs. 16.9%, P <0.5).[20] The pooled adverse event rate of ESG was approximately 2%, and no mortality has been reported. The most common severe adverse events were gastrointestinal bleeding and perigastric fluid collections, in which the incidence of each were <1%. Gastrointestinal bleeding in all cases can be managed conservatively, while the perigastric fluid collection was successfully managed by percutaneous drainage in most cases.[16] A study showed that 0.3% of the patients required reversal of ESG due to persistent symptoms of severe abdominal pain and vomiting, suggesting endoscopic reversibility of the procedure.[14] In patients with weight regain or inadequate weight loss after procedure, redo ESG or conversion to bariatric surgery (both laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass) remains an option.

In summary, this case report demonstrated the first successful application of the Overstitch Sx to perform ESG in Thailand. Our patient experienced clinically significant weight loss, defined as greater than 10% TWL, at 3 months, which was consistent with the reported data worldwide. Given a rising prevalence of obesity in Thailand, ESG may be considered an alternative treatment option in addition to pharmacotherapy and bariatric surgery.

Case 2:

A 45-year-old man presented with weight regain after Roux-en-Y gastric bypass (RYGB). His underlying medical comorbidities were hypertension, dyslipidemia, and non-alcoholic fatty liver diseases (NAFLD). He underwent RYGB in October 2015. He lost 58 kg after surgery; however, he regained 28 kg 2 years later. He developed a gastro-jejunal anastomotic (GJA) ulcer, proven by endoscopy, which was treated successfully with proton-pump inhibitors. The decision was made to proceed with transoral outlet reduction (TORe) after failing a 6-month trial of diet modification and exercise. Pre-operative evaluation, including cardiac and pulmonary assessment, psychological evaluation, abdominal ultrasound, and duplex ultrasound for DVT screening, were normal. His physical status was compatible with class II ASA.

He underwent TORe with a pre-procedural weight of 114.2 kg and a BMI of 35.2 kg/m^2. The procedure was performed with the patient in the left lateral decubitus position and under general anesthesia. ERAS principles, including short-acting anesthetic drugs, short-acting opioid, thromboprophylaxis, postoperative nausea and vomiting (PONV) prophylaxis and ventilator setting with lung protective strategy, were used. Upper endoscopy showed evidence of RYGB anatomy with a dilated GJA of 25 mm. The gastric pouch was 6 cm in length. Argon plasma coagulation (APC) was performed 1 cm circumferentially around the GJA to ablate the mucosa and facilitate submucosal-to-submucosal tissue apposition.

The APC settings were a power of 30 Watts and a flow rate of 0.8 L/min. The single-channel endoscopic suturing device was mounted on the GIF-H180 gastroscope and inserted into the gastric pouch. A simple two-stitch interrupted suture was placed at the 12 and 6 o'clock of the GJA to reduce its diameter, followed by cinching. Then, we reduced the pouch size starting with a simple interrupted pattern at the 12 and 6 o'clock on a greater curvature side of the distal pouch. Subsequently, the proximal pouch was reduced using a 6-stitch U-shape running suture pattern on the greater curvature side (Fig 2). The procedure was successfully performed with a total procedure time of 90 minutes without adverse events. The patient was discharged two days after the procedure. A 3-day course of antibiotics and a 1-month course of daily proton pump inhibitor were prescribed. He was placed on two weeks of full liquid diet, followed by four weeks of soft diet and subsequent regular diet. The patient did well and his weight decreased from 114.2 to 102 kg, representing a 10.7% TWL at a three-month follow-up.

DISCUSSION

Bariatric surgery is the most effective treatment with a durable long-term result for the treatment of obesity.[20] However, 10-20% of the patients who underwent RYGB, fail to achieve 50% EWL after one year of surgery.[22] Furthermore, a long term study revealed that most patients regained approximately a third of their lost weight, with a third of the patients regaining nearly all of their lost weight.[23] Weight regain can be caused by multiple reasons, including hormonal disturbances, patient behaviors, and anatomical factors. Anatomical characteristics, including gastro-gastric fistula and dilatation of GJA, are risk factors for weight regain.[24-26] Endoscopic therapy has become a treatment option for weight regain as it is effective and less invasive than revisional surgery. Our patient regained 48% of his lost weight two years after surgery, suggestive of failed primary bariatric operation requiring revisional procedure. Furthermore, the upper endoscopy showed a dilated GJA of 25 mm in diameter, making endoscopic therapy an attractive treatment option for outlet reduction. Therefore, we elected to perform our first case of TORe using the OverStitch Sx™ with interrupted suture pattern. The procedure was performed successfully without intra- or post-procedural adverse events. The GJA was sized to approximately 10 mm in diameter to avoid symptoms of outlet obstruction. At three-month follow-up, his %TWL was 10.7, and %EWL was 33.7%.

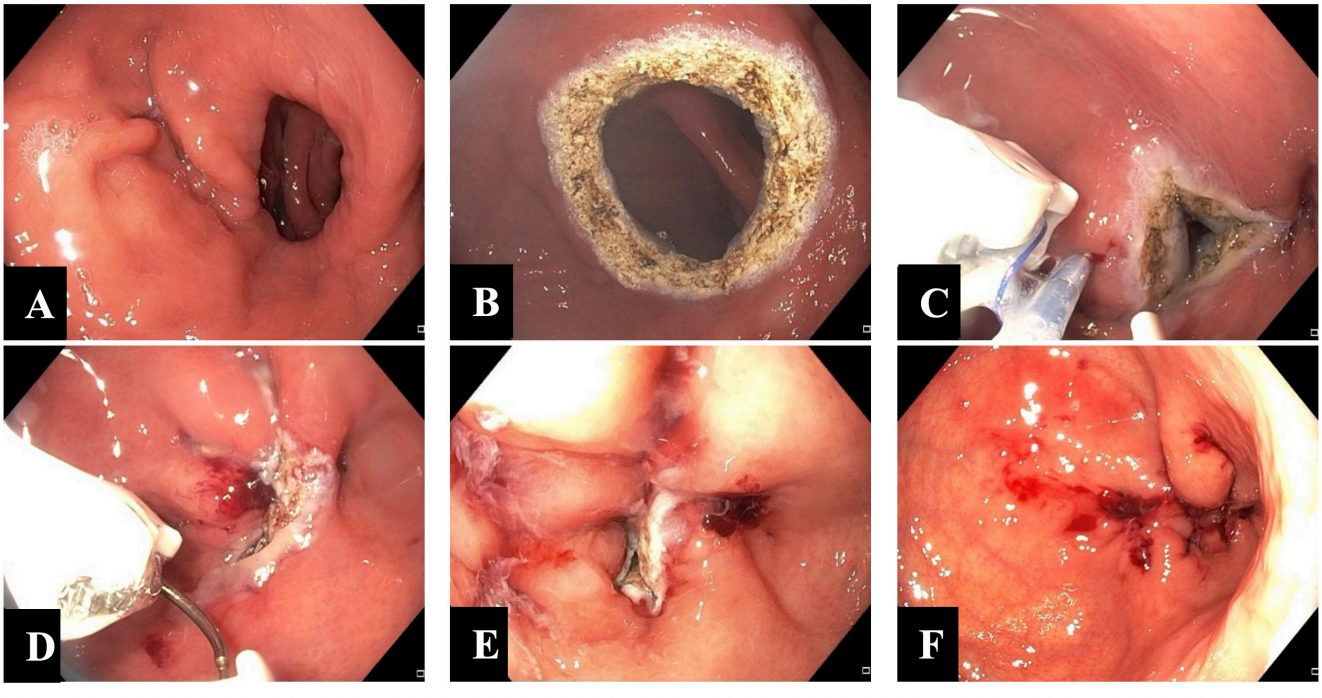

Fig 2. **(A)** Endoscopic view showing dilated gastro-jejunal anastomosis **(B)** Argon plasma coagulation was applied circumferentially around the edge of the outlet **(C)** The tissue helix was used to grasp the tissue at the gastrojejunal anastomosis **(D)** Gastro-jejunal anastomosis size reduction after first plication **(E, F)** Endoscopic view demonstrating gastrojejunal anastomosis revision and gastric pouch reduction.

Literature review

Endoscopic therapy has emerged as an alternative option for the treatment of weight regain. Various endoscopic techniques have been described, including sclerotherapy, ablation therapy, clipping, suturing and plication. TORe applies full-thickness suturing to reduce the size of the GJA. The %TWL at 1 year, 2 years, and 3 years was 9.5%, 8.1%, and 8.6%, respectively, in 150 patients post-RYGB.[27] A retrospective study of 342 patients with RYGB assessed the 5-year outcomes of TORe and demonstrated the safety and efficacy of the procedure, with a mean %TWL at 1 year, 3 years, and 5 years of 8.5%, 6.9%, and 8.8% respectively. In this series, a variety of suturing patterns were used: 76%, 17.5%, 4.4%, and 2.1% were performed using single purse-string, interrupted, double purse-string, and running suture patterns, respectively. Pouch reinforcement was performed in about 60% of the cases. About 40% required additional weight loss therapy, including medical treatment and repeat TORe (3.6%).[28] The suturing technique used for TORe can be interrupted, purse-string, running or figure-of-eight. For the interrupted suture pattern, a single suture is used to place two stitches across from each other at the GJA until the size was reduced. If the gastric pouch was dilated, interrupted stitches were placed in the distal pouch to reduce pouch volume and size. In the purse-string pattern, one suture is used to place multiple stitches around the GJA in a continuous circumferential fashion, typically requiring 8 to 12 stitches. A hydrostatic balloon was inflated to a diameter of 8 to 12 mm inside the anastomosis before cinching over the balloon. A study comparing purse-string to an interrupted suture pattern for TORe demonstrated a greater weight loss in the purse-string group (8.6% TWL vs. 6.4% TWL, p=0.02) at 12 months.[29]

Argon plasma coagulation (APC) is generally performed circumferentially around the GJA before suturing. This ablation step is believed to be vital because it ablates the mucosal layer to allow submucosal to submucosal tissue apposition during suturing steps.[30] A meta-analysis showed that the combination of APC and TORe resulted in greater weight loss compared to suturing alone.[31] A recently published novel technique for endoscopic outlet revision was a combined endoscopic submucosal resection (ESD), performed circumferentially at the GJA before suturing (ESD-TORe technique). A retrospective study comparing the outcomes of 19 patients with ESD-TORe matched with 57 patients receiving APC-TORe, demonstrated that the ESD-TORe group experienced greater %TWL than the APC-TORe group (12.1% vs. 7.5%, p=0.036) at 12 months.[30]

The safety profile has been assessed, and the pooled rate of overall adverse events was 11.4%, with abdominal pain being the most common adverse event. The pooled rate of severe adverse events was 0.57%, with the bleeding rate of 1.14%, and the perforation rate of 0.46%.[32] Therefore, TORe appears safe, effective and durable for the treatment of weight regain or inadequate weight loss after RYGB.

CONCLUSION

Bariatric endoscopy will play an essential role in treating obesity in Thailand in the future as the obesity prevalence is rising. We reported the first two cases of successful ESG and TORe performed in Thailand. The endoscopic bariatric therapy using the full-thickness suturing device is safe, feasible, and effective as primary and revisional procedures and is a good alternative treatment option for obesity. These procedures may offer a paradigm shift in obesity management as they fill the treatment gap between medical therapy and bariatric surgery.

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REFERENCES

1. World Health Organization. "Obesity and Overweight" WHO fact sheet 2020 [cited 2020 September 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. The Look ARG. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. Obesity. 2014; 22(1):5-13.
3. Yanovski SZ, Yanovski JA. Long-term Drug Treatment for Obesity: A Systematic and Clinical Review. JAMA. 2014;311(1): 74-86.
4. Kumar N, Sahdala HNP, Shaikh SN, Wilson E, Manoel GN, Zundel N, et al. Mo1155 Endoscopic Sleeve Gastroplasty for Primary Therapy of Obesity: Initial Human Cases. Gastroenterology. 2014;146.
5. Lopez-Nava G, Negi A, Bautista-Castaño I, Rubio MA, Asokkumar R. Gut and Metabolic Hormones Changes After Endoscopic Sleeve Gastroplasty (ESG) Vs. Laparoscopic Sleeve Gastrectomy (LSG). Obesity Surgery. 2020;30(7):2642-51.
6. Lopez-Nava G, Sharaiha RZ, Vargas EJ, Bazerbachi F, Manoel GN, Bautista-Castaño I, et al. Endoscopic Sleeve Gastroplasty for Obesity: a Multicenter Study of 248 Patients with 24 Months Follow-Up. Obesity Surgery. 2017;27(10):2649-55.
7. Sharaiha RZ, Kumta NA, Saumoy M, Desai AP, Sarkisian AM, Benevenuto A, et al. Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients. Clinical Gastroenterology and Hepatology. 2017;15(4): 504-10.
8. Kumar N, Abu Dayyeh BK, Lopez-Nava Breviere G, Galvao Neto

MP, Sahdala NP, Shaikh SN, et al. Endoscopic sutured gastroplasty: procedure evolution from first-in-man cases through current technique. Surgical endoscopy. 2018;32(4):2159-64.
9. Barrichello S, Hourneaux de Moura DT, Hourneaux de Moura EG, Jirapinyo P, Hoff AC, Fittipaldi-Fernandez RJ, et al. Endoscopic sleeve gastroplasty in the management of overweight and obesity: an international multicenter study. Gastrointestinal Endoscopy. 2019;90(5):770-80.
10. Jain D, Bhandari BS, Arora A, Singhal S. Endoscopic Sleeve Gastroplasty - A New Tool to Manage Obesity. Clin Endosc. 2017;50(6):552-61.
11. de Moura DTH, Badurdeen DS, Ribeiro IB, Leite EFMdSD, Thompson CC, Kumbhari V. Perspectives toward minimizing the adverse events of endoscopic sleeve gastroplasty. Gastrointestinal Endoscopy. 2020;92(5):1115-21.
12. de Moura DTH, de Moura EGH, Thompson CC. Endoscopic sleeve gastroplasty: From whence we came and where we are going. World J Gastrointest Endosc. 2019;11(5):322-8.
13. Saumoy M, Schneider Y, Zhou XK, Shukla A, Kahaleh M, Aronne L, et al. A single-operator learning curve analysis for the endoscopic sleeve gastroplasty. Gastrointestinal Endoscopy. 2018;87(2):442-7.
14. Alqahtani A, Al-Darwish A, Mahmoud AE, Alqahtani YA, Elahmedi M. Short-term outcomes of endoscopic sleeve gastroplasty in 1000 consecutive patients. Gastrointestinal Endoscopy. 2019;89(6):1132-8.
15. Hedjoudje A, Abu Dayyeh BK, Cheskin LJ, Adam A, Neto MG, Badurdeen D, et al. Efficacy and Safety of Endoscopic Sleeve Gastroplasty: A Systematic Review and Meta-Analysis. Clinical Gastroenterology and Hepatology. 2020;18(5):1043-53.e4.
16. Singh S, Hourneaux de Moura DT, Khan A, Bilal M, Ryan MB, Thompson CC. Safety and efficacy of endoscopic sleeve gastroplasty worldwide for treatment of obesity: a systematic review and meta-analysis. Surgery for Obesity and Related Diseases. 2020;16(2):340-51.
17. Li P, Ma B, Gong S, Zhang X, Li W. Efficacy and safety of endoscopic sleeve gastroplasty for obesity patients: a meta-analysis. Surgical Endoscopy. 2020;34(3):1253-60.
18. Novikov AA, Afaneh C, Saumoy M, Parra V, Shukla A, Dakin GF, et al. Endoscopic Sleeve Gastroplasty, Laparoscopic Sleeve Gastrectomy, and Laparoscopic Band for Weight Loss: How Do They Compare? Journal of Gastrointestinal Surgery. 2018;22(2):267-73.
19. Singh S, de Moura DTH, Khan A, Bilal M, Chowdhry M, Ryan MB, et al. Intragastric Balloon Versus Endoscopic Sleeve Gastroplasty for the Treatment of Obesity: a Systematic Review and Meta-analysis. Obesity Surgery. 2020;30(8):3010-29.
20. Fayad L, Adam A, Schweitzer M, Cheskin LJ, Ajayi T, Dunlap M, et al. Endoscopic sleeve gastroplasty versus laparoscopic sleeve gastrectomy: a case-matched study. Gastrointestinal Endoscopy. 2019;89(4):782-8.
21. Yang P, Chen B, Xiang S, Lin X-F, Luo F, Li W. Long-term outcomes of laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for morbid obesity: Results from a meta-analysis of randomized controlled trials. Surgery for Obesity and Related Diseases. 2019;15(4):546-55.
22. Brolin RE. Bariatric Surgery and Long-term Control of Morbid Obesity. JAMA. 2002;288(22):2793-6.
23. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects. New England Journal of Medicine. 2007;357(8):741-52.
24. O'Brien CS, Wang G, McGinty J, Agénor KK, Dutia R, Colarusso A, et al. Effects of Gastrogastric Fistula Repair on Weight Loss and Gut Hormone Levels. Obesity Surgery. 2013;23(8):1294-301.
25. Abu Dayyeh BK, Lautz DB, Thompson CC. Gastrojejunal Stoma Diameter Predicts Weight Regain After Roux-en-Y Gastric Bypass. Clinical Gastroenterology and Hepatology. 2011;9(3):228-33.
26. Heneghan HM, Yimcharoen P, Brethauer SA, Kroh M, Chand B. Influence of pouch and stoma size on weight loss after gastric bypass. Surgery for Obesity and Related Diseases. 2012;8(4):408-15.
27. Kumar N, Thompson CC. Transoral outlet reduction for weight regain after gastric bypass: long-term follow-up. Gastrointestinal Endoscopy. 2016;83(4):776-9.
28. Jirapinyo P, Kumar N, AlSamman MA, Thompson CC. Five-year outcomes of transoral outlet reduction for the treatment of weight regain after Roux-en-Y gastric bypass. Gastrointestinal Endoscopy. 2020;91(5):1067-73.
29. Schulman AR, Kumar N, Thompson CC. Transoral outlet reduction: a comparison of purse-string with interrupted stitch technique. Gastrointestinal Endoscopy. 2018;87(5):1222-8.
30. Jirapinyo P, de Moura DTH, Thompson CC. Endoscopic submucosal dissection with suturing for the treatment of weight regain after gastric bypass: outcomes and comparison with traditional transoral outlet reduction (with video). Gastrointest Endosc. 2020;91(6):1282-8.
31. Brunaldi VO, Jirapinyo P, de Moura DTH, Okazaki O, Bernardo WM, Galvão Neto M, et al. Endoscopic Treatment of Weight Regain Following Roux-en-Y Gastric Bypass: a Systematic Review and Meta-analysis. Obesity Surgery. 2018;28(1):266-76.
32. Dhindsa BS, Saghir SM, Naga Y, Dhaliwal A, Ramai D, Cross C, et al. Efficacy of transoral outlet reduction in Roux-en-Y gastric bypass patients to promote weight loss: a systematic review and meta-analysis. Endosc Int Open. 2020;8(10):E1332-E40.