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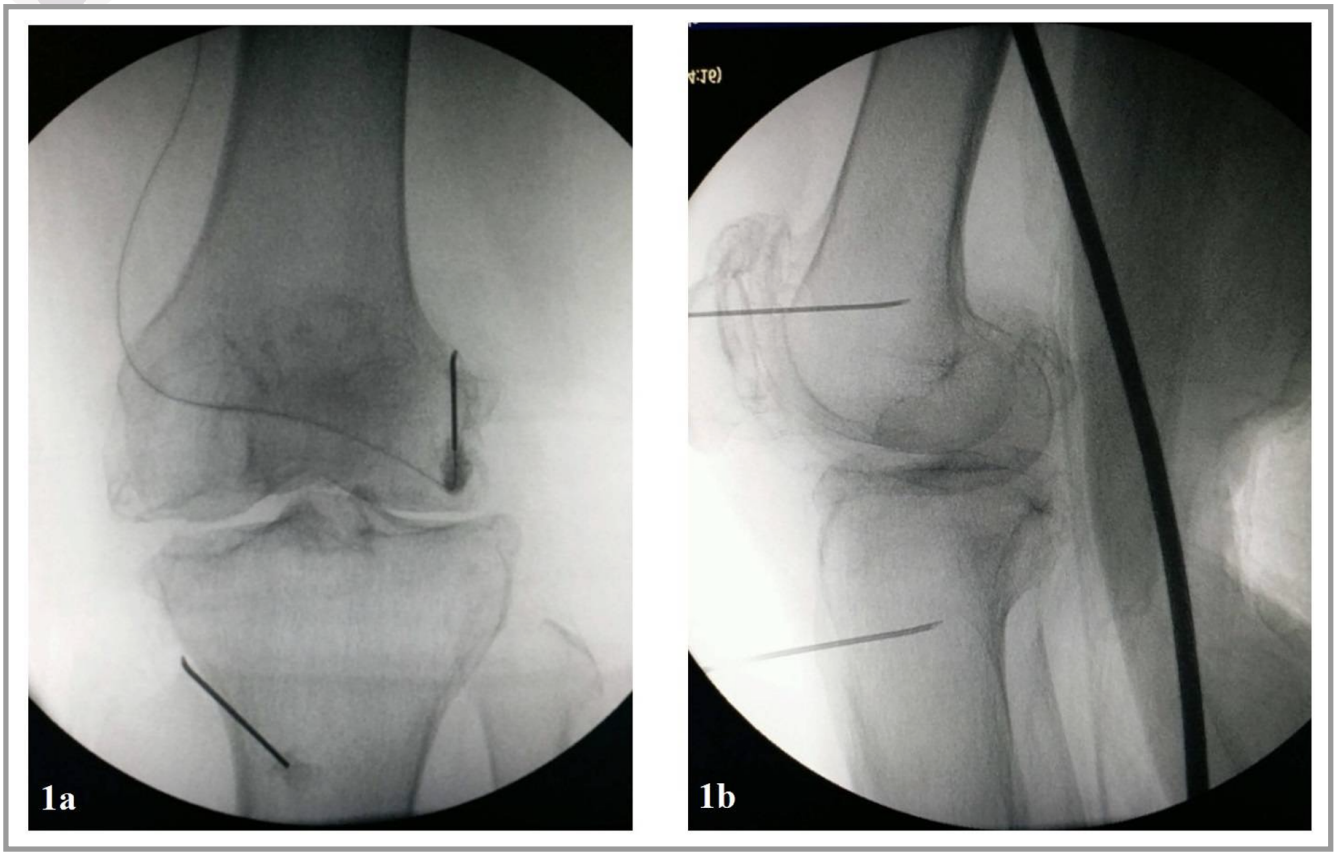

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Prevalence and Type of Human Papillomavirus Infection in Thai Males with Anogenital Warts

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ABSTRACT

Objective: Low-risk (LR) human papillomavirus (HPV) infection is a recognized cause of anogenital warts (AGW). LR-HPV 6 and 11 are the HPV types that were reported to be associated with AGW. However, data specific to the HPV types that associate with AGW in Thailand are scarce. Accordingly, this study aimed to determine the prevalence of HPV in patients with AGW, and to investigate for association between HPV types and AGW among Thai males attending the sexually transmitted disease clinic of Siriraj Hospital – Thailand's largest national tertiary referral center.

Materials and Methods: This prospective study was conducted at the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during April 2017 to December 2019. Thai males with at least one AGW were included. AGW specimens were obtained, and HPV genotyping was performed at both the genital and perianal areas.

Results: A total of 43 Thai male participants (mean age: 37.3±13.8 years; range: 19-72) with AGW were enrolled. The rate of HPV positive detection at the genital area and the perianal area was 86.0% and 72.1%, respectively. The most common HPV types at the genital area were HPV 6, followed by HPV 11. Alternatively, the most common HPV types at the perianal area were HPV 11, followed by HPV 6.

Conclusion: The findings of this study suggest LR-HPV types 6 and 11 as the culprit pathogenic causes of AGW among males in Thailand. These findings further support and emphasize the importance of HPV vaccination for prophylaxis against both HPV and AGW.

Keywords: Human papillomavirus type; anogenital warts; clinical characteristics; sexually transmitted disease (Siriraj Med J 2023; 75: 407-412)

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide[1], and more than 200 different HPV types have been identified.[2] HPV types can also be subcategorized according to their oncogenic potential into high-risk (HR) or low-risk (LR) types. Most HPV infections spontaneously resolve via host immune response within a couple of years of onset. Persistence of HPV infection is essential for disease progression from latent infection to active infection.[3] HR types are strongly associated with malignant disease, such as cervical, anogenital, and oropharyngeal cancers.[4] LR types, such as HPV 6 and 11, are the most frequently detected types in anogenital warts (AGW).[5,6] HPV induces hyperplasia

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and hyperkeratosis, which presents clinically as a wart.[7] Perianal warts might occur with genital warts due to either local spread of infection or direct contact during anal coitus.[8]

The high-risk HPV types 16 and 18 cause approximately 50% of the estimated 26,000 annual cases of penile cancer whereas the low-risk HPV types 6 and 11 carry for about 90% of AGW.[9] HPV patients are more likely to suffer from other sexually transmitted infections, such as syphilis, hepatitis B, hepatitis C, gonorrhea, chlamydia and human immunodeficiency virus (HIV).[10] Treatment for AGW is normally lengthy and painful, and AGW has a significant adverse impact on quality of life.[11] Since the HR HPV types can develop into cervical, anal, vulvar, and penile cancers, the genotyping of HPV infections is clinically important.

Data specific to the HPV types that associate with AGW in Thailand are scarce. Accordingly, the aim of this study was to determine the prevalence of HPV in patients with AGW, and to investigate for association between HPV types and AGW among Thai males attending the sexually transmitted disease (STD) clinic of Siriraj Hospital – Thailand's largest national tertiary referral center which takes care cases of skin and STD such as syphilis[12], herpes simplex virus infections.[13]

MATERIALS AND METHODS

Study population

This prospective study was conducted at the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during April 2017 to December 2019. Thai males who attended the STD clinic who were aged >18 years, who were willing to enroll in the study and sign the consent form, and who were diagnosed with AGW by clinical manifestation were included. AGW specimens were obtained, and HPV genotyping was performed at both the genital and perianal areas. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 677/2015).

Procedure

History taking and physical examination were performed in each participant. Specimens from lesions at the perianal and genital area were collected and stored at -80°C. A Roche Linear Array HPV Genotyping Test (Roche Diagnostics, Basel, Switzerland) was used to detect 37 HPV types, including 13 HR HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66), and 24 LR HPV types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 67-73, 81-84, IS39, and CP6108). A follow-up appointment was made 2 weeks later to inform the study patient of the results of testing, and to decide upon a treatment plan. Each participant was treated at our center's STD clinic.

Statistical analysis

Descriptive statistics were used to summarize patients' characteristics and HPV types (mean plus/minus standard deviation for normally distributed continuous data; and number and percentage for categorical data). Statistical analysis was performed using PASW Statistics for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

A total of 43 Thai male participants (mean age(sd): 37.3(13.8) years; range: 19-72) with AGW were enrolled. Table 1 shows the sociodemographic, behavioral/lifestyle, and clinical characteristics of study AGW patients. More than half (60.5%) of patients reported having more than one sexual partner, and most participants reported being single. Almost half (48.8%) of participants reported having a bachelor's degree and being employed as an office worker. Regarding reported sexual preference, 72.1% were heterosexual, 18.6% were homosexual, and 9.3% were bisexual.

Some participants reported having a history of other STDs. The most commonly reported disease was gonorrhea (11.6%), followed by syphilis (6.9%). The other STDs reported was non-gonorrhea (2.3%), chancroid (2.3%), and Lymphogranuloma venereum (2.3%).

All 43 participants developed at least 1 genital or perianal wart. The most common site of lesion was the genitalia (67.4%), followed by the perianal area (23.3%). Only 9.3% of participants had AGW on both areas. More than three-quarters (83.7%) of lesions were verrucous papules, and 14% were flat lesions.

The HPV positive detection rate at the genital area and perianal area was 86.0% and 72.1%, respectively (Table 2). In this study, the incidence of individual HPV types was counted regardless of whether the patient had a single-type infection or a multiple-type infection. The most common HPV types at the genital area were HPV 6, followed by HPV 11, HPV 55 and HPV 51 as shown in Fig 1A. The most common HPV types at the perianal area were HPV 11, followed by HPV 6, HPV 18 and HPV 62, as shown in Fig 1B. The prevalence of HR HPV at the genital area and perianal area was 32.6% and 34.9%, respectively.

The rate of single-type infection was 37.2% at the genital area, and 34.9% at the perianal area. The rate of dual-type (2 HPV types) infection was 14.0% at the

TABLE 1. Sociodemographic, behavioral/lifestyle, and clinical characteristics of study anogenital wart patients (N=43).

Characteristics (%)	N (%)
Age (years) mean ± SD, (range)	37.3 ± 13.8, (19-72)
Marital status	
Single	28 (65.1)
Married	9 (20.9)
Divorced/Widowed/Separated	6 (14.0)
Highest education	
Bachelor degree or higher	25 (58.1)
Under bachelor degree	18 (41.9)
Occupation	
Labor	21 (48.8)
Officer	19 (44.2)
Unemployed	3 (7.0)
Underlying diseases	
Hypertension	6 (24.0)
Allergy	3 (7.0)
Dyslipidemia	3 (7.0)
Diabetes Mellitus	2 (4.7)
Human immunodeficiency virus infection	8 (18.6)
Drug allergy	3 (7.0)
Sexual orientation	
Heterosexuality	31 (72.1)
Homosexuality or bisexuality	12 (27.9)
Sexual activities	
Vaginal sex	34 (79.1)
Insertive anal sex	10 (23.3)
Receptive anal sex	10 (23.3)
Having oral sex	20 (46.5)
Multiple sex partners	26 (60.5)
Sexworker(s) contact within 5 years	3 (7.0)
Blood transfusion within 5 years	2 (2.0)
Tattoo	10 (23.3)
Smoking	9 (20.9)
Alcohol drinking	18 (41.9)
Intravenous Drug Use	1 (2.3)
Condom used	
Never	8 (18.6)
Sometimes	30 (69.8)
Always	5 (11.6)

TABLE 2. HPV positive rate and prevalence of low-risk and high-risk HPV types at the genitalia and perianal areas in study anogenital wart patients[a] (N=43).

Location	HPV types	N (%)
Genitalia	Positive	37 (86.0)
	Low risk[b]	23 (53.5)
	High risk[c]	14 (32.5)
Perianal area	Positive	31 (72.1)
	Low risk[b]	16 (37.2)
	High risk[c]	15 (34.9)

HPV, human papillomavirus
[a] HPV types were counted regardless of the status of single- or multiple-type infections.
[b] HPV type 6, 11, 40, 42, 53, 54 ,55, 61, 62, 67, 68, 73, 81, 82, 84, CP6108, and IS39
[c] HPV type 16, 18, 39, 51, 52, 58, and 59

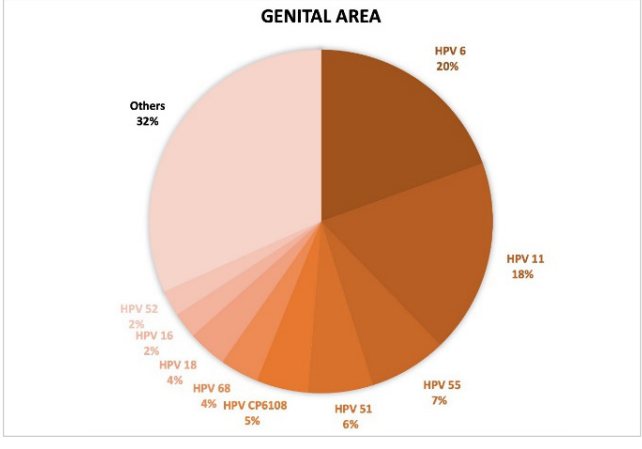

Fig 1. (A) The percentage for each type of HPV in genital area. The most common HPV types at the genital area were HPV 6, followed by HPV 11, HPV 55 and HPV 51. Others HPV typing included: HPV 39, 40, 42, 53, 54, 58, 59, 61, 62, 67, 81, 82, 84 and IS39.

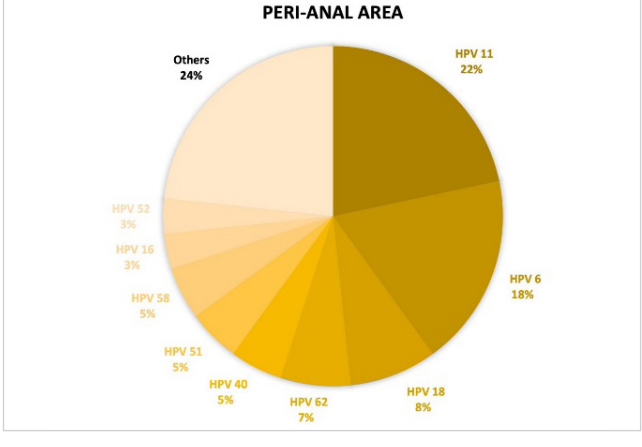

Fig 1. (B) The percentage for each type of HPV in perianal area. The most common HPV types at the perianal area were HPV 11, followed by HPV 6, HPV 18 and HPV 62. Others HPV typing included: HPV 53, 54, 59, 67, 68, 73, 81, 84 and CP6108.

genital area, and 18.6% at the perianal area. The rate of three or more HPV type coinfections was 34.9% at the genital area, and 18.6% at the perianal area (Table 3).

TABLE 3. Frequency of single and multiple HPV type infections in anogenital wart patients.

Number of HPV type	Genital Area N=43 n (%)	Perianal Area N=43 n (%)
1 (single infection)	16 (37.2)	15 (34.9)
2	6 (14.0)	8 (18.6)
3	5 (11.6)	2 (4.7)
4	6 (14.0)	2 (4.7)
5	2 (4.7)	1 (2.3)
6	0 (0.0)	1 (2.3)
7	1 (2.3)	1 (2.3)
8	1 (2.3)	0 (0.0)
9	0 (0.0)	1 (2.3)
Negative	4 (9.3)	5 (11.6)

Abbreviation: HPV, human papillomavirus

DISCUSSION

AGW is widely regarded as a benign disease that is caused by LR HPV. However, studies about HPV genotype distribution in Thai patients with genital warts are limited. To the best of our knowledge, this is the first study to evaluate the distribution pattern of HPV types at 2 anatomic sites in Thailand.

The average age of participants affected by AGW in our study was 37.3 years. This mean age is consistent with the age of manifestation of AGW reported by Clanner-Engelshofen, *et al.*[10]; however, adolescents are exposed to HPV earlier, and may develop AGW earlier due to a higher frequency of sexual activity and more sexual partners.

Most participants (72.1%) in our study reported their sexual orientation as heterosexual, which is consistent with the 76.0% rate reported by Dhumale, *et al.* (76%).[8] Our prevalence of men who have sex with men (MSM) was 18.6%, which was similarly reported by Jiamton, *et al.*[14]

In the present study, HPV was identified in 86% (37/43) and 72% (31/43) of genital and perianal samples,

respectively. The most commonly isolated HPV genotype was HPV 6, followed by HPV 11 either alone or in combination with another HPV type. This result is similar to those from previous studies in Thailand, China, Mexico, Brazil, and the United States.[15-18] Approximately 90% of anal squamous cell carcinoma can be attributed to HPV, especially HR-type (HPV 16 and 18).[19] A screening program for high-risk patients can help to prevent or early detect anal cancer.[20] HR HPV types at the anal area were also found in our study. Therefore, these high-risk cases were referred to a colorectal surgeon for clinical evaluation and follow-up.

In this study, we found multiple-type HPV infection to be common among patients with AGW. A study from Shanghai, China found the prevalence of multiple LR HPV infection to be relative low, but multiple HR HPV infection was common.[21] A study from Italy reported that multiple HPV infections occurred by chance, and no evidence supporting higher tendency of coinfections in the specific HPV types.[22]

We swabbed both the genital and anal areas of patients who had a wart in either area. Our findings showed that even though some participants did not have a lesion at the anal area, they still showed as HPV positive at the anal area. The explanation for this is that AGW are often asymptomatic. Transmission can occur via skin-to-skin contact during sexual intercourse, oral sex, anal sex, or other contact involving the genital area.[23]

The burden of this disease could be lowered by increased HPV vaccination. Bivalent HPV vaccine covers HPV 6 and 11, quadrivalent HPV vaccine covers HPV 6, 11, 16, and 18, and 9-valent HPV vaccine covers HPV types 6, 11, 16, and 18, 31, 33, 45, 52, and 58. All types of the vaccines can prevent the two predominant genital wart-associated HPV types (HPV 6 and HPV 11) in this study. According to our results, we implied that quadrivalent vaccines could prevent HPV infection at genital and perianal area at 44% and 51%, respectively. Moreover, the prevention rates increased to 50% for genital and 59% perianal area by the 9-valent HPV vaccine. However, this study was based on a very limited number of patients. We could not imply for the whole Thai population. Further studies in larger population in Thailand are needed.

In this study, we found a low prevalence of HPV 16 in AGW compared to other studies that recommended the use of quadrivalent HPV vaccine to protect against AGW.[16,21] However, the bivalent HPV vaccination might be suitable for prevention of AGW in Thai males. Future study is needed to evaluate cost-effectiveness compared between bivalent and quadrivalent HPV vaccines relative to their impact in protecting against HPV-related diseases like cervical cancer and anal cancer.

AGW is a disease that is associated with both psychological and financial burden.[24] Studies from Taiwan and the Philippines reported negative psychosocial impact of AGW on both well-being and health-related quality of life.[25,26]

Limitations

The notable limitation of this study was the lack of histologic confirmation to rule out intraepithelial lesion or squamous cell carcinoma (SCC), both of which can coexist with or appear similar to AGW.

CONCLUSION

The findings of this study suggest LR-HPV types 6 and 11 as the culprit pathogenic causes of AGW among males in Thailand. These findings further support and emphasize the importance of HPV vaccination for prophylaxis against both HPV and AGW.

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Conflict of interest statement:

All authors have no conflicts of interest to declare relevant to the contents of this article.

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Association between Body Image Focused Social Media Usage (BSMU), Resilience, Attachment and Eating-related Problems among High School Students in Bangkok

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ABSTRACT

Objective: This study aimed to find the association among body image focused social media usage (BSMU), resilience, attachment, and eating-related problems among Thai adolescents.

Materials and Methods: Cross-sectional descriptive research was conducted with a sample of 495 high school students from three schools in Bangkok. The participants answered an online questionnaire comprised of age, sex, height/weight, BSMU, Body-esteem Scale for Adolescents and Adults, Eating Attitudes Test, Inventory of Parent and Peer Attachment for Children, and the Thai Resilience Quotient. Descriptive statistics were used to analyze demographic information, body satisfaction, resilience, attachment, and eating-related problems. T-tests, chi-square, and multivariate logistic regression analysis were performed to explore the associations between these variables.

Results: Mean (SD) age was 17.06 (0.805), with 307 female participants (62%). Time spent on social media was found to be associated with increased risk of binging (AOR (CI) = 1.71 (1.14-2.56)). BSMU was associated with increased risk of inappropriate eating attitudes, binging, purging and using laxative (AOR (CI) = 1.14 (1.03-1.27), 1.14 (1.06-1.22), 1.20 (1.04-1.40), and 1.21 (1.09-1.34) respectively). Higher resilience was found to associated with lower risk in binging (AOR (CI) = 0.45 (0.21-0.97)). However, attachment is not associated with any of eating-related problems.

Conclusion: BSMU usage was associated with inappropriate eating attitudes and behavior. Findings also suggest that higher resilience and stronger attachment were associated with lower risk of eating-related problems. The effectiveness of resilience and attachment improvement programs should be explored to help protect against eating problems.

Keywords: Social media; body image; inappropriate eating behaviors; resilience; adolescent-parent relationship
(Siriraj Med J 2023; 75: 413-426)

INTRODUCTION

Social media (SM) has revolutionized communication and relationships, but it has also been linked to negative consequences for mental health, including eating problems in adolescents.[1,2] The issue of eating problems in adolescents is of significant importance and interest to the scientific community. Eating disorders are prevalent in adolescence and can have severe consequences for mental and physical health.[3,4] Previous studies have shown that significant SM use predicts increased body dissatisfaction and can

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lead to inappropriate eating behaviors such as binging and purging.[1,5-7] However, most studies only found an association between general SM use and eating-related problems, such as number of SM platforms[2,8], time spent on SM[1], frequency of SM usage[6,8], visiting or commenting on others' profile[9], general smartphone activities which might not related to body-image (e.g., browsing websites, sending and receiving text messages/e-mailing, watching TV shows).[5] Additionally, not all aspects of SM are associated with eating-related problems, and internalization and appearance comparison may be responsible for the maladaptive effects of SM use.[1,10,11]

Previous studies have examined the association between body image-related SM usage and eating-related problems, but have only focused on some body image-related SM activities such as photo-related activities (e.g., posting selfies, photo manipulation before posting, comments or likes on others' selfies)[12,13], and finding information related to body image on SM.[14] However, people engage in various body image-focused social media usage (BSMU) activities (e.g., number of selfie posts, how important of like or comments on their pictures, how often they photoshop their pictures before posting, how their profile picture looks) which might affect eating-related problems.[15-17]

SM usage has been found to have negative effects on eating-related problems, and identifying protective factors against these effects is important. Resilience is an important protective factor against many mental health problems[18,19], and studies have shown that individuals with greater resilience have fewer body image issues.[20-22] Emotional regulation, which is a components of resilience, has been found to plays a mediating role in the relationship between body image disturbance and disordered eating behavior.[23] Healthy adolescent-parent attachment has also been identified as an important protective factors against problematic eating behaviors.[24] However, spending more time on electronic media has been associated with lower quality attachment between adolescents and parent[25-27], and growing up in a dysfunctional family type has been linked to a higher risk of developing eating disorders in. female adolescents.[28] Berge et al., suggest that high quality family relationships and a sense of connection with parents may protect against problematic eating behaviors.[29] However, few studies have examined protective effect of these factors against negative effect of SM use, particularly on eating-related problems.[30,31]

There are many studies that found an association between SM activities and eating problems. However, most of them usually found an association between a few specific SM activities and eating-related problem as previously mentioned. Moreover, there are also limited studies on the protective effect of resilience and attachment against these problems. In this study, the researcher decided to explore 1) the association between BSMU and eating-related problems, 2) the association among resilience, attachment, and eating-related problems among high school students.

MATERIALS AND METHODS

Cross-sectional descriptive research was conducted to investigate the social media use behaviors, attachment, and resilience of students in grades 10 – 12 in the Thai educational system in Bangkok, and the effect on eating-related problems. The data were collected after the study received full approval from the institutional ethical review board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University under the code MURA 2020/366.

Participants and procedure

Purposive sampling was used to choose three schools, two government schools and one international school following an international curriculum within Thai educational system in Bangkok, to be included in this study. Participants were in grades 10-12 in the 2nd semester of educational year 2020 and were selected in accordance with the teachers' convenience. Sample size was calculated using the G*Power[32,33] where effect size = 0.03, α error probability = 0.05, Power = 0.95 and number of predictions = 10. The total sample size required from the result of this calculation was 436. Students who could not read Thai, would not give assent to participating in the research, and those who did not complete the questionnaire were excluded. The data was collected from 15 to 31 October 2020 through an online questionnaire. After researchers provided details of the study and inform and consents were obtained, a QR code link to the online questionnaire was provided to participants. There were 529 questionnaires returned with 34 incomplete responses (6.43% of returned responses) resulting in a total of 495 participants (93.57%) (Fig 1).

Measurement

The survey consisted of six parts. The first part is demographic data which comprise questions regarding age, sex, weight/height, and grade in school.

The BSMU questionnaire was developed by the researcher to investigate BSMU. This self-reported questionnaire consisted of 10 questions and was based on a review of studies on body image-related SM usage.[1,5,7,8,9,34,35] The draft questionnaire was evaluated for face validity by three experts in psychiatry with experience in adolescent media use, and was revised based on their feedback. The

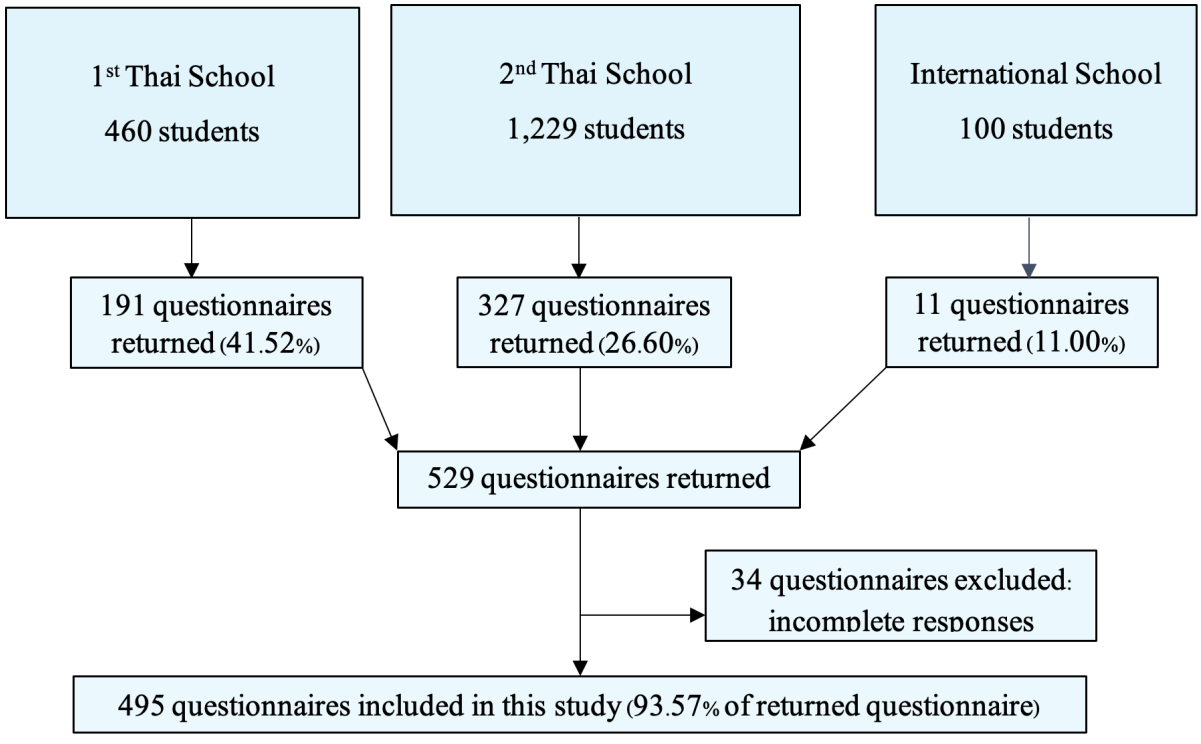

Fig 1. Participant selection for the study

questionnaire was then pilot-tested with ten students in Bangkok, and the questionnaire was revised based on feedback from the pilot test such as added a fill-in-the-blank option for the question about which social media platforms participants use most often, and the instructions for how to respond to the questions was modified to minimize confusion. The first question asked, "Which of the following SM platforms do you use most often?" The 11 most popular platforms from the website Digital 2020: Thailand[36] and a fill in the blank choice for "others" were possible replies and more than one reply was permitted. Question 2 asked how much time the respondent spent on SM following superstars/models and topics such as weight gain/loss and beauty. This response was fill in the blank. The next question (question 3) asked what the participant's profile picture was (e.g., waist-up, full body, someone/thing besides the participant). The next six questions (question 4-9) asked, within the last month how often participants conducted body image focused activities such as, posting selfies, photoshopping, and tagging/un-tagging themselves in pictures. Response options ranged from never (0) to every time (3). The final question (question 10) asked how important likes received on selfies or pictures were to the respondent. The results from last seven questions, which have responses option ranged from not at all (0) to very important (3), were summed together and resulted in a possible total score of 0 – 21 points, with higher scores indicating greater engagement in body image-focused social media usage. The reliability for this scale was questionable (Cronbach's alpha = 0.64). (the full version of BSMU questionnaire can be seen in supplementary material 1)

Eating-related problems were measured with three instruments as following:

1) The weight group was assessed using the "Nutrition Computation Program" (INMU-NutriStat), which was developed by Chittchana U and the Nutrition Institute of Mahidol University. This program computerized the nutrition of populations aged 1 day up to 19 years, and gave the results of nutrition status based on weight for age (w/a), height for age (h/a), and weight for height (w/h) for both genders. This program was widely used in a study about the weight status of children and adolescents in Thailand.[37] In this study we used only w/h because they are relevant to our outcomes. The results for each nutritional status based on w/h were divided into 3 categories which are underweight (under -1.5 SD), average weight (-1.5 to +1.5 SD), and overweight (more than +1.5 SD) compared with norms for Thai children.[37,38]

2) Body-esteem was collected using the 23-question Body-esteem Scale for Adolescents and Adults (BESAA) developed by Mendalson et al.[39], and translated into Thai by Gunta A. (Cronbach's Alpha = 0.9).[40] Response options ranged from never agree (0) to always agree (4). Scores for each question were summed and divided into three ranges, low (0.0 – 30.6), medium (30.7 – 61.3), and high

satisfaction (61.4 – 92.0) based on class interval analysis. Participants who had medium or high body satisfaction were grouped together to compare with those who had low body satisfaction. The reliability for this scale was excellent (Cronbach's alpha = 0.9) and validity was assessed with two experts on woman health.[40]

3) To evaluate eating attitudes and behaviors the EAT-26 (Eating Attitudes Test – 26 Questions) developed by Garner et al., and translated by Kaewpornsawan, (Cronbach's Alpha = 0.7) [41,42] was used. Eating attitudes was evaluated with first twenty-six items of the questionnaires (e.g., I Am terrified about being overweight, I Avoid eating when I am hungry) with response options ranged from never (0) to always (3). Inappropriate eating behaviors was assessed using five additional questions which asked how often participants binge, purge, use laxatives/drugs for weight control, exercise longer than 60 minutes, and have participants lost/gained more than 9 kilograms in the past 6 months. Choices were, never, once/month or less, 2-3 times/month, once/week, 2-6 times/week, and once/day or more often. For binging, anything more than once/month, and answers other than never for purging and laxative/drug use were considered at risk. Exercising more than 60 minutes/ day was only considered at-risk if the reply was once/day or more. Weight fluctuation was a simple yes or no reply and participants would be considered at risk if they reply with "yes". The first 26 questions were summed with scores over 12 indicating that the respondent was at risk for developing an eating disorder. The reliability of the scale was excellent (Cronbach's alpha=0.86).

To analyze resilience, the Thai Resilience Quotient Questionnaire (RQ), developed by the Thai Ministry of Public of Mental Health[43], was utilized and demonstrated good reliability (Cronbach's alpha = 0.749). The RQ contains 20 questions with response options ranging from not true (1) to very true (4). There were 3 subscales, emotional stability (questions 1-10), willpower (11-15), and problem-solving (16-20). Each subscale was graded separately and then a total RQ score was summed. Emotional stability was scored as, lower-than- (< 27), normal (27-34), and higher-than-normal (> 34). Willpower was scored as, lower-than- (< 14), normal (14-19), and higher-than-normal (> 19), and problem-solving as, lower-than- (< 13 normal (13-18), and higher-than-normal (> 18). Total RQ score was scored as, lower-than- (< 55), normal (55-69), and higher-than-normal (> 69). The Cronbach's alpha value for this scale was 0.83 which indicate excellent reliability and face validity was evaluated with experts on mental health and psychology.[43]

Adolescent-parent relationship was evaluated using only the parent part (28 questions) of the Inventory of Parent and Peer Attachment – Revised (IPPA-R).[44] The questionnaire was translated into Thai by Lucktong, and demonstrated good reliability (Cronbach's alpha = 0.88) and face validity was evaluated by psychology experts.[45] Responses ranged from never (1) to always true (3). Questions were grouped into 3 subscales, communication (7), trust (8), alienation (8), and non-categorized (5 questions) which were negatively worded and reversed scored. Communication subscale included questions regarding seeking parent's viewpoints, telling parents about problems, and parental support. Trust subscale was made up of questions related to parents respecting their child's opinions, parental acceptance, trust, and understanding. Alienation questions concerned being ashamed around parents, getting easily upset and angry with parents, and lack of parental understanding. The higher the score on each subscale, the greater that attribute, and for total IPPA-R score, the higher the score the stronger the relationship.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 software (IBM, Armonk, NY USA). Descriptive statistics were used to detail demographics (sex, age, grade, weight group), and BSMU, BESAA, EAT-26, IPPA-R, and RQ. T-tests were used to analyze the number of SM accounts classified by sex, grade level, and weight group. Chi-square (X^2) was used to analyze the association among BSMU and weight group, body-esteem, and inappropriate eating behaviors, and to analyze the association between resilience and attachment, and body-esteem, and inappropriate eating behaviors.

Multivariate logistic regression analysis was performed at a 5% level of significance. The associations between demographic data (sex and age), BSMU, IPPA-R, and RQ and outcomes such as weight status, body esteem, eating problems were analyzed using a multivariate logistic regression model. Adjusted Odd Ratio (AOR) was presented for determining the impact of those factors and outcome, while body weight was analyzed by linear regression as a continuous outcome. The model was used to find the association between demographic characteristics, BSMU, resilience, attachment, and eating-related problems.

RESULTS

Demographics, eating-related problems, resilience, and attachment

Out of the 495 participants, 307 were female (62%), and the mean age of all respondents was 17.01 (SD = 0.92). Participants were grouped into under-, average,

and overweight, resulting in a total of 140 overweight (28.3%) and 49 underweight (9.9%). The BESAA found 66 participants (13.3%) had low body-esteem. There were 56 participants (11.3%) in the EAT-26 high-risk group. There was a greater percentage of females admitting to binging (47.6% and 41.0%), purging (6.2% and 5.9%), and laxatives/drug use, (16.9% and 5.3%) at p-value < 0.001. A greater percentage of males excessive exercised (12.2% and 2.6%; p-value < 0.001) and had 9-kilogram weight fluctuations (19.1% and 10.7%; p-value = 0.009). One hundred and eighty-two participants (36.8%) were in low total RQ group. Mean score on the IPPA-R was 58.45 (SD = 5.14). (Table 1)

Body image focused social media usage and association with eating-related problems

Female participants had a greater number of SM accounts (3.20 and 2.83), spent more time on SM (5.38 and 3.82 hours/day), and their overall BSMU score was higher than males (6.84 and 5.31 all at p-value < 0.001). The mean number of SM accounts and time spent on SM were 3.07 (SD = 1.20) and 4.79 hours/day (SD = 4.35) respectively (Table 1). BSMU mean scores of the overweight group (5.78; SD = 2.87) were significantly lower than average weight group (6.48; SD = 3.12) at p-value = 0.024, but not for the under- and the average weight group. Mean BSMU was higher for the EAT-26 high-risk group (7.09 and 61.5) at p-value = 0.029 and for those admitting to binging and laxative/drug use (6.87 and 5.76; 7.77 and 6.04; at p-value < 0.001) and purging (7.40 and 6.18) at p-value = 0.33. Those with binging behaviors spent more time on SM (mean = 5.36 hours) than those who did not (4.32 hours) at p-value = 0.008. Those admitting to laxative/drug use spent more time on SM (mean = 6.50 hours) than those who did not (4.54) at p-value = 0.008 (Table 2).

Association among resilience, attachment, and eating-related problems

Participants in lower RQ group (both total RQ and every subscale) tended to significantly have low body-esteem. Moreover, lower-than-normal willpower scores tended to be in the binging, purging, and laxative/drug use groups (p-value < 0.001, p-value = 0.046 and 0.015, respectively). Lower-than-normal RQ problem-solving subscale scores were mostly in the laxative/drug use group at p-value = 0.005, while those with lower-than-normal total RQ scores tended to be in the binging and laxative/drug use groups at p-value = 0.005 and p-value < 0.001 (Table 3). As for attachment, higher parental alienation and IPPA-R total scores tended to be in the low body-esteem group at p-value = 0.044 and 0.024 respectively (Table 2). Moreover, higher IPPA-R total scores tended to be in the purging group at p-value = 0.026 (Table 3).

Regression analysis for BSMU, resilience, attachment, and eating-related problems

The results found that increased time spent on SM is associated with being in the over-weight group (AOR = 1.07 (1.02-1.12)). However, the BSMU and total IPPA-R scores were associated more with a decreased risk for being in over-weight group (AOR = 0.93 (0.86-0.99) and 0.62 (039-099), respectively). The number of SM accounts is not associated with weight group and low BESAA. Additionally, Resilience (RQ) and IPPA-R are not associated with BESAA. (Table 4)

The higher number of SM accounts is associated with lower risk of purging (AOR 0.62, CI 0.42-0.93), while both time on SM and BMSU scores are associated with higher risk of binging (AOR 1.71, CI 1.14-2.56 and AOR 1.14, CI 1.06-1.22, respectively). In addition to binging, BMSU scores are also associated with being in the EAT-26 high-risk group (AOR 1.14, CI 1.03-1.27), risk of purging (AOR 1.20, CI 1.04-1.40), and risk of drug/laxative use (AOR 1.21, CI 1.09-1.34). While participants who are in high willpower RQ subscale and normal total RQ groups tended to have lower risk of binging (AOR = 0.18 (0.03-0.98) and 0.45 (0.21-0.97), respectively). Participants who are in high emotion RQ subscale tended to have higher risk for excessive exercise (AOR = 16.6 (1.63-169.1)). However, IPPA-R is not associated with any of those factors when analyzed by regression analysis. (Table 5)

DISCUSSION

The result of this study found that having multiple social media accounts, spending more time on SM and having higher BSMU was associated with an increased risk of inappropriate eating attitudes and inappropriate eating behaviors such as binging, purging, using laxative drugs. These findings supported our aims to find that not just overall social media usage, but specifically body-image focused social media usage which have effects on eating-related problems. Moreover, the study found that having higher resilience had a lower risk of binging. However, higher emotional stability (which is a subscale of resilience) associated with an increased risk of overexercise.

In this study, we found that 9.9% of participants were underweight and 28.3% were overweight. While the prevalence of overweight students was similar to a previous study in Thailand, which reported 29.3%

TABLE 1. Descriptive analysis of demographics, eating-related problems, resilience, and attachment.

			Total n = 495 n (%)/mean (SD)	Male n = 188 (38) n (%)/mean (SD)	Female n = 307 (62) n (%)/mean (SD)	*X2/t*	*P*
Number SM Accounts[a]			3.07 (1.20)	2.83 (1.24)	3.20 (1.15)	-3.392	<0.001***
Time on SM[a] (hours)			4.79 (4.35)	3.82 (4.29)	5.38 (4.28)	-3.923	<0.001***
BSMU Total[a]			6.26 (3.02)	5.31 (2.86)	6.84 (2.98)	-5.641	<0.001***
Weight groups	*Average Weight*		306 (61.8)	99 (52.7)	207 (67.4)		
	Underweight		49 (9.9)	25 (13.3)	24 (7.8)	11.206	0.004**
	Overweight		140 (28.3)	64 (34.0)	76 (24.8)		
BESAA	*Low*		66 (13.3)	14 (7.4)	52 (16.9)	9.09	0.003**
	Med-High		429 (86.7)	174 (92.6)	255 (83.1)		
EAT-26	*Low-Risk of attitude*		439 (88.7)	163 (86.7)	276 (89.9)	1.19	0.275
	High-Risk of attitude		56 (11.3)	25 (13.3)	31 (10.1)		
Inappropriate Eating	*Binging*	*Y*	223 (45.1)	77 (41.0)	146 (47.6)	2.051	0.152
		N	272 (54.9)	111 (59.0)	161 (52.4)		
	Purging	*Y*	30 (6.1)	11 (5.9)	19 (6.2)	0.023	0.878
		N	465 (93.9)	177 (94.1)	288 (93.8)		
	Laxatives, etc.	*Y*	62 (12.5)	10 (5.3)	52 (16.9)	14.367	<0.001***
		N	433 (87.5)	178 (94.7)	255 (83.1)		
	Excessive	*Y*	31 (6.3)	23 (12.2)	8 (2.6)	18.412	<0.001***
	exercise	*N*	464 (93.7)	165 (87.8)	299 (97.4)		
	lost/gained	*Y*	69 (13.9)	36 (19.1)	33 (10.7)	6.858	0.009**
	> 9 kg	*N*	426 (86.1)	152 (80.9)	274 (89.3)		
RQ	*Emotional*	*Low*	183 (37.0)	60 (32.8)	123 (67.2)		
	Stability	*Norm*	272 (54.9)	106 39.0)	166 (61.0)	7.128	0.028*
		High	40 (8.1)	22 (55.0)	18 (45.0)		
	Willpower	*Low*	153 (30.9)	56 (36.6)	97 (63.4)		
		Norm	322 (65.1)	119 (37.0)	203 (63.0)	6.466	0.039*
		High	20 (4.0)	13 (65.0)	7 (35.0)		
	Problem	*Low*	115 (23.2)	39 (33.9)	76 (66.1)	8.339	0.015*
	Solving	*Norm*	339 (68.5)	125 (36.9)	214 (63.1)		
		High	41 (8.3)	24 (58.5)	17 (41.5)		
	Total	*Low*	182 (36.8)	59 (32.4)	123 (67.6)		
		Norm	271 (54.7)	102 (37.6)	169 (62.4)	14.743	<0.001***
		High	42 (8.5)	27 (64.3)	15 (35.7)		
IPPA-R[a]	*Communication*		15.33 (3.17)	14.93 (3.07)	15.57 (3.21)	-2.185	0.029*
	Trust		19.17 (3.33)	18.87 (3.53)	19.34 (3.19)	-1.527	0.127
	Alienation		14.42 (2.79)	14.52 (2.80)	14.35 (2.78)	0.655	0.512
	Total Score		58.45 (5.14)	57.79 (4.95)	58.85 (5.22)	-2.223	0.027*

Abbreviations: SM = social media, BSMU = body image focused social media usage, *BESAA* = Body Esteem Scale for Adolescents and Adults, *EAT-26* = Eating Attitudes Test-26 item, kg = kilograms, *RQ* = Resilience Quotient, *IPPA-R* = Inventory of Parent and Peer Attachment – Revised, a = mean (SD), * = *p-value* < 0.05, ** = *p-value* < 0.01, *** = *p-value* < 0.001

TABLE 2. Analysis of body image focused social media usage, resilience, parental attachment and association with weight group, and body-esteem

			WT Group						BESAA				
			Average weight	Underweight			Overweight		Low	Med-High			
			n (%)/mean (SD)		*X2/t*	*p*[c]	n (%)/mean (SD)	*X2/t*	*p*[d]	n (%)/mean (SD)		*X2/t*	*p*
SM accounts[a]			3.06 (1.16)	2.29 (1.08)	-0.794	0.428	3.11 (1.31)	-0.449	0.654	2.92 (1.21)	3.08 (1.20)	-0.994	0.321
Time on SM[a]			4.62 (4.10)	4.29 (4.57)	-0.515	0.607	5.34 (4.76)	-1.618	0.106	5.70 (4.42)	4.65 (4.33)	1.835	0.067
BSMU[a]			6.48 (3.12)	6.24 (2.70)	-0.499	0.618	5.78 (2.87)	2.259	0.024*	6.59 (3.27)	6.21 (2.98)	0.959	0.338
RQ[b]	*Emotional*	*low*	112 (36.6)	23 (46.9)	2.979	0.561	48 (34.3)	0.521	0.771	38 (57.6)	145 (33.8)	13.918	< 0.001***
	stability	*normal*	171 (55.9)	22 (44.9)			79 (56.4)			24 (36.4)	248 (57.8)		
		high	23 (7.5)	4 (8.2)			13 (9.3)			4 (6.1)	36 (8.4)		
	Willpower	*low*	90 (29.4)	19 (38.8)	1.834	0.4	44 (31.4)	2.774	0.25	34 (51.5)	119 (27.7)	15.727	< 0.001***
		normal	206 (67.3)	29 (59.2)			87 (62.1)			29 (43.9)	293 (68.3)		
		high	10 (3.3)	1 (2.0)			9 (6.4)			3 (4.5)	17 (4.0)		
	Problem	*low*	70 (22.9)	14 (28.6)	2.146	0.342	31 (22.1)	4.588	0.101	24 (36.4)	91 (21.2)	8.879	0.012*
	solving	*normal*	217 (70.9)	30 (61.2)			92 (65.7)			40 (60.6)	299 (69.7)		
		high	19 (6.2)	5 (10.2)			17 (12.1)			2 (3.0)	39 (9.1)		
	RQ score	*low*	111 (36.3)	23 (46.9)	4.871	0.887	48 (34.3)	1.931	0.381	39 (59.1)	143 (33.3)	16.415	< 0.001***
		normal	174 (56.9)	20 (40.8)			77 (55.0)			24 (36.4)	247 (57.6)		
		high	21 (6.9)	6 (12.2)			15 (10.7)			3 (4.5)	39 (9.1)		
IPPA-R[a]	*Communication*		15.52 (3.03)	14.94 (3.72)	-1.199	0.231	15.05 (3.26)	1.473	0.141	15.59 (3.17)	15.29 (3.17)	0.725	0.469
	Trust		19.33 (3.10)	18.88 (3.91)	-0.913	0.362	18.90 (3.58)	1.294	0.196	19.18 (3.42)	19.16 (3.32)	0.048	0.962
	Alienation		14.33 (2.70)	14.53 (3.19)	0.47	0.638	14.56 (2.85)	-0.835	0.404	15.06 (2.62)	14.31 (2.81)	2.022	0.044*
	Total		58.60 (5.22)	57.82 (6.07)	0.959	0.338	58.32 (4.61)	0.551	0.582	59.77 (4.38)	58.24 (5.22)	2.261	0.024*

Abbreviations: BESAA = Body Esteem Scale for Adolescents and Adults, SM = social media, BSMU = body image focused social media usage, RQ = resilience quotient, *IPPA-R* = Inventory of Parent and Peer Attachment, a = mean (SD) and independent t-test was used to analyze, b = n (%) and chi-square test was used to analyze, c = statistically significant between frequencies or means of participants in underweight group and average weight group, d = statistically significant between frequencies or means of participants in overweigh, * = *p-value* < 0.05, ** = *p-value* < 0.01, *** = *p-value* < 0.001

TABLE 3. Analysis of body image focused social media usage, resilience, attachment and association with inappropriate eating attitudes and behaviors (EAT-26)

			Inappropriate eating attitudes				Inappropriate Eating Behaviors																	
			Low Risk	High Risk			Binging				Purging				Laxative/Other Drug Use				Excessive Exercise				lost/gained weight > 9 kg/6 months			
							"No"	"Yes"			"No"	"Yes"			"No"	"Yes"			"No"	"Yes"			"No"	"Yes"		
			N (%)/mean (SD)		X^2/t	*p*	mean (SD)		X^2/t	p	mean (SD)		X^2/t	p	mean (SD)		X^2/t	p	mean (SD)		X^2/t	p	mean (SD)		X^2/t	p
SM Accounts[a]			3.04 (1.22)	3.25 (1.03)	-1.26	0.209	3.03 (1.20)	3.10 (1.19)	-0.64	0.523	3.08 (2.73)	2.73 (0.98)	1.547	0.123	3.03 (1.20)	3.31 (1.14)	-1.73	0.084	3.07 (1.20)	2.87 (1.15)	0.911	0.363	3.09 (1.20)	2.86 (1.14)	1.539	0.12
Time on SM[a] (hours)			4.85 (4.37)	4.30 (4.16)	0.879	0.380	4.32 (4.43)	5.36 (4.53)	-2.665	0.008*	4.81 (4.39)	4.40 (3.77)	0.571	0.617	4.54 (4.12)	6.50 (5.44)	-2.73	0.008*	4.69 (4.22)	6.23 (5.87)	-1.432	0.162	4.78 (4.29)	4.80 (4.71)	-0.025	0.98
BSMU[a]			6.15 (2.96)	7.09 (3.36)	-2.19	0.029*	5.76 (2.85)	6.87 (3.13)	-4.109	<0.001***	6.18 (3.06)	7.40 (2.20)	-2.14	0.033*	6.04 (3.05)	7.77 (2.34)	-4.3	<0.001***	6.30 (3.01)	5.58 (2.90)	1.291	0.197	6.31 (3.06)	5.94 (2.78)	0.938	0.35
RQ[b]	*Emotional*	*low*	161 (36.7)	22 (39.3)	2.139	0.343	94 (34.6)	89 (39.9)	2.677	0.262	167 (35.9)	16 (53.3)	3.988	0.136	145 (33.5)	38 (61.3)	18.3	<0.001***	174 (37.5)	9 (29.0)	3.215	0.200	152 (35.7)	31 (44.9)	4.518	0.1
	stability	*norm*	245 (55.8)	27 (48.2)			152 (55.9)	120 (53.8)			259 (55.7)	13 (43.3)			250 (57.7)	22 (35.5)			255 (55.0)	17 (54.8)			242 (56.8)	30 (43.5)		
		high	33 (7.5)	7 (12.5)			26 (9.6)	14 (6.3)			39 (8.4)	1 (3.3)			38 (8.8)	2 (3.2)			35 (7.5)	5 (16.1)			32 (7.5)	8 (11.6)		
	Willpower	*low*	135 (30.8)	18 (32.1)	1.178	0.424	71 (26.1)	82 (36.8)	14.9	<0.001***	138 (29.7)	15 (50.0)	6.168	0.046*	124 (28.6)	29 (46.8)	8.356	0.015*	146 (31.5)	7 (22.6)	1.221	0.543	134 (31.5)	19 (27.5)	0.805	0.67
		norm	288 (65.6)	34 (60.7)			183 (67.3)	139 (62.3)			307 (66.0)	15 (50.0)			291 (67.2)	31 (50.0)			299 (64.4)	23 (74.2)			274 (64.3)	48 (69.6)		
		high	16 (3.6)	4 (7.1)			18 (6.6)	2 (0.9)			20 (4.3)	0 (0.0)			18 (4.2)	2 (3.2)			19 (4.1)	1 (3.2)			18 (4.2)	2 (2.9)		
	Problem	*low*	13 (23.5)	12 (21.4)	0.133	0.936	56 (20.6)	59 (26.5)	8.906	0.120	105 (22.6)	10 (33.3)	4.063	0.131	91 (21.0)	24 (38.7)	10.62	0.005*	107 (23.1)	8 (25.8)	0.248	0.883	100 (23.5)	15 (21.7)	0.256	0.88
	solving	*norm*	300 (68.3)	39 (69.6)			185 (68.0)	154 (69.1)			319 (68.6)	20 (66.7)			303 (70.0)	36 (58.1)			319 (68.8)	20 (64.5)			290 (68.1)	49 (71.0)		
		high	36 (8.2)	5 (8.9)			31 (11.4)	10 (4.5)			41 (8.8)	0 (0.0)			39 (9.0)	2 (3.2)			3 (8.2)	3 (9.7)			36 (8.5)	5 (7.2)		
	Total	*low*	160 (36.4)	22 (39.3)	3.411	0.182	85 (31.3)	97 (43.5)	10.58	0.005*	165 (35.5)	17 (56.7)	5.707	0.058	143 (33.0)	39 (62.9)	21.12	<0.001***	173 (37.3)	9 (29.0)	0.852	0.653	156 (36.6)	26 (37.7)	0.376	0.83
		norm	245 (55.8)	26 (46.4)			157 (57.7)	114 (51.1)			259 (55.7)	12 (40.0)			250 (57.7)	21 (33.9)			252 (54.3)	19(61.3)			235 (55.2)	36 (52.2)		
		high	34 (7.7)	8 (14.3)			30 (11.0)	12 (5.4)			41 (8.8)	1 (3.3)			40 (9.2)	2 (3.2)			39 (8.4)	3 (9.7)			35 (8.2)	7(10.1)		
IPPA-R[b]	*Communication*		15.33 (3.12)	15.27 (3.58)	0.149	0.882	15.33 (3.42)	15.33 (2.84)	-0.001	1.000	15.30 (3.21)	15.70 (2.55)	-0.66	0.507	15.33 (3.23)	15.34 (2.74)	-0.03	0.976	15.32 (3.14)	15.48 (3.62)	-0.284	0.777	15.40 (3.14)	14.88 (3.36)	1.253	0.21
	Trust		19.21 (3.31)	18.91 (3.49)	0.604	0.546	19.23 (3.45)	19.09 (3.17)	0.475	0.635	19.12 (3.37)	19.77 (2.61)	-1.03	0.306	19.16 (3.34)	19.21 (3.26)	-0.12	0.907	19.14 (3.33)	19.48 (3.36)	-0.553	0.580	19.19 (3.29)	19.01 (3.59)	0.49	0.69
	Alienation		14.26 (2.75)	5.64 (2.86)	-3.53	<0.001***	14.26 (2.92)	14.61 (2.61)	-1.367	0.172	14.37 (2.80)	15.20 (2.50)	-1.59	0.112	14.37 (2.81)	14.71 (2.62)	-0.89	0.376	14.43 (2.81)	14.23 (2.47)	0.392	0.695	14.39 (2.76)	14.61 (2.96)	0.613	0.54
	Total		58.33 (5.09)	59.36 (5.47)	-1.41	0.159	58.29 (5.31)	58.64 (4.93)	-0.763	0.446	58.32 (5.14)	60.47 (4.84)	-2.23	0.026*	58.35 (5.16)	59.10 (4.96)	-1.07	0.287	58.45 (5.16)	58.45 (4.97)	-0.006	0.995	58.52 (5.05)	58.00 (5.68)	0.213	0.44

Abbreviations: SM = social media, BSMU = body image focused social media usage, *RQ* = Resilience Quotient, a = mean (SD) and independent t-test was used to analyze, b = n (%) and chi-square test was used to analyze, * = *p-value* < 0.05, ** = *p-value* < 0.01, *** = *p-value* < 0.001

TABLE 4. Multivariate logistic regression testing association between BSMU, resilience, attachment and weight group, and body esteem (BESAA)

			WT Group Under WT		Over WT		Low *BESAA*	
			AOR (CI)	*P*	*AOR (CI)*	*P*	*AOR (CI)*	*P*
SM Accounts			0.99 (0.76-1.31)	0.964	1.15 (0.96-1.37)	0.119	0.79 (0.60-1.03)	0.078
Time on SM			1.01 (0.93-1.08)	0.900	1.07 (1.02-1.12)	0.007**	1.03 (0.96-1.11)	0.422
BSMU			1.00 (0.89-1.12)	0.989	0.93 (0.86-0.99)	0.035*	1.05 (0.94-1.17)	0.387
RQ	*Emotional stability*	*low*	Ref		Ref		Ref	
		normal	0.50 (0.07-3.48)	0.485	1.13 (0.32-3.97)	0.846	0.52 (0.19-1.43)	0.206
		high	0.83 (0.30-2.28)	0.715	0.98 (0.49-1.98)	0.976	2.02 (0.27-14.7)	0.489
	Willpower	*low*	Ref		Ref		Ref	
		normal	0.23 (0.02-2.55)	0.230	0.78 (0.21-2.83)	0.703	0.48 (0.22-1.07)	0.074
		high	0.74 (0.31-1.75)	0.491	0.69 (0.38-1.28)	0.242	5.68 (0.59-54.1)	0.131
	Problem solving	*low*	Ref		Ref		Ref	
		normal	1.36 (0.28-6.57)	0.700	1.74 (0.59-5.13)	0.314	0.91 (0.42-1.94)	0.799
		high	0.91 (0.39-2.09)	0.818	0.99 (0.54-1.82)	0.982	0.11 (0.01-1.11)	0.061
	RQ Score	*low*	Ref		Ref		Ref	
		normal	2.51 (0.29-21.4)	0.399	1.25 (0.28-5.66)	0.769	0.71 (0.22-2.31)	0.569
		high	0.81 (0.24-2.79)	0.741	1.37 (0.58-3.25)	0.471	0.29 (0.02-4.03)	0.362
IPPA-R	*Communication*		1.37 (0.66-2.84)	0.392	1.69 (0.98-2.67)	0.058	0.99 (0.49-2.03)	0.990
	Trust		1.49 (0.69-3.22)	0.303	1.69 (1.01-2.84)	0.051	0.99 (0.48-2.08)	0.987
	Alienation		1.46 (0.71-3.03)	0.305	1.57 (0.96-2.57)	0.071	0.82 (0.41-1.63)	0.570
	Total		0.70 (0.35-1.39)	0.309	0.62 (0.39-0.99)	0.046*	1.08 (0.56-2.08)	0.828

Abbreviations: SM Accts = social media accounts, Tm on SM = time on social media, BSMU = body image focused social media usage, *RQ* = Resilience Quotient, Emo Stab = emotional stability, Prob Sol = problem solving, Comms = communication, Alien = alienation; Data were adjusted for sex and age; * = *p-value* < 0.05, ** = *p-value* < 0.01, *** = *p-value* < 0.001

overweight participants, the prevalence of underweight students was unexpectedly high. Our study found a rate two times greater than previous studies, which reported only 5.2% of participants as underweight.[46] Further investigation is necessary to understand the reasons behind this discrepancy. One possible explanation could be the demographic differences between our sample and previous studies, as our sample had a higher mean age. Our study found that participants had a mean of 3.07 SM accounts, which is lower than previous studies.[36,47] This could be due to the difference in ages of the respondents as studies have shown that the number of SM accounts increases with age (up to age 34).[48] However, the mean number of hours spent on SM was higher, at 4.79 hours/day, consistent with other studies reporting adolescents spending 3–5 hours/day on SM.[1,49,50] Our study also found that females had higher body image-related SM activities than males. which aligns with previous research on self-objectification.[51,52] However, the COVID-19 pandemic and resulting regulations have led to an increased reliance on technology for social interactions and entertainment, which could have influenced the results of this study. Previous studies have shown an increase in social media use during the pandemic, particularly among adolescents.[53,54] In addition, the pandemic might effect on various mental health problems among adolescents which might affect the results of eating-related problems in our study.

The current study found a lower prevalence of low body-esteem (13.3%) compared to previous study in Western countries, which have reported up to 27% of

TABLE 5. Multivariate logistic regression testing association between BSMU, resilience, attachment and inappropriate eating attitudes/behaviors (EAT-26)

			High risk *eating attitudes*		Binging		Purging		Drug/Laxative use E		xcessive Exercise		Weight Fluctuation	
			AOR (CI)	*p*	*AOR (CI)*	*p*	*AOR (CI)*	*p*	*AOR (CI)*	*p*	*AOR (CI)*	*p*	*AOR (CI)*	*p*
SM Accts			1.10 (0.85-1.43)	0.477	0.98 (0.83-1.15)	0.783	0.62 (0.42-0.93)	0.020*	1.05 (0.82-1.34)	0.723	0.98 (0.68-1.40)	0.905	0.86 (0.68-1.10)	0.234
Time on SM			0.76 (0.40-1.45)	0.408	1.71 (1.14-2.56)	0.010*	0.59 (0.25-1.37)	0.217	1.01 (0.53-1.93)	0.997	2.08 (0.82-5.26)	0.120	1.17 (0.65-2.09)	0.599
BSMU			1.14 (1.03-1.27)	0.015*	1.14 (1.06-1.22)	<0.001***	1.20 (1.04-1.40)	0.015*	1.21 (1.09-1.34)	0.001**	1.01 (0.87-1.17)	0.881	0.99 (0.91-1.09)	0.907
RQ	*Emotional*	*low*	Ref		Ref		Ref		Ref		Ref		Ref	
	Stability	*normal*	0.88 (0.34-2.30)	0.800	1.67 (0.89-3.14)	0.110	0.93 (0.29-2.97)	0.906	0.66 (2.73-1.59)	0.352	1.60 (0.31-8.22)	0.572	0.47 (0.19-1.15)	0.099
		high	1.19 (0.21-6.82)	0.841	2.05 (0.63-6.65)	0.233	0.34 (0.01-13.6)	0.565	0.80 (0.10-6.22)	0.833	16.6 (1.63-169.1)	0.018*	1.01 (0.22-4.59)	0.991
	Willpower	*low*	Ref		Ref		Ref		Ref		Ref		Ref	
		normal	1.11 (0.47-2.61)	0.819	0.93 (0.54-1.57)	0.776	0.69 (0.24-1.97)	0.493	0.88 (0.41-1.90)	0.749	2.30 (0.72-7.39)	0.162	1.46 (0.67-3.17)	0.337
		high	1.88 (0.32-11.03)	0.485	0.18 (0.03-0.98)	0.047*	0.92 (0.54-1.57)	0.998	3.77 (0.28-51.5)	0.320	0.69 (0.05-9.95)	0.791	0.76 (0.12-4.82)	0.775
	Problem	*low*	Ref		Ref		Ref		Ref		Ref		Ref	
	Solving	*normal*	1.08 (0.46-2.54)	0.854	1.03 (0.60-1.74)	0.926	0.86 (0.33-2.27)	0.757	0.69 (0.33-1.40)	0.302	0.60 (0.19-1.84)	0.372	1.14 (0.53-2.46)	0.731
		high	0.75 (0.16-3.59)	0.715	0.64 (0.22-1.82)	0.397	0.41 (0.09-1.68)	0.997	0.27 (0.02-3.19)	0.297	0.67 (0.11-4.13)	0.668	0.77 (0.18-3.26)	0.718
	Total	*low*	Ref		Ref		Ref		Ref		Ref		Ref	
		normal	0.74 (0.23-2.45)	0.626	0.45 (0.21-0.97)	0.041*	0.61 (0.15-2.46)	0.484	0.47 (0.16-1.37)	0.166	0.57 (0.09-3.54)	0.548	1.11 (0.38-3.26)	0.845
		high	1.45(0.19-10.91)	0.710	0.41 (0.09-1.68)	0.214	2.56 (0.53-127.7)	0.631	0.32 (0.03-3.89)	0.369	0.107 (0.01-1.90)	0.128	1.20 (0.18-7.87)	0.849
IPPA-R	*Communication*		0.78 (0.39-1.52)	0.465	0.94 (0.60-1.47)	0.785	0.96 (0.38-2.41)	0.935	1.87 (0.92-3.77)	0.082	0.47 (0.17-1.29)	0.146	0.99 (0.53-1.87)	0.996
	Trust		0.83 (0.41-1.68)	0.599	0.90 (0.56-1.44)	0.670	1.06 (0.39-2.82)	0.909	2.06 (0.99-4.29)	0.054	0.46 (0.16-1.33)	0.155	1.08 (0.56-2.10)	0.815
	Alienation		0.64 (0.33-1.26)	0.195	0.89 (0.57-1.39)	0.608	0.78 (0.31-1.98)	0.604	1.79 (0.90-3.57)	0.096	0.49 (0.18-1.33)	0.161	1.05 (0.56-1.96)	0.874
	Total		1.26 (0.67-2.37)	0.474	1.09 (0.72-1.66)	0.689	1.09 (4.56-2.59)	0.846	0.55 (0.29-1.06)	0.076	2.06 (0.79-5.35)	0.134	0.95 (0.53-1.72)	0.867

Abbreviations: SM Accts = social media accounts, Tm on SM = time on social media, BSMU = body image focused social media usage, *RQ* = Resilience Quotient; Data were adjusted for sex and age; * = *p-value* < 0.05, ** =*p-value* < 0.01, *** = *p-value* < 0.001

adolescents having body image dissatisfaction.[55] Cross-regional differences in the ideal female figure and body dissatisfaction have been reported, with Americans exhibiting greater body dissatisfaction.[56] One study found that the ideal body weight is slimmer in Westernized countries as opposed to less socioeconomically developed or traditional societies.[57] These finding may explain why this study which did not find an association between SM usage, resilience, attachment to parent, and body-esteem. This study also found that 11.3% of the participants had inappropriate eating attitudes, with a comparable rate between male and female participants (13.3% and 10.1%, respectively). These results are consistent with previous studies reporting that eating disorders affect 9 - 10% of the world population[58,59], with no gender differences in frequency of disordered weight control and overall prevalence of eating disorders study in Singapore. Further studies are required to understand effect of culture and gender specific factors on increase prevalence of male eating-related problems in Asia.[60]

The study found that participant in the overweight group spent the most time on SM, which is consistent with previous studies linking greater time spent on SM with higher body weight.[61] However, overweight participants in this study conducted less body image focused social media activities, which is supported by an Italian study that found women dissatisfied with their body image posted fewer selfies.[61] These results may be attributed to overweight stigma and are consistent with previous study linking higher BMI with greater body dissatisfaction.[62] In addition, participants spending more time on SM in the current study tended to be at-risk for binging, and those with higher BSMU scores had inappropriate eating attitudes and were at risk for binging, purging, and laxative/drug use. This is consistent with previous research showing that elevated appearance exposure on Facebook was significantly correlated with weight dissatisfaction, drive for thinness, thin ideal internalization, and self-objectification. Body image dissatisfaction has been shown to lead to inappropriate eating behaviors[63], so it becomes a viscous cycle.

Higher resilience was associated with a lower risk for problematic eating behaviors in the current study, consistent with a previous research.[64] Greater resilience has been shown to help adolescent cope with online risks and is associated with lower incidence of eating problems.[65] Lower resilience is associated with a higher likelihood of demonstrating a variety of mental health problems, including eating disorders.[66] Higher resilience may have "emotion-regulatory benefits" that mitigate the development of disordered eating behaviors[67], and lead to improved body image and less body image dissatisfaction.[20]

Our study revealed that higher parental attachment was associated with lower risk of being in the overweight group. These findings are consistent with previous research that had shown weaker adolescent-parent communication wo be associated with unhealthy weight control behaviors, body dissatisfaction, and low self-esteem.[68,69] Moreover, positive relationships with parents have been found to be significant predictors of body image satisfaction.[62] Family cohesion has also been shown to be correlated with resilience, which is associated with emotional regulation and can mitigate the development of disordered eating behaviors.[70] A healthy family environment and positive communication have been found to be significant protective factors against eating problems.[29]

The study suggest that parents and caregivers should monitor their children's social media usage and educate them on how body-related content can affect their body-esteem. It also suggests that content creators should be made aware of the unintended effects of unrealistic body image content on adolescents. Schools should implement training programs to increase resilience in early years so that adolescents have established healthy eating habits and do not rely on social media for guidance. Programs to strengthen the adolescent-parent relationship can help build the child-parent bond, which can assist with both body image issues and potential eating problems.

Strengths and limitations

This is a few study which aimed to investigate the relationship between various social media activities centered on body image, resilience, parental attachment, and eating-related problems. However there are a number of limitations in this study. Firstly, this study was cross-sectional descriptive research, therefore a causal relationship could not be concluded. Secondly, due to the COVID-19 situation, many of randomized schools were unwilling to participate in this study, so purposive sampling was used to choose three schools to be included in this study. In addition, classrooms and students were selected based on teacher convenience, which may have introduced potential bias. Thirdly, this study relied on respondent self-report which can result in report bias. Fourthly, the low Cronbach's alpha score of BSMU questionnaire indicates that the reliability of the scale may be limited. However, the BSMU questionnaire was developed to measure a complex construct such as body image-related social media use, which may have multiple dimensions. In addition, due to normal behaviors of SM usage which one might do each SM activity with different frequency (such as one might be more likely to click

"like" on pictures or comments, but rarely posting or vice versa). Therefore, these could result in poor Cronbach's alpha values of the questionnaire. Further testing of the BSMU questionnaire in future studies with larger sample sizes to evaluate the psychometric properties of the questionnaire are recommended. Finally, this study was comprised of only students in the educational system in Bangkok, which could not be a good representation of the general population. Finally, the pandemic might have also affected various mental health problems among adolescents,[71] which in turn might have influenced the results of eating-related problems in our study.

CONCLUSION

This study investigates the association between body-image focused social media usage and eating-related problems, as well as the relationships between resilience, attachment, and these problems among high school students. The study highlights the negative impact of social media on body image and eating behaviors and suggests that resilience and adolescent-parent relationship may serve as protective factors against these negative effects.

Declarations

Ethical approval

This study received full approval from the institutional ethical review board of the Faculty of Medicine Ramathibodi Hospital, Mahidol University under the code MURA2020/366. The authors confirm that all the methods were carried out in accordance with relevant guidelines and regulations.

Informed consent

Written informed consent was obtained from all the subjects before answering the questionnaires.

Consent for publication

All participants and authors have approved the publication.

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest statement

The authors have no conflict of interest relevant to this article.

Authors' contribution

CN, KK, HS and PC conceived and designed the study and acquired the data. CN and KK analyzed and interpreted the data. CN and KK drafted the manuscript. The manuscript was critically revised by KK, HS and PC. CN, KK, HS and PC read and approved the final version of the manuscript.

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Abbreviations

SM = social media
SM Accts = social media accounts
Tm on SM = time on social media
BSMU = body image focused social media usage
RQ = Resilience Quotient
Emo Stab = emotional stability
Prob Sol = problem solving
Comms = communication
Alien = alienation

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Stability of Extemporaneously Prepared Amitriptyline Hydrochloride Topical Preparations for the Treatment of Neuropathic Pain

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ABSTRACT

Objective: The aim of this study was to investigate the physicochemical and microbiological stability of extemporaneous amitriptyline hydrochloride (AMH) topical preparations for the treatment of neuropathic pain.

Materials and Methods: AMH tablets were triturated to produce fine powders with a mortar and pestle. These powders were levigated and separately incorporated into four compounding bases: hydrophilic petrolatum USP, anionic cream, cold cream USP, and pluronic lecithin organogel (PLO) having the concentration of 2%w/w AMH.

Results: In the *in vitro* release study, the most significant amount of AMH was released from the PLO, followed by cold cream, anionic cream and hydrophilic petrolatum, respectively; therefore, the compounded AMH in cold cream and AMH in PLO were selected for the evaluation of the *in vitro* permeation and product stability. The permeation of AMH from PLO across human epidermal membrane was significantly greater than that from the cold cream. Product stability was characterized as having no remarkable change in color or texture and AMH remaining in the range of 90–110% of the initial concentration quantified by high-performance liquid chromatography. Compounded AMH in cold cream was stable at 2–8 °C and 30 °C for 60 days, and 40 °C for 30 days, whereas compounded AMH in PLO was stable at 30 °C and 40 °C for 14 days. There was no visible microbial growth in any of the samples.

Conclusion: Taken together with the *in vitro* permeation and product stability studies, the present study suggests that AMH in cold cream could be prepared and used as extemporaneous topical preparations with a beyond-use date of 60 days when kept at 2–8 °C and 30 °C.

Keywords: Amitriptyline hydrochloride; neuropathic pain; cold cream; pluronic lecithin organogel; extemporaneous topical preparations (Siriraj Med J 2023; 75: 427-435)

INTRODUCTION

Chronic pain is usually caused by an initial trauma, such as a back sprain or muscle strain.[1] It is believed that chronic pain develops after nerves become impaired. Chronic pain is associated with a diminished quality of life, increased health expenditure, and high economic costs. It persists for months or years and can interfere with daily life activities, such as working, having a social life, and taking care of oneself and others. It has been estimated that chronic pain affects 10 percent of the world's population.[2] However, the phrase "neuropathic pain" which reflects both peripheral and central sensitization mechanisms, came into common use only in the last decade. Important pathophysiologic mechanisms of neuropathic pain are sodium-and calcium-channel upregulation, spinal hyperexcitability, descending facilitation, and aberrant sympathetic-somatic nervous system interactions.[3] Current recommended first-line

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treatments include antidepressants (tricyclic agents and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin).[3]

Amitriptyline is a dibenzocycloheptene-derivative tricyclic antidepressant agent that acts upon many sites. It can act within the central nervous system by inhibiting neuronal reuptake of norepinephrine and serotonin. Moreover, amitriptyline can act within the periphery by blocking Na^+, K^+, and Ca^{2+} voltage-gated ion channels and various receptors (muscarinic, cholinergic, nicotinic, histaminergic, α_2-adrenergic, adenosine, and N-methyl-D-aspartate receptors).[4-6] Amitriptyline, administered orally, is currently one of the treatment options available for managing neuropathic pain. However, the following adverse effects have been reported for oral administration of amitriptyline: drowsiness, dizziness, dry mouth, constipation and sweating.[7] Nowadays, topical treatments for managing peripheral neuropathic pain are gaining popularity due to the excellent safety profiles and preferences. Due to its physicochemical properties (MW 277.4 g/mole and log P 4.92),[8] amitriptyline is a promising candidate for delivery as a topical analgesic. In a recent review, topically applied amitriptyline at concentrations between 2% and 10% were successfully used for clinical neuropathic pain treatment.[9-12] Thompson and Brooks[13] found that patients who received higher concentration of amitriptyline experienced greater pain relief, but there were also more reports of adverse effects, including systemic absorption and skin irritation at the site of application. To avoid these adverse effects, a topical preparation of 2% amitriptyline hydrochloride (AMH) was chosen. However, the information regarding the types of compounding bases and the formulations is limited. In addition, there are no marketed topical amitriptyline products currently available. In this study, AMH compounded with four compounding bases (i.e., hydrophilic petrolatum USP, anionic cream, cold cream USP, and pluronic lecithin organogel (PLO)) were prepared. The *in vitro* drug release was carried out in order to identify the formulations with suitable drug release profiles. Furthermore, *in vitro* skin permeation and stability studies were conducted to evaluate their potential for use as extemporaneous topical preparations for the treatment of neuropathic pain.

MATERIALS AND METHODS

AMH (≥98% purity analyzed by thin layer chromatography) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The commercial AMH tablets (containing 25 mg per tablet) were kindly provided by the Government Pharmaceutical Organization, Thailand. Tryptic soya agar (TSA) and sabouraud dextrose agar (SDA) were supplied by Becton, Dickinson and Company (Franklin Lakes, New Jersey). High-performance liquid chromatography (HPLC) grade methanol and acetonitrile were supplied by Honeywell Burdick and Jackson (Ulsan, Korea). All the other materials and solvents used were of analytical reagent grade.

Human abdominal skin (HEM) of female patients aged 30 – 60 years was obtained from abdominoplastic surgical operations (Department of Surgery, Yanhee General Hospital, Thailand). HEM, which includes the stratum corneum and viable epidermis, was separated from the dermis by heat separation technique as described by Chantasart et al.[14] The use of human tissue was reviewed and approved by the committee on human rights related to human experimentation, Mahidol University, Thailand (COE. No. MU-DT/PY-IRB 2016/014.0208).

Preparation of AMH formulations

Four compounding bases (i.e., hydrophilic petrolatum USP, anionic cream, cold cream USP, and PLO) were prepared in accordance with the art, science, and technology of pharmaceutical compounding.[15] These compounding bases were selected because of their frequency of use in many topical formulations. In addition, hydrophilic petrolatum, anionic cream, and cold cream are official USP ointment bases, and it has been reported that PLO promotes the release of hydrophobic drugs.[16-19] Therefore, they were selected as the compounding bases in this study. The compositions and preparation of the four compounding bases are provided in the Supplementary Materials.

To prepare 2%w/w AMH in each compounding base, an appropriate amount of AMH tablets were weighed and triturated to produce fine powders with a mortar and pestle. The powders were levigated and incorporated separately into each of the compounding bases. Mineral oil was the levigating agent used with the incorporation of the drug powders into the hydrophilic petrolatum and cold cream, whereas purified water was the levigating agent used with the drug powders in the anionic cream and PLO. The required levigating agent was introduced to the fine powders in order to achieve a smooth paste. Each compounding base was then added to the prepared paste using the geometric dilution method. All AMH preparations were packed into plastic containers, as shown in Fig 1.

HPLC analysis for AMH

Experiments were performed on a Shimadzu LC-10A system (Shimadzu, Kyoto, Japan) equipped with a model

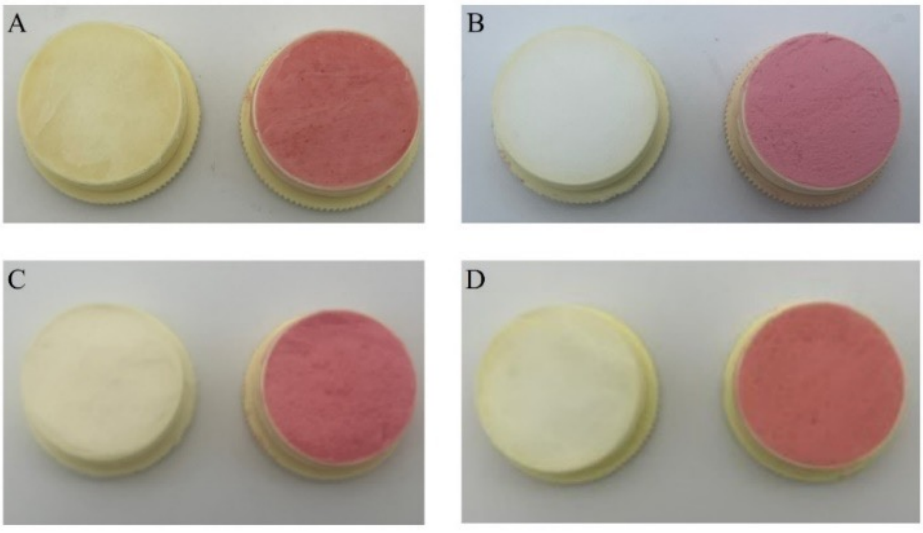

Fig 1. Appearance of the formulations in various compounding bases, which are (A) hydrophilic petrolatum USP, (B) anionic cream, (C) cold cream USP, and (D) PLO. White or yellowish color represents compounding bases (without drug). Pink color creams represent bases that 2% AMH was incorporated.

series LC-10AD pump, CBM-10A system controller, DGU-12 A degasser and an SPD-10A diode array detector with C8 column (5 µm, 150 mm×4.6 mm) (GL Sciences, Netherlands). The mobile phase consisted of a phosphoric acid, pH 2.0, and acetonitrile (60:40, v/v). The column temperature and flow rate were kept at 25 °C and 1 mL/min, respectively. The diode array detector was set at 240 nm, and the injection volume was 50 µL.

Sample preparation

On the day of the analysis, the samples were placed at room temperature for 1 h, and 200 mg of each formulation (equivalent to 4 mg of AMH) was mixed with 10 mL of methanol in a 15-mL centrifuge tube. The mixture was then heated at 80 °C in a water bath for 10 min with occasional shaking. Each tube was then removed from the bath, sonicated for 10 min, followed by 5 min of vigorously shaking, before being promptly centrifuged. The supernatant was then transferred to a 100-mL volumetric flask. The extraction procedure was repeated twice, using 10 mL of methanol in the centrifuge tube each time. The combined supernatant in the volumetric flask was diluted with methanol to reach the desired volume, mixed thoroughly volume, mixed, and filtered with a polytetrafluoroethylene membrane of 0.45 µm before injection. The % of AMH remaining in each formulation was calculated using the calibration curve.

Method validation

The chromatographic method was validated for specificity, linearity, range, precision, and accuracy according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline.[20] Forced degradation studies on AMH in cold cream were carried out to investigate the specificity of the method. The AMH in the cold cream base was exposed to water, 0.05 N hydrochloric acid, 0.05 N sodium hydroxide, and 0.3%w/v hydrogen peroxide at 80 °C for 2 h. The samples were then extracted as described in the sample preparation. The selectivity of the method was achieved as the peak purity of the AMH peak was more than 0.95. The method's linearity was tested using AMH concentrations ranging from 10 to 100 µg/mL, and the linear regression and correlation coefficient (r) were calculated. Accuracy was measured by standard addition at three different concentrations of AMH (10, 20, and 40 µg/mL) to the AMH in cold cream. Then, the % recovery of AMH was calculated. The intra-day precision or repeatability of the method was estimated by calculating the relative standard deviation (%RSD) of a sample spiked with three concentrations of standard AMH from the recovery study (n = 9) on two different days and analysis of intermediated precision (n = 18).

For the *in vitro* skin permeation study, specificity was assessed by comparing the chromatograms of AMH in the receptor medium alone and each sample solution from receiving chamber of the cold cream and PLO. The linearity of the method was in the range of 0.63-10 µg/mL. Accuracy was evaluated by standard addition at three different concentrations of AMH (1.25, 2.5, 5 µg/mL) to each sample solution obtained from the cold cream and PLO's donor chamber. Precision was evaluated by analyzing the sample solutions at 8 µg/mL (n = 6) on the same day for repeatability and on two different days as well as analysis for intermediated precision (n = 12). Finally, the %RSD was calculated.

***In vitro* drug release study**

The *in vitro* release of AMH from four formulations was studied using Franz diffusion cells with an effective area of ~2.40 cm^2. Each formulation was spread onto a

regenerated cellulose membrane (Spectra/Por®4 MWCO 12,000–14,000, Spectrum Laboratories, Inc., Rancho Dominguez, California) that had been treated with citrate buffer pH 5.5. The receiver chamber was filled with a precise amount of degassed citrate buffer pH 5.5 (~10 mL) and continuously stirred with a magnetic stir bar. The temperature of receiver solution was maintained at 32 ± 1°C. An aliquot of 300 µL receiver fluid was collected at specified time intervals (i.e., 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 h) and immediately replaced in the chamber with the same volume of citrate buffer pH 5.5 to maintain a constant volume. The AMH content in the collected sample was analyzed by HPLC. Data are expressed as the cumulative amount of AMH release per surface area (µg/cm^2).

In vitro skin permeation study

The *in vitro* drug permeation of AMH from AMH in cold cream and PLO across HEM was studied using Franz diffusion cells. HEM (~4x4 cm^2) was mounted on the diffusion cells with an effective area of ~2.40 cm^2. A regenerated cellulose membrane was placed between the viable epidermis side of the HEM sample and the receiver chamber.[14,21] Each formulation was spread onto the epidermis side of the HEM. The receiver chamber was filled with a precise amount of degassed citrate buffer pH 5.5 (~10 mL) and continuously stirred with a magnetic stir bar. The temperature of receiver was maintained at 32 ± 1 °C. An aliquot of 300 µL solutions were collected from the receiver chambers at specific time intervals (4, 6, 8, 10, 12, and 24 h), and then replaced with the same volume of fresh receptor media. The AMH content in the collected sample was analyzed by HPLC. Data are expressed as the cumulative amount of AMH permeation per surface area (µg/cm^2).

Stability study

In order to study the stability of the AMH formulations, AMH in cold cream was studied under three conditions, including in refrigerator (2–8 °C), room temperature (30 °C), and an accelerated condition (40 °C). Poloxamer 407, a thermosensitive gel forming agent, changes to a fluid state at 2–8 °C; therefore, the stability of AMH in PLO was studied under two conditions, including 30 °C and 40 °C.

Physical stability testing

The physical characteristics of AMH in cold cream and in PLO were investigated. The physical appearance, color, homogeneity, phase separation, and texture were monitored at each sampling time point. The formulation viscosity was measured using a rheometer (HAAKE RotoVisco 1 Rotational Rheometer, Therma Fisher Scientific, Germany) with a cone and plate (35/2° Ti) model at 5.00 s^{-1} shear rate at 30 °C for 5 min. The sample tests were conducted on days 0, 14, 30 and 60.

Chemical stability testing

Chemical stability testing was conducted with a quantitative analysis of AMH using HPLC. The sample tests were conducted on days 0, 14, 30, and 60.

Microbiological stability testing

The AMH in cold cream and in PLO kept under room temperature were tested for their microbiological specifications following the United States Pharmacopeia 41 (USP41) Chapter <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Test.[22] The total aerobic microbial count (TAMC) was conducted using the pour plate method with TSA incubated at 30 °C to 35 °C for three days. In addition, the total combined yeasts and molds count (TYMC) was conducted using the pour plate method with SDA incubated at 20 °C to 25 °C for five days.

Data analysis

Data are expressed as mean ± SD, and statistical significance was determined using repeated measures and the Two-way ANOVA multiple comparisons test. All statistical tests were performed using GraphPad Prism version 7.00 for Windows (GraphPad Software, California). A *p*-value of less than 0.05 was considered significant.

Stability was defined as no dramatic changes in appearance, color or viscosity. Moreover, the initial AMH concentration (day 0) analyzed by HPLC was defined as 100%, and the subsequent concentrations of each time point were calculated as percentages of the initial concentration. According to the USP, the acceptable limit for most compounded pharmaceutical preparations is typically ± 10%, or within the range of 90.0% to 110.0 % of the active pharmaceutical ingredient.[23,24]

RESULTS AND DISCUSSION

HPLC method validation

The analysis of the cold cream base and forced degradation samples prepared in the same manner as the samples under the proposed chromatographic conditions showed no interference with the AMH peak, indicating the specificity of the method. Forced degradation is the degradation of AMH in cold cream in conditions that are more severe than accelerated conditions, which is

necessary to demonstrate the specificity of the methods to determine stability. Fig 2 shows the chromatograms of AMH compounded in cold cream. The various stability behaviors of AMH were observed when subjected to neutral (Fig 2B), acidic (Fig 2C), basic (Fig 2D), and oxidizing (Fig 2E) conditions. Although AMH in cold cream remained chemically stable when heated at 80 °C for 2 h (neutral hydrolysis), it degraded under the acidic, basic, and oxidizing conditions at a rate of 22.2%, 27.8% and 47.5%, respectively. The fact that the degradation peaks and AMH were separated under our chromatographic conditions with a peak purity of more than 0.95 indicated the reliability of the assay for stability evaluation.

For the HPLC analysis in the skin permeation study, the chromatograms of AMH in the receptor medium and the samples from the receiving chamber of either the cold cream base or PLO base showed no interference with regard to the AMH peak, revealing the specificity of the method. As shown in Table 1, HPLC method was found to be linear, accurate and precise for the assay of AMH in the formulations and skin permeation study.

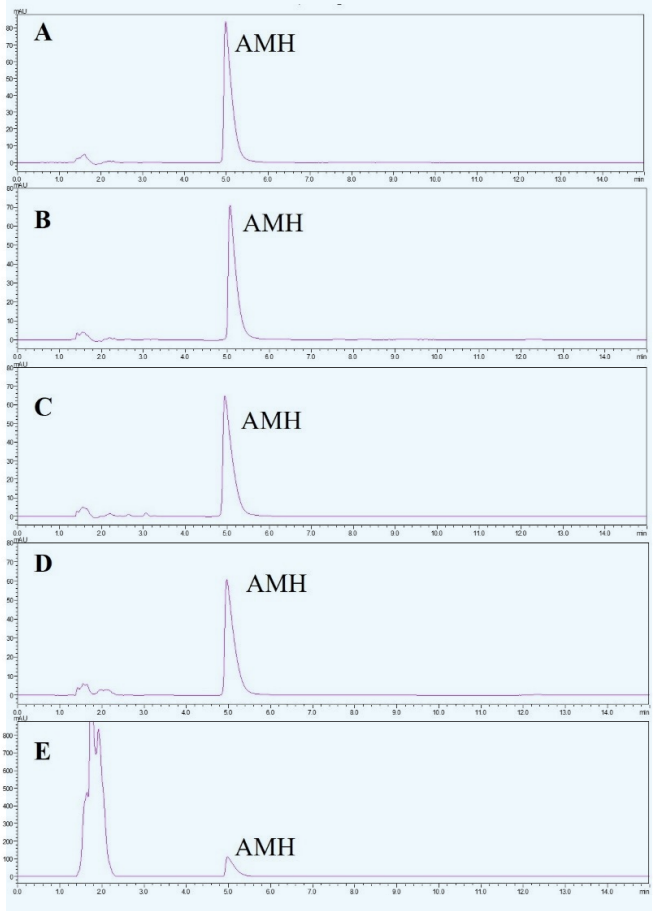

Fig 2. Chromatograms of AMH compounded in cold cream under various conditions
(A)control, (B) heat condition, (C) acidic condition, (D) basic condition, and (E) oxidizing condition

Preparation of extemporaneous AMH topical formulations

Four separate AMH topical formulations were prepared (Fig 1). Each formulation had a pink color and good spreadability. However, the AMH in hydrophilic petrolatum and the AMH in cold cream had a greasy texture and were difficult to wash out with water, whereas the AMH in anionic cream and AMH in PLO had a light non-greasy texture and were easy to wash out with water.

***In vitro* drug release study**

Because the drugs need to be released from the topical base before permeating through the skin, *in vitro* drug release tests from drug preparations across cellulose membranes are often performed before skin permeation studies.[25] It is possible to determine how the physicochemical properties of the topical bases and the ingredients affect each formulation's drug release profiles. The release profiles of AMH from the various topical bases over 24 h are shown in Fig 3. It is clearly illustrated that AMH exhibits the highest drug release performances from the PLO (5,025 ± 682 μg/cm^2), followed by cold cream (1,609 ± 299 μg/cm^2), anionic cream (484 ± 256 μg/cm^2) and hydrophilic petrolatum (134 ± 33 μg/cm^2), respectively. The results obtained could be explained by AMH's physicochemical properties and the formulations of the topical vehicles.

Based on the fact that electrolytes dissociate in ion forms when dissolved in water, in the topical base containing water, AMH, the salt form of the weak base would dissociate into amitriptyline and hydrochloride. Consequently, amitriptyline is dissolved in an oil phase. Several studies have reported that the PLO promotes the release of hydrophobic drugs.[16-19] Together with the weak affinity between the poloxamer and amitriptyline, the coexistence of organic and aqueous phases through the structurally well-defined micellar network of phospholipids of PLO, in which low water-soluble amitriptyline can be entrapped within the gel matrix,[26] may facilitate the release of amitriptyline (expressed as AMH) from PLO.[19]

The presence of surfactants in the system can impact the solubility of the hydrophobic drug and improve the drug release rate. The hydrophobic nature of the external environment of a w/o emulsion facilitates the release of the hydrophobic drug from the external oil phase.[27] Therefore, the release of amitriptyline from cold cream would be faster than that from anionic cream (o/w emulsion). In the case of hydrophobic petrolatum, an absorption base, that contains the water-absorbing material of white wax, the ointment matrix was completely immiscible with water and the AMH was dispersed in the base.

TABLE 1. HPLC method validation data of AMH.

Validation parameter		Assay	Skin permeation study
Linearity		y = 43885x - 83043 r = 0.9997	y = 27948x + 283.54 r = 0.9999
Range		10 - 100 µg/mL	6.25 - 10 µg/mL
Accuracy	Cold cream	95.13 - 101.69 %	97.01 - 102.03%
	PLO	95.99 - 102.36%	94.87 - 101.28%
Repeatability (%RSD)	Cold cream	< 2.14	< 1.20
	PLO	< 1.98	< 0.10
Intermediate Precision (%RSD)	Cold cream	2.09	1.79
	PLO	1.74	0.13

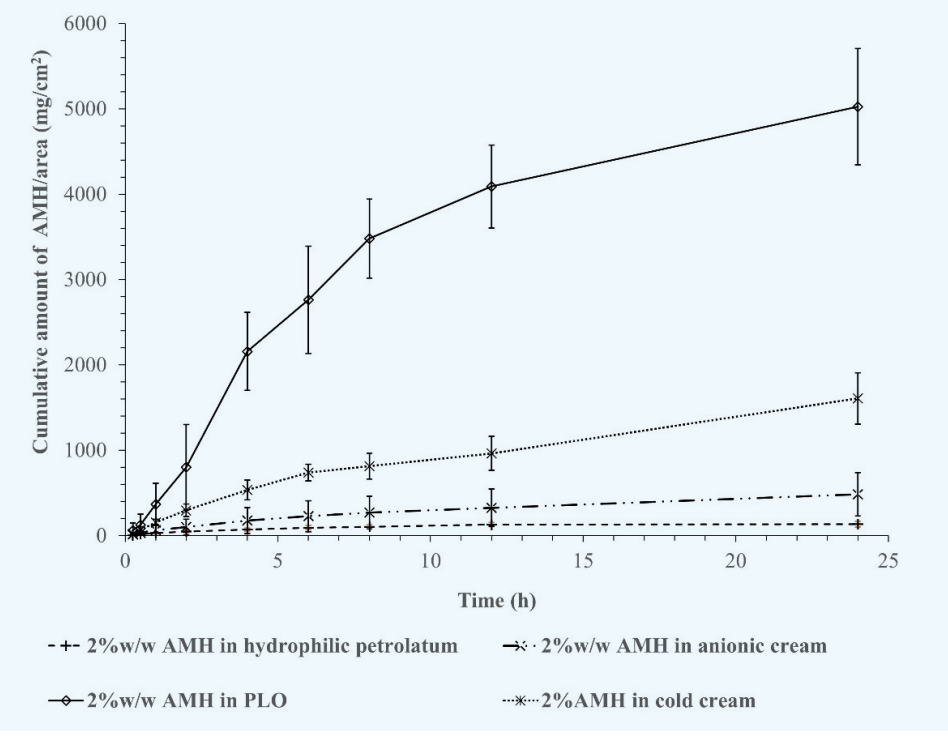

Fig 3. *In vitro* release profiles of AMH from 2%w/w AMH in various compounding bases. Data represent the mean ± SD (n=4-5).

Moreover, the drug molecules had limited mobility due to the viscosity of the ointment base. Consequently, the dissolution and dissociation of AMH likely occurred at or near the physical boundary.[28] Together with the low water solubility of amitriptyline, the result was that the release of amitriptyline from the hydrophilic petrolatum was the lowest.

In vitro skin permeation study

Based on the *in vitro* release studies, it was found that cold cream and PLO are suitable for further skin permeation studies to examine the possibility of using AMH extemporaneous preparations as topical analgesics.

Fig 4 shows the cumulative amount of amitriptyline expressed as AMH in µg/cm^2 transferred from PLO and cold cream to the receptor compartment of citrate buffer pH 5.5. Throughout the experimental period of 24 h, the PLO showed significantly higher levels of amitriptyline skin permeability (37.4 ± 6.9 µg/cm^2) than the cold cream (20.3 ± 5.2 µg/cm^2). These results seem to confirm the conclusions reached by several studies that the PLO provides enhancement of drug transport into or across the skin and is thus widely used in pharmaceutical compounding to enhance the skin permeability of many therapeutic drugs.[26] The permeation enhancement effect of PLO is from its structural matrix. The PLO is a colloidal system

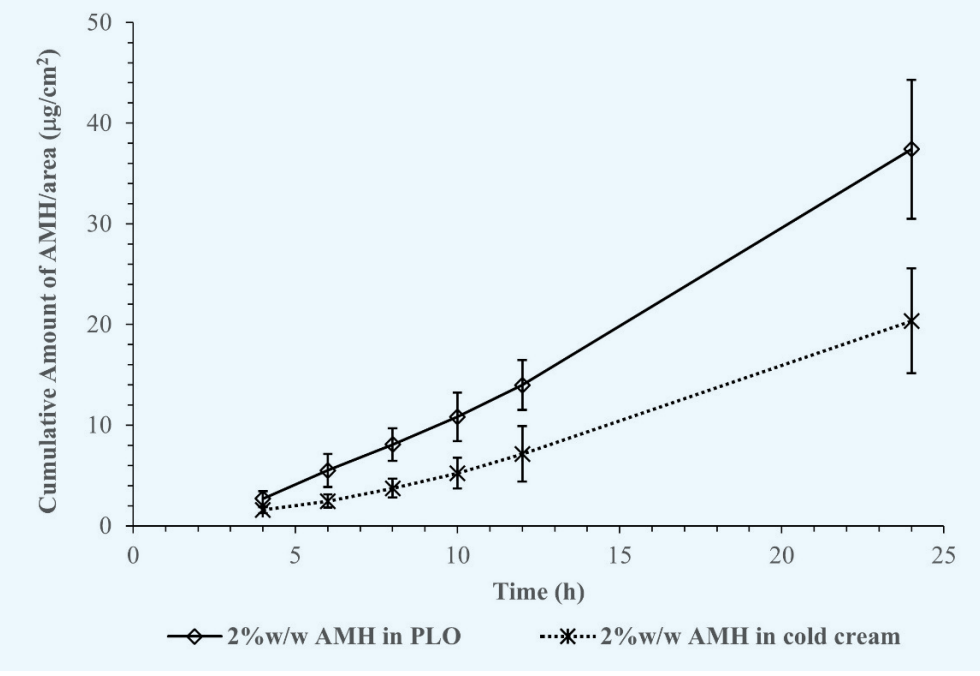

Fig 4. *In vitro* drug permeation profiles of AMH from 2%w/w AMH in PLO and 2%w/w AMH in cold cream. Data represent the mean ± SD (n=5).

that cylindrical inverted micelles of lecithin entrapped in the three-dimensional network of the external aqueous phase.[29] The micelles of the surfactant disorganize the stratum corneum, promoting lipid fluidity, decreasing the barrier function and enhancing drug permeation through the skin.[30]

Stability study

Physical stability testing

The organoleptic properties of AMH compounded in cold cream and PLO remained relatively consistent in all storage conditions. However, AMH compounded in cold cream was slightly more viscous but still spreadable after 60 days stored at 2–8 °C. The same consistency was observed when the cold cream formulations were kept at 30 °C and 40 °C after 14 days. However, regarding the viscosity of the formulations kept at room temperature, AMH in cold cream had a lower viscosity (5,900 cps to 10,900 cps) than the AMH prepared in PLO (124,000 cps to 136,000 cps), as shown in Fig S1A and S1B, respectively. The viscosity of AMH in cold cream was significantly increased when kept at higher temperatures, namely 30 °C for 60 days and 40 °C for 30 days (5,900 cps to 10,900 cps) ($p<0.05$). For the AMH in PLO, the viscosity presented a slight change after being kept at 30°C (124,000 cps to 136,000 cps), and significant increasing after being kept at 40 °C (132,000 cps to 220,000 cps) for 60 days ($p<0.05$).

Chemical stability testing

The percentage of the initial concentration of AMH in the formulations at each time point and storage condition are summarized in Table 2. AMH in cold cream base stored at 2–8 °C and 30 °C, had a significant decrease in the percentage of drug remaining after day 14 compared to day 0 ($p < 0.05$). However, after 60 days, the percentage of drug remaining was still within the acceptable range of 90–110 % of the initial AMH concentration. When AMH in cold cream preparations were stored at 40°C, there was a significant decrease in the percentage of drug remaining after day 14 and 30 ($p < 0.05$). Since the phase separation was detected in AMH in the cold cream after being stored at 40 °C for 60 days, i.e. some oil spreading on the surface of the preparation (Fig S2), the percentage of drug remaining was not reported. However, AMH compounded in PLO showed a significant increase in drug concentration after being stored at both 30 °C and 40 °C compared to day 0 ($p < 0.05$). After 30 days, the percentage of drug remaining of AMH at both 30 °C and 40 °C exceeded the acceptable range of drug remaining. This may be due to water loss from non-airtight plastic containers used in the study, resulting in increased potency of AMH.

Microbiological stability

The microbial content of the formulations of AMH in cold cream and AMH in PLO were determined. According to USP41, Chapter <1111> Microbial Examination of Nonsterile Product Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use, the total aerobic microbial count must have ≤200 cfu/g after the plate is incubated at 30 °C to 35 °C for 3 days. The total combined yeasts and molds count (must have ≤ 200 cfu/g after the plate is incubated at 20 °C to 25 °C

TABLE 2. Percentage of AMH (% drug remaining) in cold cream and PLO under various storage conditions.

Base	Condition	% Drug remaining			
		Day 0	Day 14	Day 30	Day 60
Cold cream	2-8 °C	100.0 ± 0.0	95.8 ± 4.2	91.0 ± 2.7	95.8 ± 1.3
	30 °C	100.0 ± 0.0	96.0 ± 3.5	93.9 ± 3.9	96.9 ± 3.4
	40 °C	100.0 ± 0.0	97.0 ± 3.4	98.1 ± 2.9	NA
PLO	30 °C	100.0 ± 0.0	109.8 ± 2.9	110.5 ± 2.2	116.4 ± 1.4
	40 °C	100.0 ± 0.0	109.4 ± 1.7	112.6 ± 1.3	119.5 ± 2.6

Data represent mean ± SD (n = 4).
*NA = not available

for 5 days. Both formulations complied with the USP41 standard. After 60 days of the study period, both formulations in all conditions above were examined. Microbial growth was absent in all samples tested.

We were able to prepare 2%w/w AMH in hydrophilic petrolatum USP, anionic cream, cold cream USP and PLO. Significant drug release from the cold cream and PLO was found. Compounded preparations of AMH in cold cream and PLO were further studied for *in vitro* permeation and stability. The compounded preparations of AMH in cold cream were stable at 2–8 °C and 30 °C for 60 days and at 40°C for 30 days, whereas AMH in PLO were stored and found to be stable at 30 °C and 40 °C for 14 days. The organoleptic properties of AMH compounded in cold cream and PLO remained relatively consistent, and the AMH remaining concentration was within the range of 90–110% in all storage conditions. There was no visible microbial growth in any of the sample.

Shakshuki et al.[31] investigated *in vitro* amitriptyline permeation across simulated skin from 1%,5% and 10% formulations in each of 3 bases (Lipoderm base, Emollient cream, and Mediflo 30 PLO). They found that amitriptyline 5% or 10% compounded in Lipoderm base or Emollient cream has the highest drug permeation. Kung et al.[32] determined skin drug delivery across porcine skin from a 4% amitriptyline formulation comprising isopropyl alcohol combined with propylene glycol or isopropyl myristate. They found that the high concentration of isopropyl alcohol in isopropyl myristate/isopropyl alcohol binary formulations greatly contributes to an increased skin permeation of amitriptyline. Based on the data generated through permeation experiments from previous and our studies, the higher drug permeation could potentially result in greater therapeutic efficacy. Available evidence supports the effectiveness of topical amitriptyline alone and in combination with other agents (i.e, ketamine and lidocaine) in the treatment of neuropathic pain.[12,33] Therefore, it is expected that the AMH topical formulations developed in this study could be used in clinical practice.

CONCLUSION

Based on the results of *in vitro* permeation and product stability studies in the present study, it is suggested that AMH in cold cream could be prepared and used as extemporaneous topical preparations with a beyond-use date of 60 days when kept at 2–8 °C and 30 °C. AMH in PLO can also be prepared and used as extemporaneous topical preparations with a beyond-use date of 14 days when kept at 30 °C, which is a shorter stability period than that of AMH in cold cream. Changing the plastic containers to glass containers or airtight containers may increase the beyond-use date, leading to significant cost savings for patients as these products tend to be expensive.

Declaration of conflicts of interest

The authors declare that they have no conflicts of interest with the manufacturers or suppliers of any of the products or materials in this study.

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Long-term Efficacy of Genicular Nerve Ablation for Chronic Osteoarthritic Knee Pain: A Prospective Observational Longitudinal Study

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ABSTRACT

Objective: When patients with chronic osteoarthritis (OA) knee pain do not respond to conservative treatment and are not suitable for knee arthroplasty, radiofrequency ablation (RFA) of the genicular nerve is probably an alternative treatment. This study aimed to evaluate the efficacy and safety of genicular nerve ablation in severe osteoarthritic knee pain patients.

Materials and Methods: Patients with severe chronic OA knee pain were recruited and performed a genicular nerve block (GNB). The patients' demographic data, numerical rating scale (NRS) at rest and on movement, Thai Oxford knee score (Thai OKS), Thai knee injury and osteoarthritis outcome score physical function short form (Thai KOOS-PS), timed up and go test, brief pain inventory, fall evaluation, and EuroQol 5D-5L were recorded. For the positive block patients (≥50% pain relief for 24 hours), genicular nerve RFA was performed under fluoroscopic or ultrasound guidance. All patients were followed up at the 1st, 3rd, 6th, 9th and 12th months.

Results: 21 patients were included in the study, but only 17 were completely followed up for 12 months. At the 12th month, genicular nerve RFA reduced the mean NRS on movement from 7.9±1.6 to 4.0±2.6 (p=.005), improved knee function (Thai OKS from 18.8±5.3 to 28.5±10.1; p=.006), but did not significantly improve quality of life (EuroQol-5D-5L from 0.43±0.20 to 0.69±0.33; p=.130). No adverse events were observed.

Conclusion: Genicular nerve radiofrequency ablation in severe chronic OA knee patients demonstrated significant pain relief and functional improvement for up to 12 months without serious adverse events.

Keywords: Knee pain; joints; osteoarthritis; radiofrequency ablation; genicular nerve; conservative treatment (Siriraj Med J 2023; 75: 436-444)

INTRODUCTION

Chronic knee osteoarthritis is a disease causing a worldwide health problem because patients suffer from pain, restricted movement, and functional disability[1], leading to increased risks of morbidity and mortality.[2] In Thailand, the prevalence of knee osteoarthritis is almost 60% in the elderly.[3,4]

Regarding osteoarthritis of the knee, the clinical manifestations are pain, stiffness, and a limited range of motion, with the osteoarthritic change visible on X-rays. The

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first step of management usually starts with conservative treatment, such as weight reduction[5], quadriceps exercise[6], lifestyle modification, medications for pain control[7], acupuncture[8], intra-articular steroid injection[9], hyaluronic acid (HA) injection[10,11], and platelet-rich plasma (PRP) injection.[12] However, if the patients do not respond to conservative strategies, surgical management, especially knee arthroplasty, is the indicated treatment that can provide good pain relief and increase quality of life.[13,14] Unfortunately, some patients are unsuitable for surgery because of age or medical comorbidities, and for these radiofrequency ablation (RFA) of the genicular nerve may be considered as an alternative treatment.[15,16]

Radiofrequency ablation (RFA) of the genicular nerve can be performed under fluoroscopic or ultrasound guidance to identify the structures around the knee and to denervate the sensory nerve supply to the painful structure, which helps to relieve pain and improve knee function.[15]

Although current several evidence showed the good short-term (3- to 6-month) efficacy of genicular nerve ablation for knee osteoarthritis[17-19], data on the long-term one-year follow-up efficacy are still scarce. In the clinical practice guideline for knee osteoarthritis, denervation therapy is mentioned but with a limited strength of recommendation, so genicular nerve RFA may not be considered as a treatment option for knee osteoarthritis, especially in Thailand.[20] Therefore, this study aimed to evaluate the efficacy and safety of genicular nerve RFA in severe osteoarthritic knee pain patients.

MATERIALS AND METHODS

This prospective observational study was conducted at the Pain Clinic, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. After approval by the Institutional Review Board (COA no. Si 292/2019), informed consent was obtained from all participants.

Participants

Chronic osteoarthritic knee patients were recruited if they were 50 years old or over with moderate to severe pain (scoring ≥4 on the numeric rating scale), grades 3–4 according to the Kellgren–Lawrence classification, had refused knee arthroplasty within 1 year, and did not obtain pain relief with conservative treatments, including oral analgesics and physiotherapy, more than 2 months prior to the study.

The exclusion criteria included coagulopathy or bleeding disorders, systemic infection, infection around the knees, previous treatment with visco-supplements within three months, connective tissue diseases that involved the knees, being on a pacemaker, unknown history of previous treatments, history of schizophrenia, major depressive disorder, and uncontrolled generalized anxiety disorders.

The participants were not allowed to receive other interventional treatments such as intra-articular steroid or visco-supplement injection during the study period. However, the participants could continually receive analgesics or physical therapy as they previously used.

Intervention

Baseline data were recorded as follows: demographic data, numerical rating scale (NRS) at rest and on movement, range of motion (ROM), Thai Oxford knee score (Thai OKS)[21,22] Thai knee injury and osteoarthritis outcome score physical function short form (Thai KOOS-PS)[23,24] timed up and go (TUG) test[25], the Thai version of the brief pain inventory (BPI-T)[26], fall evaluation questionnaire (12 questions, score ranging from 0–12, where 0 means the highest to 12 means the lowest risk of falling), and EuroQol 5D-5L.[27]

Diagnostic genicular nerve block procedure

Diagnostic genicular nerve block (GNB) under fluoroscopic or ultrasound guidance was performed with 0.5% bupivacaine 1 ml for each genicular nerve (superior medial, superior lateral, and inferior medial genicular nerves). Pain scores (i.e., NRS) were recorded before and after the nerve block for 24 hours. If the diagnostic block was positive (≥50% pain relief from baseline NRS for 24 hours), patients were then appointed for genicular nerve ablation.

Genicular nerve radiofrequency ablation procedure

Genicular nerve ablation was performed in the operating room under standard monitoring, with an aseptic technique and under sedation with fentanyl 1–2 mcg/kg. A 16G radiofrequency (RF) cannula, 10 cm long with a 10 mm active tip, was inserted to the target point (superior medial (SM), superior lateral (SL), and inferior medial (IM) genicular nerves) under fluoroscopic or ultrasound guidance depending on the interventionist's preference (Figs 1 & 2). An RF probe was inserted into the RF cannula and connected to an RF generator (NT1100, NeuroTherm™, USA). Sensory and motor stimulation were tested, less than 0.5 volts and up to 2 volts, respectively, to identify the proper position of the RF cannula. Subsequently, 2% lidocaine 1 ml was injected for reducing pain before applying conventional radiofrequency ablation at 80 degrees Celsius, for 3 minutes for 2 cycles per target nerve.

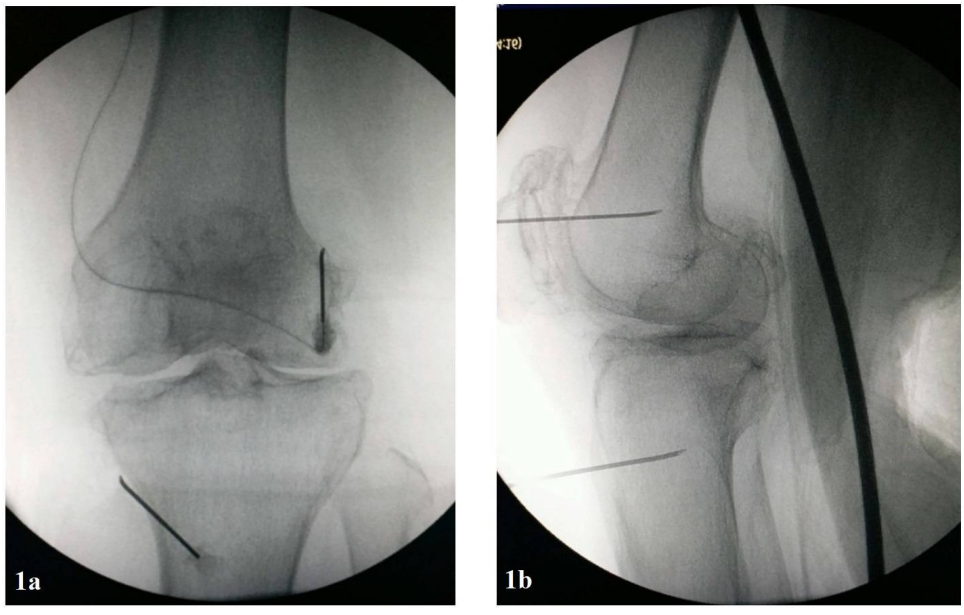

Fig 1. Fluoroscopic guidance imaging of (1a) antero-posterior and (1b) lateral views of the knee joint demonstrated the position of the radiofrequency cannula at superior lateral and inferior medial genicular nerves.

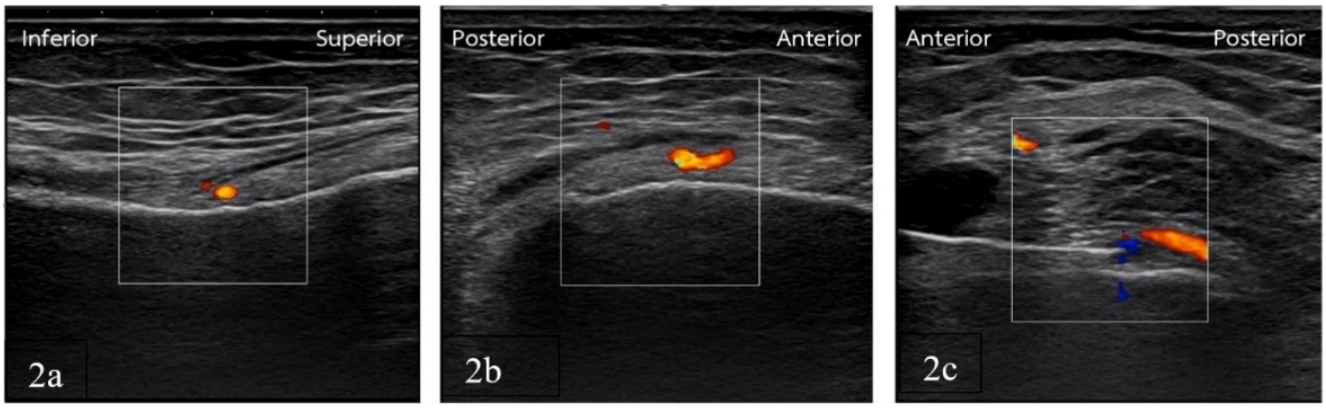

Fig 2. Ultrasound guidance imaging of (2a) inferior medial (longitudinal view), (2b) superior medial (transverse view) and (2c) superior lateral (transverse view) genicular nerves accompanying vascular flow above the bony cortex.

Data collection and outcome measures

All of the patients were followed up at the 1st, 3rd, 6th, 9th, and 12th month after the procedure for clinical assessment and data collection. The primary outcome was the reduction of the mean NRS on knee movement at the 1st, 3rd, 6th, 9th, and 12th month after the procedure. The patients' improvement in physical function and quality of life were evaluated by questionnaires (Thai OKS, Thai KOOS-PS, BPI-T, and EuroQol 5D-5L) for the secondary outcomes. The risk of a fall was also assessed for the secondary outcome using the fall evaluation questionnaire and TUG test. Adverse outcomes including infection, bleeding, bruising, skin burns and local numbness were also recorded. Patients who were unable to present at the Pain clinic were contacted by telephone and interviewed using those questionnaires except the TUG test.

Sample size calculation

The sample size calculation was based on a previous study by Hunter[28], considering the mean pain score of knee osteoarthritis of 6.6±2.5. We estimated that genicular RFA could reduce the pain score by approximately 30% at the 12th month. The sample size was calculated by the nQuery program (two dependent means) with an alpha error of 0.05 and study power of 80%. The calculated sample size was 13. We estimated a loss to follow-up of about 20%, and hence factored for 16 patients.

Statistical analysis

The collected data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, Illinois, United States). Data were described in terms of the frequency (number and percent of cases), mean±SD, and median (IQR) where appropriate. A repeated-measures 1-way analysis of variance and Friedman's 2-way ANOVA were used to determine the continuous data with normal distribution variables and nonparametric variables, respectively, over

the 6 timepoints; that is, at baseline and 1, 3, 6, 9, and 12 months after the intervention. McNemar's test was used for categorical variables compared with the baseline.

RESULTS

Study sample description

Thirty-one patients were recruited initially for a genicular nerve block. However, five patients were excluded due to a negative genicular nerve block, five patients were withdrawn because of cognitive problems, procedure intolerability, and a change in plan to surgery. Thus, 21 patients underwent RFA genicular nerve and were followed up at 1, 3, 6, 9, and 12 months. Of these 21, 5 patients were incompletely followed-up, as shown in Fig 3. However, one patient, who did not visit at the 9th month, returned to follow up at the last visit. Therefore, 17 patients were completely followed up at the 12th month.

The patients' baseline characteristics are shown in Table 1. About half of the patients were Grade 4 osteoarthritis from radiographic findings. The mean pain duration before intervention was approximately 5 years. Fluoroscopic-guided genicular nerve RFA was performed in 7 out of the 21 included patients. No

TABLE 1. Patients' baseline characteristics.

Parameter	Total (n = 21)
Age (years)	74.29±10.57
Sex (Female)	17 (81%)
Body mass index (kg/m^2)	26.68±5.62
Preexisting disease	
Hypertension	15 (71.4%)
Coronary artery disease	3 (14.3%)
Diabetes mellitus	11 (52.4%)
Kellgren–Lawrence grading scale	
Grade 3	9 (42.9%)
Grade 4	12 (57.1%)
Imaging guidance	
Fluoroscopic	7 (33.3%)
Ultrasound	14 (66.7%)
Duration of pain (years)	5 (1, 20)

Data are presented as the mean±SD, median (min, max), or number (%).

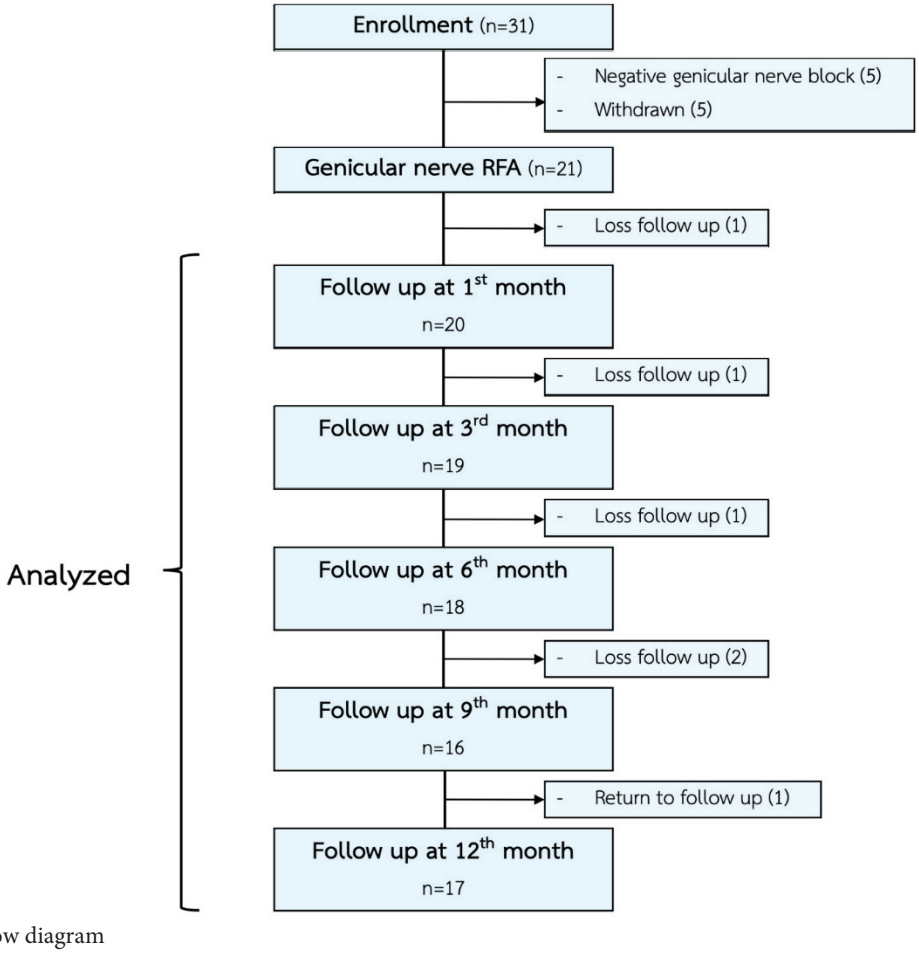

Fig 3. Participants' flow diagram

participant had proceeded for knee arthroplasty surgery during the 12-month follow-up. However, one patient underwent total knee arthroplasty 28 months after the RFA treatment. Moreover, there was one patient receiving additional treatment of Thai traditional massage and acupuncture.

Effects of genicular nerve RFA on pain reduction

As for the primary outcome, the NRS on movement significantly decreased from 7.9±1.6 at baseline to 2.8±2.7, 3.8±2.3, 4.4±1.9, 3.6±1.9, 4.0±2.6 at the 1st, 3rd, 6th, 9th, and 12th months, respectively, after genicular nerve RFA (p = .005), as shown in Fig 4.

Effects of genicular nerve RFA on physical function and quality of life

Regarding the secondary outcomes of knee function evaluation, the Thai OKS continued to increase over time from 18.8±5.3 at baseline to 28.5±10.1 at the 12th month, with a significant change from baseline since the 1st month (Table 2). The number of patients who were categorized in the moderate to severe OKS classification also decreased from baseline after the procedure (Table 2). The Thai KOOS-PS significantly decreased from baseline at the 1st, 3rd, and 6th months after intervention (Table 3). BPI-T and EuroQol 5D-5L utility were significantly improved in most of the follow-up months after the procedure, as shown in Table 3. However, the fall evaluation score did not show a significant difference from the baseline (Table 3). The median (IQR) time in the TUG test did not demonstrate a significant change over time from baseline, but the number of patients who had a TUG of more than 12 seconds (risk of falling) seemed to decrease over time, but not with statistical significance (Table 4). No adverse events were detected.

DISCUSSION

In this prospective observational study, we found that radiofrequency ablation (RFA) of the genicular nerve could effectively reduce the mean NRS on movement, and improve knee function and the quality of life of severe osteoarthritic knee patients who did not respond to conservative treatment.

Pain is a major problem for knee osteoarthritis patients. Pain sensation in the knee is conducted by genicular nerves, specifically the articular branches around the knee joint from the femoral, obturator, common peroneal, and tibial nerves.[29,30] Blocking sensations from these sensory nerves should result in pain relief. Currently, RFA is one of the popular techniques to ablate the nerves originating from the treatment of low back pain. Consequently, genicular nerve neurotomy by RFA has emerged, as first proposed by Choi et al.[15], targeting the superomedial (SM), superolateral (SL), and inferomedial (IM) genicular nerves. According to the diagnostic nerve block, if the result is positive, patients should respond to genicular nerve ablation and could have a reduced NRS after the intervention.

As RFA denervates the genicular nerves, painful sensations should decrease for a longer period. The duration of the reduced painful sensations may depend on the magnitude of nerve ablation and the rate of regeneration of the nerve after RFA.[31] One study in nerve regeneration after RFA found evidence of complete regeneration at 90 days after RFA.[32] However, many clinical studies about knee osteoarthritis pain relief after genicular RFA showed that the effect of RFA may last for up to 6 to 12 months[33-36], similar to our study. Moreover, some studies have demonstrated that pain relief after genicular RFA can even last for 24 months.[28]

Recently, Fonkoue and colleagues proposed that targeting two additional genicular nerves (the recurrent fibular nerve and infrapatellar branch of the saphenous nerve) could improve the pain relief outcome.[37,38] However, this is still questionable and long-term study is still lacking on this topic. Regarding the RFA technique, a meta-analysis covering conventional, pulsed, and cooled RFA found no difference in analgesic outcome among these RFA techniques.[39] Variations in the efficacy of genicular RFA among patients could result from variations in the patients' genicular nerve anatomy, the knee position of the patient affecting the path of the nerve, or the interventional technique applied in targeting the nerves.

Among the non-surgical management options for knee osteoarthritis, genicular nerve RFA is perhaps the most attractive treatment option. Pain relief from RFA genicular nerve seems to be more effective and lasts longer than intra-articular steroid injection, which is typically effective for 4–6 weeks.[36,40] This results trend was also found when comparing genicular nerve RFA with intra-articular hyaluronic acid (HA) injection as well.[35,51,42] Although intra-articular platelet-rich plasma (PRP) injection might manifest a favorable outcome at 6–12 months[43], there has been no head-to-head comparison study performed between genicular RFA and intra-articular PRP injection. Nevertheless, Shen et al. found that the pain score was more significantly reduced when combining genicular nerve RFA with intra-articular HA and PRP than both without RFA.[44]

Furthermore, beyond the pain improvement, genicular nerve RFA also improved knee function and quality of life as a consequence of reducing pain, such as

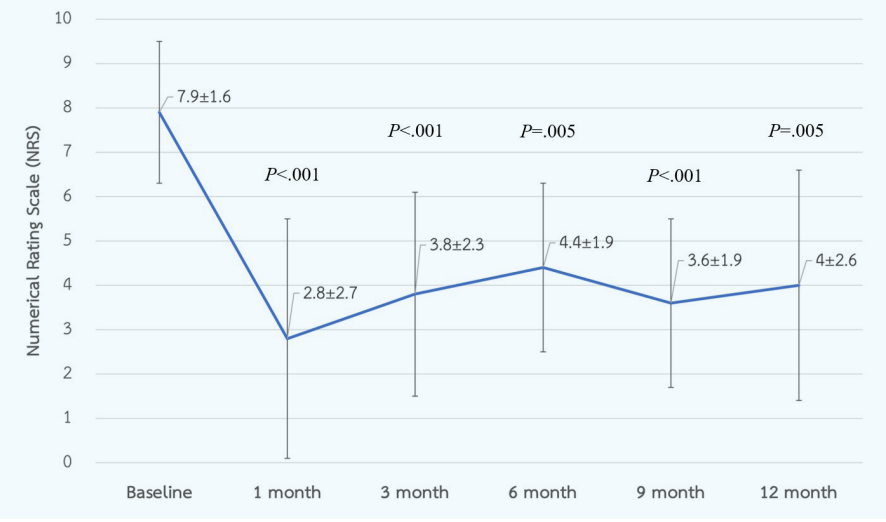

Fig 4. Numerical rating scale (NRS) of pain intensity at baseline and after genicular nerve ablation up to 12 months.
Data are presented as mean±SD.
P<.05 indicates statistical significance, compared to the baseline.

TABLE 2. Thai Oxford knee score (OKS) at baseline and after genicular nerve ablation up to 12 months.

	Baseline (n = 21)	1st month (n = 20)	3rd month (n = 19)	6th month (n = 18)	9th month (n = 16)	12th month (n = 17)
Thai OKS	18.8±5.3	31.5±11.9	29.9±8.7	27.0±8.8	30.4±10.8	28.5±10.1
P		.001*	<.001*	.008*	.002*	.006*
OKS classification						
Score 0–19 (severe)	11 (52.4%)	4 (19.0%)	2 (9.5%)	2 (9.5%)	2 (9.5%)	2 (9.5%)
Score 20–29 (moderate to severe)	10 (47.6%)	5 (23.8%)	8 (38.1%)	9 (42.9%)	6 (28.6%)	8 (38.1%)
Score 30–39 (mild to moderate)	-	6 (28.6%)	7 (33.3%)	6 (28.6%)	5 (23.8%)	5 (23.8%)
Score 40–48 (satisfactory function)	-	5 (28.6%)	2 (9.5%)	1 (4.8%)	3 (14.3%)	2 (9.5%)

Data are presented as the mean±SD or number (%).
**P*<.05 indicates statistical significance, comparing to baseline.

TABLE 3. Thai KOOS-PS, BPI-T, EuroQol 5D-5L and fall evaluation at baseline and after genicular nerve ablation up to 12 months.

	Baseline (n = 21)	1st month (n = 20)	3rd month (n = 19)	6th month (n = 18)	9th month (n = 16)	12th month (n = 17)
Thai KOOS-PS	18.3±5.5	11.2±7.7	12.0±7.2	12.4±6.9	11.6±8.0	12.8±7.0
P		.001*	.002*	.001*	.063	.075
BPI-T	26 (19.5, 37.8)	11.5 (3, 15.8)	12.5 (0.5, 24.5)	17.5 (6.3, 27)	12.5 (5.5, 28.5)	18 (5.8, 28.3)
P		<.001*	<.001*	.020*	.017*	.027*
EuroQol 5D-5L	0.43±0.20	0.79±0.17	0.76±0.22	0.70±0.18	0.75±0.20	0.69±0.33
P		.001*	.001*	.001*	.001*	.130
Fall evaluation	10 (6, 11)	10 (7.5, 11)	11 (7.25, 12)	11 (7.5, 12)	10.5 (7.25, 12)	11 (8.25, 12)
P		.422	.065	.089	.299	.299

Data are presented as the mean±SD or median (IQR).
**P*<.05 indicates statistical significance, comparing to baseline.
EQ-5D-5L, EuroQol Group questionnaire with 5 dimensions and 5 levels of severity; Thai KOOS-PS, Thai knee injury and osteoarthritis outcome score physical function short form; BPI-T, brief pain inventory.

TABLE 4. TUG test at baseline and after genicular nerve ablation up to 12 months.

	Baseline (n = 21)	1st month (n = 17)	3rd month (n = 15)	6th month (n = 15)	9th month (n = 12)	12th month (n = 13)
TUG test (seconds)	28 (15, 40)	17 (14, 32)	17 (10, 40)	17 (12, 31)	11 (9, 35)	15 (9, 24)
TUG ≥12 secs (risk of falling)	18 (85.7%)	14 (66.7%)	12 (57.1%)	7 (33.3%)	6 (28.6%)	7 (33.3%)
P		.500	.500	.250	.125	.250

Data are presented as the median (IQR) or number (%).
TUG test, timed up and go test.

increasing the range of knee motion, more knee stability, better sleep, and being able to do more activities of daily living using the knee by themselves, including working, shopping, doing hobbies, and using public transport, as shown by the improved Thai OKS, Thai KOOS-PS, BPI-T, and EuroQol 5D-5L evaluations. The previous studies showed similar functional and quality of life improvement outcomes with the same and different questionnaires, including Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Global Perceived Effect (GPE).[15,28,36] Although we found a non-homogenous result from each questionnaire at each time point, the trend for the score seemed to be ameliorated.

In our study, we found no different improvement in the risk of a fall from the fall evaluation questionnaire, which might have been because of the already low risk of a fall in the baseline characteristics of the patients (median score of 10 out of 12). The median time for the TUG test and the number of patients who had a TUG test time over 12 seconds (risk of falling) seemed to be lower after genicular nerve RFA, although without statistical difference. Therefore, the improvement in the falling risk was not clear. However, we might interpret the findings as suggesting that genicular nerve RFA did not increase the risk of falling or the walking ability. However, the pain relief would encourage the patients to participate in an intensive rehabilitation and physiotherapy program, which could indirectly reduce the falling risk.

Genicular nerve RFA is quite a low-risk procedure. We did not detect any significant adverse events after the procedure. Most previous studies about genicular nerve RFA did not report any major adverse events[45], while some studies found only mild localized side effects.[17] Nevertheless, there were some case reports about some serious side effects of genicular nerve RFA, including knee hematoma or hemarthrosis, septic arthritis, severe skin burn, tendon injury, and complex regional pain syndrome (CRPS).[46-50]

There are some limitations of our study to note, including the small sample size. This was in part due to the COVID rules at the time of the pandemic, where many elective cases in the hospital were postponed. A larger sample size should be considered in further study to ensure the efficacy and safety of genicular nerve ablation. Also, a sham-controlled study, the prevention of fall-associated morbidity and mortality, and the impact of pain-free rehabilitation and muscle strengthening should be considered in further studies.

CONCLUSION

Genicular nerve RFA demonstrated efficacy in pain relief and functional improvement of severe osteoarthritis of the knee for up to 12 months after the procedure without any serious adverse events. This intervention might be considered as an alternative treatment option, especially in patients who could not undergo knee arthroplasty.

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Conflict of interest

All authors declare no personal or professional conflicts of interest.

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Early Surgical Complications Following Transanal Endorectal Pull-through for Hirschsprung's Disease

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ABSTRACT

Objective: The purpose of this study was to examine factors affecting early complications following transanal endorectal pull-through (TERPT) in patients with Hirschprung's disease.

Materials and Methods: Retrospective chart reviews of patients with Hirschsprung's disease who underwent TERPT/ abdominal assisted TERPT at Siriraj Hospital between January 2009 and December 2019 was carried out.

Results: The overall complication rate was 26% (43/163). The complications were as follows: 14 cases of anastomotic strictures (32.6%), five cases of abscess at anastomosis (11.6%), and three cases of anastomotic leakages (7.0%). In regards to preoperative bowel preparation, when comparing those with and those without post-operative complications, the amount of NSS for rectal irrigation (ml/Kg), duration required (days), and duration of changed diet (days) were the same. Colostomy prior to a pull-through operation could not prevent post-operative complications following endorectal pull-through (p = 1.000). The incidences of early complications following TERPT and abdominal assisted TERPT was the same (p = 0.344). Abdominal assisted TERPT had a higher incidence (4%) of anastomotic leakages whereas TERPT had a higher rate of anastomosis strictures (12%) compared to o abdominal assisted TERPT (5%). The higher the transitional zone, the higher the complication rate. Anastomotic leakages, the most serious complication, rarely occurred following TERPT in the low transitional zone.

Conclusion: There was no significant risk factor associated with early surgical complications following TERPT. Abdominal assisted TERPT should be selected properly according to the level of transitional zone. The complications correlate with whether a perfect pull-through operation could be performed or not.

Keywords: Hirschsprung; endorectal pullthrough; complications; anastomosis; bowel preparation (Siriraj Med J 2023; 75: 445-453)

INTRODUCTION

Hirschsprung's disease (HD) is caused by the absence of ganglion cells in the myenteric and submucosal plexus of the colon, resulting in a lack of propagation of the peristaltic wave of the colon. The incidence of HD is approximately 1 in 5,000 live births.[1] Effective surgical treatment includes resection of the aganglionic portion of the bowel and identification of normally ganglionated proximal bowel with a leveled coloanal anastomosis. Many operative approaches to correct HD are derived from original concepts by Swenson, Duhamel, and Soave-Boley.[2-4] The standard Soave-Boley endorectal pull-through procedure uses both the abdominal and transanal approach[3,4] and was popularized after the introduction of the laparoscopic pull-through.

The Soave-Boley endorectal pull-through procedure was transformed into a solely transanal approach named "transanal endorectal pull-through (TERPT)" by L De la Torre and J A Ortega in 1988.[5-7] If the transanal approach cannot be performed perfectly, a combination of abdominal and transanal approaches, named "abdominal assisted transanal endorectal pull-through," (abdo + TERPT) is used.

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During the transanal endorectal pull through procedure, a submucosal dissection of the rectum after a circumferential incision of the rectal mucosa is performed. Following a submucosal dissection, a seromuscular layer of the rectum is incised circumferentially. A mucosectomy of the rectum, leaving a muscular cuff is also performed. The ganglionated colon is pulled through the aganglionic rectal cuff, and a coloanal anastomosis is performed.[5-7]

When the transition zone is proximal to the mid-sigmoid colon, abdominal assisted transanal endorectal pull-through is considered.[6] A pedicled colon flap must be developed to provide adequate length for colon pull-through. In this situation, it might be necessary to ligate and divide either the inferior mesenteric artery just distal to its origin from the aorta or the left colic artery just after it rises from the inferior mesenteric artery. By ligating these vessels at these sites, the arterial supply through the marginal artery should not be compromised.[6]

The primary pull-through method for HD has been in use since 1980.[7,8] A single-stage procedure avoids the complications associated with a colostomy and the need for another operation to close the colostomy. A primary single-stage pull-through is appropriate for most infants and children diagnosed with HD. Contraindications to primary pull-through include severe enterocolitis[7-9], massive proximal dilatation[7-9], an inability to determine the transition zone[7,8], life-threatening comorbidities[7,8] and colonic perforation[9]

Early postoperative complications include anastomotic leaks and cuff abscess, bowel obstruction, perineal excoriation, stoma complications, and wound infection. On the other hand, late complications include bowel obstruction, constipation, enterocolitis, incontinence, and stricture. In this study, complications that happened in less than or equal to 30 days post-operatively were included.

Major complications mostly occur at coloanal anastomosis. Anastomotic leaks have been reported in 5% to 10% of cases, while cuff abscess is seen in about 5% of cases.[10-12] Factors increasing the risk of these complications include tension on the anastomosis or ischemia of the pull-through segment.[10-12]

Factors affecting anastomotic leakage include:

1. Levels of transitional zone. When the transition zone is located too high, abdominal assisted transanal endorectal pull-through is considered. The levels of transitional zone required for an abdominal assisted transanal endorectal pull-through instead of an isolated transanal endorectal pull-through is still controversial.

2. Preoperative bowel preparation. The Division of Pediatric Surgery, Faculty of Medicine, Siriraj Hospital uses a preoperative bowel preparation regimen with rectal NSS irrigation of 30-50 ml/Kg/, twice a day. This amount of NSS is not proven to be efficient nor is known to be enough to do rectal NSS irrigation. A reduction of stool production by changing the diet was also done pre-operatively. At Siriraj Hospital, a low residual diet was introduced on the third day before operation. On the second day before operation, a liquid diet was prescribed, and on the day before operation, patients were given only a clear liquid diet. The question of how many days is required to change the diet regimen remains.

3. Malnutrition. Whether malnutrition caused more complications was questioned.

4. Colostomy. Whether colostomy proximal to coloanal anastomosis would prevent anastomotic complications remains debatable.

An anastomotic stricture after the pull-through procedure is another important postoperative complication. The risk factors include anastomotic ischemia, cuff ischemia, anastomotic leak, and small circular anastomosis.[13]

If all factors affecting early anastomosis complications are clarified, there would be a reduction of early complications following transanal endorectal pull-through.

MATERIALS AND METHODS

Following approval by the Siriraj Institutional Review Board, (COA no. Si 276/2020), a retrospective study was carried out in children with Hirschsprung's disease who underwent either a transanal endorectal pull-through or abdominal assisted transanal endorectal pull-through at Siriraj Hospital between January 2009 and December 2019. Children with another diagnosis (rectal stenosis, meconium plug syndrome), those who underwent other pull-through operations, and incomplete medical information, were excluded from the study.

Patients' demographic data, nutritional status, transitional zone level, colostomy, bowel preparation before surgery, types of operation, complications following either transanal endorectal pull-through or abdominal assisted transanal endorectal pull-through was collected. Complications, including anastomotic leakage, abscess at anastomosis, intraabdominal collection, anastomotic stricture, rectal cuff stricture, were also recorded. The collected data was analyzed using SPSS software version 18 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc). Continuous data was expressed as median and IQR and categorical data was expressed as numbers and percentages. A Chi square test or Fisher's exact test was used to compare the without post-operative complications and post-operative complication groups. A p-value of <0.05 indicated statistical significance.

RESULTS

Of the 222 patients whose medical records were reviewed, 59 were excluded (41 had other pull-through operations, and 18 had incomplete medical information). One hundred and sixty-three patients were included in this study. Complications were found in 43 patients or 26% (43/163). Post-operative complications are demonstrated in Table 1. Anastomotic strictures were the most common complication (32.6%). Other complications included five cases (11.6%) of abscess at anastomosis, and three cases (7.0%) of anastomotic leakages.

Demographic data and location of the transitional zone in the non-complication (n=120) and complication group (n = 43) is shown in Table 2. The median age of the non-complication group was 3.8 months, and the median age of the complication group was 5.4 months. However, the difference in age and weight of patients in both groups during the operation was not statistically significant.

The most common location of the transitional zone in this study was the rectosigmoid colon (46.3%). Comparing levels of the transitional zone in patients in the non-complication and complication group revealed no statistical significance (p = 0.403).

Whether nutritional status affected post-operative complications was also studied. Nutritional parameters, such as percentile of body weight according to the WHO Growth Chart, total lymphocyte count, Hct, albumin and globulin were collected and compared between those without complications and those with complications. The effect of nutritional status on post-operative complications is demonstrated in Table 3. Nutritional status seemed to have no impact on the complication rate following endorectal pull-through.

TABLE 1. Post-operative complications.

Complication	n	Percent
Anastomotic stricture	14	32.6
Abscess at anastomosis	5	11.6
GI obstruction	4	9.3
Retained aganglionosis bowel	4	9.3
Anastomotic leakage	3	7.0
Rectal cuff stricture	3	7.0
Injury to other organs	1	2.3
Bowel perforation	1	2.3
Other complications	8	18.6
Total	43	100.0

TABLE 2. Demographic data and location of transitional zone compared between the non-complication group (n =120) and complication group (n = 43)

	No complications (n = 120)	Complications (n = 43)	Total (n = 163)	P value
Gender, n(%)				1.000
Male	89 (74.2%)	32 (74.4%)	121 (74.2%)	
Female	31 (25.8%)	11 (25.6%)	42 (25.8%)	
Age (months)				0.657
Median ± IQR	3.8 ± 14.4	5.4 ± 34.8	4.0 ± 14.8	
Body weight (Kg)				0.935
Median ± IQR	5.8 ± 5.9	5.3 ± 6.8	5.6 ± 6.4	
Underlying disease, n(%)				0.209
No underlying disease	116 (96.7%)	39 (90.7%)	155 (95.1%)	
With underlying disease	4 (3.3%)	4 (9.3%)	8 (4.9%)	
Level of transitional zone				0.403
Rectum	33 (27.7%)	9 (22.0%)	42 (26.3%)	
Rectosigmoid colon	55 (46.2%)	19 (46.3%)	74 (46.3%)	
Descending colon	10 (8.4%)	5 (12.2%)	15 (9.4%)	
Transverse colon	14 (11.8%)	6 (14.6%)	20 (12.5%)	
Ascending colon	2 (1.7%)	1 (2.4%)	3 (1.9%)	
Total colonic aganglionosis	5 (4.2%)	1 (2.4%)	6 (3.8%)	

TABLE 3. Effects of nutritional status on post-operative complications.

	No complications (n = 120)	Complications (n = 43)	Total (n = 163)	P value
Age (months)				0.657
Median ± IQR	3.8 ± 14.4	5.4 ± 34.8	4.0 ±14.8	
Body weight (Kg)				0.935
Median ± IQR	5.8 ± 5.9	5.3 ± 6.8	5.6 ± 6.4	
Percentile, n(%)				0.935
P<2536 (30%)	13 (30.2%)	49(30%)		
P25-5023 (19.2%)	10 (23.3%)	33(20.2%)		
P50-7538 (31.7%)	13 (30.2%)	51(31.3%)		
P>9523 (19.2%)	7 (16.3%)	30(18.4%)		
Laboratory				
Total lymphocyte count (cells/mm^3)				
(Median ± IQR)	5611 ± 4338	4889 ± 3703	5155 ± 3886	0.191
Hct (%) (Mean ± SD)	36.1 ± 0.5	35.2 ± 1.2	35.8 ± 6.5	0.436
Albumin (mg/L) (Mean ± SD)	3.9 ± 0.1	3.9 ± 0.2	3.8 ± 0.1	0.594
Globulin (mg/L) (Mean ± SD)	1.8 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	0.644

Pre-operative risk factors for post-operative complications include pre-operative bowel preparation, previous history of Hirschsprung's associated enterocolitis, and colostomy prior to pull-through operation. All pre-operative risk factors for post-operative complications were compared between those without complications and those with complications and are demonstrated in Table 4.

Bowel preparation for a pull-through operation at the Division of Pediatric Surgery, Faculty of Medicine, Siriraj Hospital used rectal NSS irrigation of 30-50 ml/Kg/ twice a day. Comparing those without and those with post-operative complications, the amount of NSS for rectal irrigation (ml/Kg), duration required for rectal NSS irrigation (days), and duration of changing diet (days) were the same (p = 0.961, p = 0.553 and p = 0.296, respectively), The minimum NSS volume for rectal irrigation without any complications in this study was just 10 ml/kg. A previous history of Hirschsprung's associated enterocolitis may increase post-operative complications (p = 0.072).

Colostomy prior to a pull-through operation could not prevent post-operative complications following endorectal pull-through (p = 1.000).

The intra-operative risk factors for post-operative complications were compared between those without complications and those with complications and are shown in Table 5.

When the transition zone was proximal to the mid-sigmoid colon, an abdominal assisted transanal endorectal pull-through (abdo + TERPT) was considered. Early complications following endorectal pull through, whether transanal endorectal pull through or abdominal assisted transanal endorectal pull-through, were the same (p = 0.344). In abdominal assisted transanal endorectal pull-through, division of the inferior mesenteric artery (IMA) to create a pedicled colon flap with adequate length for endorectal pull-through was considered. By ligating the inferior mesenteric artery, there was concern of the compromised arterial supply. In this study, inferior mesenteric artery ligation did not affect complications following abdominal assisted transanal endorectal pull-through (p = 1.000).

Two types of coloanal anastomosis for endorectal pull-through were described. The standard technique was two-layer anastomosis. The first layer sutured the seromuscular layer of the pull-through colon to the rectal cuff, and then the second layer sutured full thickness of the pull-through colon to the rectal mucosa and lower rectal cuff at 0.5 cm above the dentate line. There were only a few patients who received one layer of coloanal anastomosis by suturing full thickness of the pull-through

TABLE 4. Pre-operative risk factors for post-operative complications compared between those without complications and those with complications.

	No complication (n = 120)	Complication (n = 43)	Total (n = 163)	P value
Pre-operative bowel preparation				
Amount of rectal irrigated NSS (ml/kg/dose) (Mean ± SD)	30.3 ± 1.1	30.3 ± 1.9	30.3 ± 1.0	0.961
Duration of rectal NSS irrigation (Days) (Mean ± SD)	6.3 ± 0.5	6.4 ± 0.7	6.4 ± 0.4	0.553
Duration of changing diet (Days) (Means ± SD)	2.1 ± 1	2.2 ± 0.8	2.0 ± 0.9	0.296
Hirschsprung's associated enterocolitis				0.072
No 101 (84.2%)	30 (69.8%)	131 (80.4%)		
Yes19 (15.8%)	13 (30.2%)	32 (19.6%)		
Colostomy prior to pull-through				1.000
No 85 (70.8%)	30 (69.8%)	115 (70.6%)		
yes 35 (29.7%)	13 (30.7%)	48 (29.4%)		

TABLE 5. The intra-operative risk factors of post-operative complications compared between those without complication and those with complications.

	No complication (n = 120)	Complication (n = 43)	Total (n =163)	P value
Type of operations				0.344
TERPT	65 (54.2%)	19 (44.2%)	84 (51.5%)	
Abdo + TERPT	55 (45.8%)	24 (55.8%)	79 (48.5%)	
IMA (in Addo + TERPT only)				1.000
Divided IMA	41 (80.4%)	15 (83.3%)	56 (81.2%)	
Not divided IMA	10 (19.6%)	3 (16.7%)	13 (18.8%)	
Coloanal anastomosis				0.713
2 layers (Seromuscular + all colonic layers	98 (83.8%)	36 (87.8%)	134 (84.8%)	
1 layer (all colonic layers)	19 (16.2%)	5 (12.2%)	24 (15.2%)	

colon to the rectal mucosa and lower rectal cuff 0.5 cm above the dentate line. In our study, both types of coloanal anastomosis had no difference in complication rates (p = 0.713).

The incidence of post-operative complications when comparing levels of transitional zone are demonstrated in Table 6. The results show a higher transitional zone meant more complications. The complication rates following pull-through for Hirschsprung's disease with transitional zone proximal to sigmoid colon (except total colonic aganglionosis (TCA)) was about 30.0%-33.3% whereas complications in patients with a transitional zone at the rectum and rectosigmoid colon was about 21%-25.6%. The complications after a pull-through operation for classical Hirschsprung's disease were minor. The incidence of anastomotic strictures in patients who had a transitional zone at the rectum and rectosigmoid colon was 16% and 5% respectively. Anastomotic leakage, which was the

TABLE 6. Incidences of post-operative complications comparing levels of transitional zone.

Level of transitional zone	Total complications	Anastomotic complications		
		Anastomotic stricture	Abscess at anastomosis	Anastomotic leakage
Rectum	9/42 (21%)	7/42 (16%)	0/42 (0%)	0/42 (0%)
Rectosigmoid colon	19/74 (25.6%)	4/74 (5%)	4/74 (5%)	1/74 (1%)
Descending colon	5/15 (33.3%)	1/15 (6%)	1/15 (6%)	1/15 (6%)
Transverse colon	6/29 (30%)	0/29 (0%)	0/29 (0%)	1/29 (3%)
Ascending colon	1/3 (33.3%)	0/3 (0%)	0/3 (0%)	0/3 (0%)
Total colonic aganglionosis	1/6 (16.6%)	1/6 (16%)	0/6 (0%)	0/6 (0%)

most serious complication, was found in Hirschsprung patients with a transitional zone at the descending colon and transverse colon. This leakage seldom occurs in classical Hirschsprung's disease.

When the transition zone was proximal to the mid-sigmoid colon, abdominal assisted transanal endorectal pull-through (abdo + TERPT) was considered. A comparison of the incidences and types of complications between the transanal endorectal pull-through and abdominal assisted transanal endorectal pull-through is demonstrated in Table 7.

Abdominal assisted endorectal pull-through had a higher incidence (4%) of anastomotic leakage whereas there were no anastomotic leakages in transanal enorectal pull through. Transanal endorectal pull-through had a higher rate of anastomotic strictures (12%) compared to

TABLE 7. Incidences and types of complications comparing transanal endorectal pull-through (TERPT) and abdominal assisted transanal endorectal pull-through (Abdo + TERPT).

	Complications, n (%)	
	TERPT (n= 84)	Abdo + TERPT (n = 79)
Levels of transitional zone		
Rectum	7 (8%)	2 (3%)
Rectosigmoid colon	11 (13%)	8 (10%)
Descending colon	0 (0%)	5 (6%)
Transverse colon	1 (1%)	5 (6%)
Ascending colon	0 (0%)	1 (1%)
Types of complications		
Anastomotic leakage	0 (0%)	3 (4%)
Abscess at anastomosis	3 (4%)	2 (3%)
Anastomotic stricture	10 (12%)	4 (5%)
GI obstruction	0 (0%)	4 (5%)
Retained aganglionosis	2 (2%)	2 (3%)
Rectal cuff stricture	2 (2%)	1 (1%)
Injury to other organs	0 (0%)	1 (1%)
Other complications	1 (1%)	7 (8%)
Bowel perforation	1 (1%)	0 (0%)

abdominal assisted endorectal pull-through (5%). Those who had a transitional zone located at the descending colon or transverse colon, complications of abdominal assisted endorectal pull-through was around 6%. Although complications following these two techniques of pull-through are comparable, abdominal assisted endorectal pull-through had a higher incidence of leakages. The complications correlate with whether a pull-through operation could be done safely. Moreover, retained aganglionosis colon was observed in 3% of abdominal assisted pull-through, even if exploratory laparotomy was done.

DISCUSSION

The aim of this study was to identify possible risk factors of postoperative complications within 30 days of transanal endorectal pull-through (TERPT) and/or abdominal assisted transanal endorectal pull-through (abdo + TERPT). The overall complication rate in this study was 26% (43/163), which is comparable to 22% seen in a study by *Hoff N, et al.*[14]

Major complications mostly occurred in coloanal anastomosis. Besides the high incidence of anastomotic strictures in our study, complications at coloanal anastomosis were comparative to other studies. In our study, anastomotic leaks were seen in 7% of cases whereas other studies reported 5% to 10%.[10-12] In our series, anastomotic abscess was present in 11.6% of all cases whereas others reported 5%.[10-12] The risk of leakages and cuff abscess was caused by tension on the anastomosis or ischemia of the pull-through segment.[10-12] In our series, this complication mostly occurred in abdominal assisted transanal endorectal pull-through in a higher transitional zone. This might be the result of ischemia of the pull-through segment.

The most common location of the transitional zone in this study was the rectosigmoid colon (46.3%). In this study, the levels of the transitional zone had no impact on the complication rate following the pull-through operation (p = 0.403). This might be the result of a high percentage of abdominal assisted transanal endorectal pull though performed in our series.

Although, nutritional status in our study seemed to have had no impact on complication rates following endorectal pull-through, complete nutritional status could not be evaluated in many cases. Albumin and globulin levels were not measured in many patients before the operation.

Various bowel preparation regimens using rectal NSS irrigation before a definite pull-through operation were followed. The Royal Children's Hospital, Melbourne[15] as well as the Children's Hospital, Pittsburgh[16] recommend using NSS irrigation of 20 ml/Kg. However, there is no study comparing the efficiency of these regimens. The Division of Pediatric Surgery, Faculty of Medicine, Siriraj Hospital used a bowel preparation regimen using a rectal NSS irrigation amount of 30-50 ml/Kg twice a day. Comparing those without and with post-operative complications, the amount of NSS for rectal irrigation (ml/Kg), duration required to do this rectal NSS irrigation (days) and duration of changing diet (days) were the same (p = 0.961, p = 0.553 and p = 0.296, respectively).

Colostomy before operations were performed in cases where contraindications to primary pull-through were found, and included: severe enterocolitis, massive proximal dilatation, inability to determine the transition zone and life-threatening comorbidities.[17,18] In this multi-step surgical treatment for Hirschsprung's disease, a colostomy helped with bowel preparation before the operation was performed.. In our study, a colostomy prior to a pull-through operation could not prevent post-operative complications following endorectal pull-through (p = 1.000).

When the transition zone was proximal to the mid-sigmoid colon, abdominal assisted transanal endorectal pull-through (abdo+ TERPT) was considered. Early complications following endorectal pull through, whether transanal endorectal pull through or abdominal assisted transanal endorectal pull-through, were the same (p = 0.344). Therefore, the level of transitional zone could not have a direct impact on complications which were linked to whether pull-through operations could be performed safely.

Abdominal assisted endorectal pull-through had an incidence of 4% for anastomotic leakage, while no anastomotic leakages were found in transanal enorectal pull-through. However, transanal endorectal pull-through had higher rate of anastomosis strictures (12%) compared to abdominal assisted endorectal pull-through (5%). In our study, a high incidence of anastomotic stricture could be the result of tight coloanal anastomosis in patients without laparotomy. A minor degree of anastomotic ischemia and stricture was also encountered.

In abdominal assisted transanal endorectal pull-through, a pedicled colon flap must be developed for endorectal pull-through. In this situation, the pull-through colon derives its vascular supply from the marginal artery. Therefore, to mobilize the descending colon and splenic flexure, it might be necessary to ligate and divide either the inferior mesenteric artery just distal to its origin from the aorta or the left colic artery just after it rises from the inferior mesenteric artery. By

ligating these vessels at these sites, the arterial supply through the marginal artery should be preserved.[6] The appropriate length of the pedicle can be determined by pulling the intended site of anastomosis down into the pelvis and allowing a few extra centimeters for a tension-free coloanal anastomosis. However, in our study, patients with abdominal assisted transanal endorectal pull-through with inferior mesenteric artery ligation were not affected by complications following the operation ($p = 1.000$).

Surprisingly, in our study, anastomotic stricture was the most common complication (32.6%). Anastomosis stricture was found frequently in those with a low transitional zone. Sixteen percent of patients with transitional zones located in the rectum had anastomotic stricture. In our series, transanal endorectal pull-through had higher risk (12%) of anastomotic strictures than abdominal-assisted transanal endorectal pull-through (5%). Other studies[13,19] have reported that anastomotic strictures are the result of anastomotic ischemia, cuff ischemia, anastomotic leaks, and small circular anastomosis. In our study, the reason why abdominal assisted transanal endorectal pull-through had a lower rate of anastomotic stricture might be due to less tight coloanal anastomosis and/orlower levels of rectal cuff resection during laparotomy. Some reports[6,20] suggest that the posterior wall of the cuff should be split to the intended point of anastomosis. The rectal cuff should also be inspected to ensure it is straight and does not fold down into the anorectal canal. A short rectal muscular cuff might also decrease the incidence of enterocolitis by reducing obstructions caused by the spastic cuff.[20] Most strictures can be managed by daily home dilatation. Occasionally, a repeat pull-through is needed to ameliorate the problem.

The higher the transitional zone, the higher the complication rate. Excluding total colonic aganglionosis (TCA), complications following pull-through for Hirschsprung's disease with transitional zone proximal to sigmoid colon was about 30%-33%, whereas complications following those with a transitional zone at the rectum and rectosigmoid colon was about 21.0%-25.6%. There were only minor complications of classical Hirschsprung disease. Anastomotic strictures in patients with a transitional zone at the rectum and rectosigmoid colon occurred in 16% and 5%, respectively. Anastomotic leakage, which was the most serious complication, was found in Hirschsprung patients with a transitional zone at the descending colon and transverse colon. These leakages seldom occur in classical Hirschsprung's disease.

Transanal endorectal pull-through might not show the level of the transitional zone as clearly as abdominal assisted transanal endorectal pull-through. During transanal endorectal pull-through, pulling the colon during anorectal surgery might make it more difficult to identify the transitional zone, leading to a retained aganglionosis segment. However, retained aganglionosis was still found in 3% of abdominal assisted pull-through cases, even if laparotomy was done.

Our study did have some limitations.

First, it had a retrospective design which meant some information may be missing. Fifty-nine patients were excluded (41 had other pull through operations, and 18 had incomplete medical information), which meant only 163 patients were included in the study.

Second, the type of operation, whether transanal endorectal pull-through, abdominal assisted transanal endorectal pull-through, or whether pre-operative colostomy should be done, depended on each surgeon's preference.

Third, the generalizability of the results is restricted. The study was conducted in one university hospital, and thus, there may be complications following operation that are not evident elsewhere. This study was conducted in Siriraj Hospital, in which only the traditional surgical techniques were applied. The youngest pediatric surgical staff in here had at least ten-year experience in surgical treatment for Hirschsprung's disease.

CONCLUSION

No significant risk factors were associated with early surgical complications following TERPT. The incidence of early complications following TERPT and abdominal assisted TERPT was the same ($p = 0.344$). Abdominal assisted TERPT had a higher incidence (4%) of anastomotic leakages whereas TERPT had higher rate of anastomosis strictures (12%) compared to abdominal assisted TERPT (5%). The higher the transitional zone, the higher the complication rate was. Abdominal assisted TERPT should be selected properly for higher level of the transitional zone. The complications correlated with whether a perfect pull-through operation could be performed or not.

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The Benefit of Unattended Automated Office Blood Pressure Measurement on the White-coat Effect: A Cross-sectional Study

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ABSTRACT

Objective: To compare blood pressure (BP) and heart rate measured by attended and unattended automated office blood pressure measurement (AOBPM) versus home blood pressure measurement (HBPM) and the effect of unattended AOBPM on the classification of BP phenotypes.

Materials and Methods: The cross-sectional study was conducted at the outpatient department in Siriraj Hospital, Thailand. All participants measured their office BP using attended and unattended techniques in random order and recorded home BP twice a day for consecutive 7 days. The agreement between office BP from both AOBPM methods and that from HBPM was analyzed using the Bland-Altman plot. The change in the proportion of each BP phenotype was also analyzed.

Results: We included 114 participants. The mean age was 57.96 ± 15.07 years. The average BP from attended AOBPM, unattended AOBPM, and HBPM were 150.52 ± 16.12/81.77 ± 11.04, 139.68 ± 13.80/78.55 ± 11.71, and 126.91 ± 9.80/76.40 ± 8.37 mmHg, respectively. The BP and heart rate measured by these techniques were significantly different (p-value of <0.001). Bland-Altman analysis showed the biases of attended and unattended SBP versus home SBP were 23.61 and 12.77 mmHg, respectively. Unattended AOBPM significantly decreased the numbers of patients classified as white-coat and sustained hypertension regardless of BP thresholds (p-value of <0.001 for both groups).

Conclusion: Unattended AOBPM significantly minimizes the white-coat effect in real-life clinical practice and may help physicians avoid overdiagnosis of hypertension. Nevertheless, it does not replace HBPM.

Keywords: Attended automated blood pressure measurement; unattended automated blood pressure measurement; home blood pressure; white-coat hypertension; masked hypertension (Siriraj Med J 2023; 75: 454-465)

INTRODUCTION

Nowadays hypertension is still a major problem of public health worldwide, and it is one of the etiologies of premature cardiovascular morbidity and mortality.[1] The early diagnosis and treatment of hypertension are important to prevent *de novo* hypertension-mediated organ damage and reduce cardiovascular risk. Blood pressure (BP) measurement is an essential part of hypertension management. According to the growing pieces of evidence which have indicated the better cardiovascular predictive power of home blood pressure (HBPM) over office blood pressure measurement (OBPM)[2,3], the current hypertension guidelines have not only emphasized the standard technique of OBPM but have also recommended using out-of-office BP measurement, especially HBPM.[4-7] Because of numerous interfering factors in the process of OBPM, including patients' effect, observers' effect, and the hospital's environment, the office BP may be

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inaccurate.[8,9] The white-coat effect is an important cause of inaccurate BP from conventional, or attended, OBPM.[9] Unattended OBPM is a newly developed technique that can be used to measure patients' BP by using automated BP devices in a private area without observers. It can be called unattended automated office blood pressure measurement (unattended AOBPM). This technique which was adopted in the systolic blood pressure intervention trial (SPRINT), has been widely debated in regard to BP values.[10-13] Some recent evidence has shown that unattended OBPM gets rid of the white-coat effect and results in a lower BP reading than attended OBPM.[14-16] However, the application of unattended OBPM in real-world clinical practice remains limited and the BP values resulting from different techniques of BP measurement are controversial due to the heterogeneity of the protocol of BP measurement.[14,17] The primary objective of this study was to investigate the difference and agreement of BP parameters and heart rate between attended AOBPM, unattended AOBPM, and HBPM in real-world clinical practice in the outpatient department of a tertiary care hospital. Moreover, this study aimed to investigate the proportion of BP phenotypes that were classified by the different OBPM techniques and BP thresholds.

MATERIALS AND METHODS

Study population

The cross-sectional study was conducted from March 1, 2021 to October 31, 2022, at the hypertension clinic, which is a part of the outpatient department of Siriraj Hospital, Bangkok, Thailand. We included clinically stable patients with an age of at least 18 years who visited the hypertension clinic and were able to completely measure their BP on the arm following this study's protocol. All eligible participants gave their informed consent. The exclusion criteria were pregnancy, cardiac arrhythmia, and incomplete data from BP records. This study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 085/2021). The Thai Clinical Trials Registry number is TCTR20230122002 (https://www.thaiclinicaltrials.org/show/TCTR20230122002).

Blood pressure measurement protocol

The techniques of BP measurement consisted of attended OBPM, unattended OBPM, and HBPM. Well-trained nurses informed all participants about avoiding caffeine intake and exercise at least 30 minutes before the BP measurement and emptying the urinary bladder before BP measurement as well as all steps of the BP measurement protocols. All these methods were performed in a sitting position on a chair with back support and both feet were placed on the floor. An appropriate-sized cuff was placed on the non-dominant arm at the same level as the heart. A period of 5 minutes of resting was required before taking a BP measurement. In both office BP measurement techniques, an automated Omron HEM-907 (Omron Healthcare Co. Ltd.) device was used for three repeated BP measurements with a 1-minute of interval between each one. Attended AOBPM was performed by a nurse, who started the program of the automated BP device and then stayed in the same place as the patients until the measurement was finished. On the other hand, the only patients who performed unattended AOBPM were in a private room. There, the patients activated the automated BP device by themselves for three serial BP measurements one minute apart. There were no nurses or staff in the room until the BP measurement was completed. All records of office BP parameters and heart rates from each method were considered when calculating the average value from each one. The nurses and the investigators were independent. The sequence of attended and unattended AOBPM was randomized by the nurses in a 1:1 ratio.

The HBPM method was begun in a manner to the aforementioned OBPM method on the day after the OPD visit. Validated oscillometric BP devices including Omron HEM-7130 and HEM-7211 (Omron Healthcare Co. Ltd.) were recommended for use in HBPM. The patients were asked to perform two repeated BP measurements each morning and evening for consecutive 7 days. The data of the HBPM records were sent to the investigators at the next follow-up visit. All numbers of BP and heart rate were used to calculate to the average home BP. In addition, the average BP measurements, namely, the average morning and evening BP, were separately calculated.

Definition of BP phenotypes

We identified four BP phenotypes based on the type of BP measurement (office and home BP), with two different thresholds according to the 2017 American and 2018 European hypertension guidelines[4,5]; these phenotypes were as follows; normotension (both office and home BPs were normal), white-coat hypertension (office BP was abnormally high while home BP was normal), masked hypertension (office BP was normal but home BP was abnormally high), and sustained hypertension (both office and home BPs were abnormally high). Abnormal office and home BPs following the 2017 American hypertension guideline were defined as a systolic BP (SBP) which was at least 130 mmHg and/or a diastolic BP (DBP) which was at least 80 mmHg.[4] On the contrary, the 2018 European

hypertension guidelines defined an abnormal office SBP as an office SBP which was at least 140 mmHg and/or an office DBP was at least 90 mmHg.[5] An abnormal home BP was defined as a home SBP which was at least 135 mmHg and/or a home DBP which was at least 85 mmHg.[5]

Data collection

The demographic data were collected from the participants and their electronic medical records at Siriraj Hospital. They consisted of age, gender, body mass index, comorbidities (i.e., diabetes mellitus, dyslipidemia, coronary artery disease, cerebrovascular disease, and chronic kidney disease), current smoking status, use of antihypertensive medications and their types, and laboratory results (i.e., fasting plasma glucose, glycated hemoglobin, serum creatinine, estimated glomerular filtration rate (eGFR), and lipid profiles).

Statistical analysis

Based on a previous study that investigated the association between unattended office BP and home BP[17], we planned to enroll at least 55 participants to provide 90% statistical power for the detection of an approximately 10 mmHg difference in BP between unattended AOBPM and HBPM at a two-sided alpha level of 0.05.

Continuous variables of demographic data were recorded as mean ± standard deviation and median and interquartile range depending on the data' distribution. The Kolmogorov-Smirnov equality-of-distributions test was analyzed for identifying the normal distributed continuous variables. Categorical variables were recorded as number and percentage. The analysis of the difference and agreement of BP parameters and heart rates between the three different techniques of BP measurement was performed by using Bland-Altman plots. One-way analysis of variance (ANOVA) with the Bonferroni test was used for the comparison of the BP and heart rate parameters of the three techniques. A Pearson correlation was performed to analyze the relationship between the results of the three BP measurement techniques. The chi-square test or Fisher's exact test was used for the analysis of comparing the proportions of the BP phenotypes that were classified by using attended and unattended AOBPM at each BP threshold. The statistical significance was designated as a p-value of <0.05. Stata Statistical Software version 17 (StataCorp LLC, College Station, TX) was used for all analyses.

RESULTS

A total of 114 patients were enrolled in this study. Most of them were female patients (62.3%). Of all patients, 94% were taking at least one antihypertensive medication. Dyslipidemia was the most common comorbidity (81.6%). The mean age was 57.96 ± 15.07 years and the median body mass index was 24.59 kg/m^2. The details of the demographic data are shown in Table 1. The results of Kolmogorov-Smirnov equality-of-distributions test of the continuous variables (i.e., age, eGFR, cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, SBP, DBP, and heart rate) indicated the normal distribution (p-value of >0.05).

Comparison of the BP and heart rate of the different BP measurement techniques

Table 2 shows the data of systolic and diastolic BP that were measured; they were calssified by attended OBPM, unattended OBPM, and HBPM. The average morning home BP was 127.19 ± 10.28/77.30 ± 8.39 mmHg and the average evening home BP was 126.63 ± 11.05/75.50 ± 9.27 mmHg. Overall analysis revealed that that SBP, DBP, and heart rate from the different methods of measurement were significantly different. Bonferroni's post-hoc analysis indicated that attended OBPM provided the significantly highest systolic blood pressure (SBP), with significance, among all BP measurement techniques. The average home SBP was significantly lower than office SBP as well. Only the diastolic blood pressure (DBP) from attended OBPM was significantly higher than the average home DBP. Moreover, the average heart rate from HBPM was significantly lower than the office heart rate that was measured during both attended and unattended OBPM. Even though the DBP and heart rates of both attended and unattended OBPMs were not significantly different, unattended OBPM provided a lower DBP and heart rate than attended OBPM.

Bland-Altman plot analysis is shown in Table 3 and Fig 1 – 3. The results revealed that the biases of attended versus unattended office SBP, DBP, and heart rate were 10.83 mmHg, 3.23 mmHg, and 3.42 beats/minute, respectively. Both OBPM techniques had higher biases of SBP, DBP, and heart rate than the HBPM technique. The BP and heart rate of all techniques of BP measurement were significantly associated, as shown in Table 4. The correlation between BP and heart rate was particularly high between attended and unattended OBPMs. Notwithstanding, the correlation coefficients of the SBP from both OBPM technique versus HBPM technique were quite low (r = 0.19, p-value of 0.041 for attended office SBP versus average home SBP; r = 0.28, p-value of 0.003 for unattended office SBP versus average home SBP).

TABLE 1. Demographic data.

Parameter	Results (N = 114)
Age (years)	57.96 ± 15.07
Male, number (%)	43 (37.72)
Body mass index (kg/m^2)	24.59 (22.40, 27.47)*
Comorbidity, number (%)	
Diabetes mellitus	32 (28.07)
Dyslipidemia	93 (81.58)
Coronary artery disease	1 (0.88)
Cerebrovascular disease	3 (2.63)
Chronic kidney disease	13 (11.40)
Current smoking, number (%)	1 (0.88)
Number of antihypertensive medications, number (%)	
0	7 (6.14)
1 – 2	74 (64.91)
≥ 3	33 (28.95)
Type of antihypertensive medication, number (%)	
Diuretics	16 (14.04)
Calcium channel blockers	81 (71.05)
Angiotensin converting enzyme inhibitors	18 (15.79)
Angiotensin-II receptor blockers	38 (33.33)
Beta blockers	34 (29.82)
Others	34 (29.82)
Laboratory result	
Fasting plasma glucose (mmol/l)	5.61 (5.16, 6.44)*
Hemoglobin A1C (%)	6.00 (5.60, 6.50)*
Serum creatinine (µmol/l)	75.14 (61.00, 101.66)*
Estimated glomerular filtration rate (ml/min/1.73m^2)	80.20 ± 26.40
Cholesterol (mmol/l)	4.74 ± 1.06
Triglycerides (mmol/l)	1.20 (0.87, 1.75)*
HDL-C (mmol/l)	1.52 ± 0.48
LDL-C (mmol/l)	2.54 ± 0.86

*median and interquartile range

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

TABLE 2. Blood pressure and heart rate of the different blood pressure measurement techniques.

Parameter (N = 114) mean ± SD	Attended office BP measurement	Unattended office BP measurement	Home BP measurement (average home BP)	P-value*
SBP (mmHg)	150.52 ± 16.12	139.68 ± 13.80†	126.91 ± 9.80‡⁋	<0.001
DBP (mmHg)	81.77 ± 11.04	78.55 ± 11.71	76.40 ± 8.37‡	0.001
HR** (beats/min)	83.16 ± 17.74	79.74 ± 16.52	72.97 ± 11.79‡⁋	<0.001

*p-value for overall comparison of attended office BP versus unattended office BP versus average home BP

**The presented numbers of the HR of home BP measurement were calculated from 111 subjects' records due to the missing HR data of 3 subjects.

†p-value of <0.001 for comparing attended vs unattended office BP

‡p-value of <0.001 for comparing attended office BP vs average home BP

⁋p-value of <0.005 for comparing unattended office BP vs average home BP

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SD, standard deviation

TABLE 3. Bland-Altman plot analysis of blood pressure and heart rate from the different blood pressure measurement techniques.

BP measurement method	Bias	95% CI of bias	Lower 95% LoA	95 % CI of lower LoA	Upper 95% LoA	95% CI of upper LoA
Systolic blood pressure (mmHg)						
Attended versus unattended office BP measurement	10.83	8.51 to 13.16	-13.73	-18.17 to -10.18	35.40	31.84 to 39.84
Attended office versus home BP measurement	23.61	20.42 to 26.79	-10.08	-16.17 to -5.21	57.29	52.42 to 63.38
Unattended office versus home BP measurement	12.77	10.07 to 15.47	-15.77	-20.93 to -11.64	41.31	37.18 to 46.47
Diastolic blood pressure (mmHg)						
Attended versus unattended office BP measurement	3.23	2.05 to 4.40	-9.20	-11.44 to -7.40	15.65	13.86 to 17.90
Attended office versus home BP measurement	5.38	3.52 to 7.23	-14.18	-17.72 to -11.35	24.93	22.10 to 28.47
Unattended office versus home BP measurement	2.15	0.36 to 3.94	-16.75	-20.16 to -14.01	21.04	18.31 to 24.46
Heart rate (beats/minute)						
Attended versus unattended office HR measurement	3.42	2.44 to 4.39	-6.88	-8.74 to -5.39	13.71	12.22 to 15.57
Attended office versus home HR measurement	10.10	7.44 to 12.76	-17.59	-22.67 to -13.53	37.79	33.73 to 42.87
Unattended office versus home HR measurement	6.59	4.18 to 9.00	-18.49	-23.10 to -14.82	31.67	28.00 to 36.28

Abbreviations: BP, blood pressure; CI, confidence interval; LoA, limits of agreement; HR, heart rate

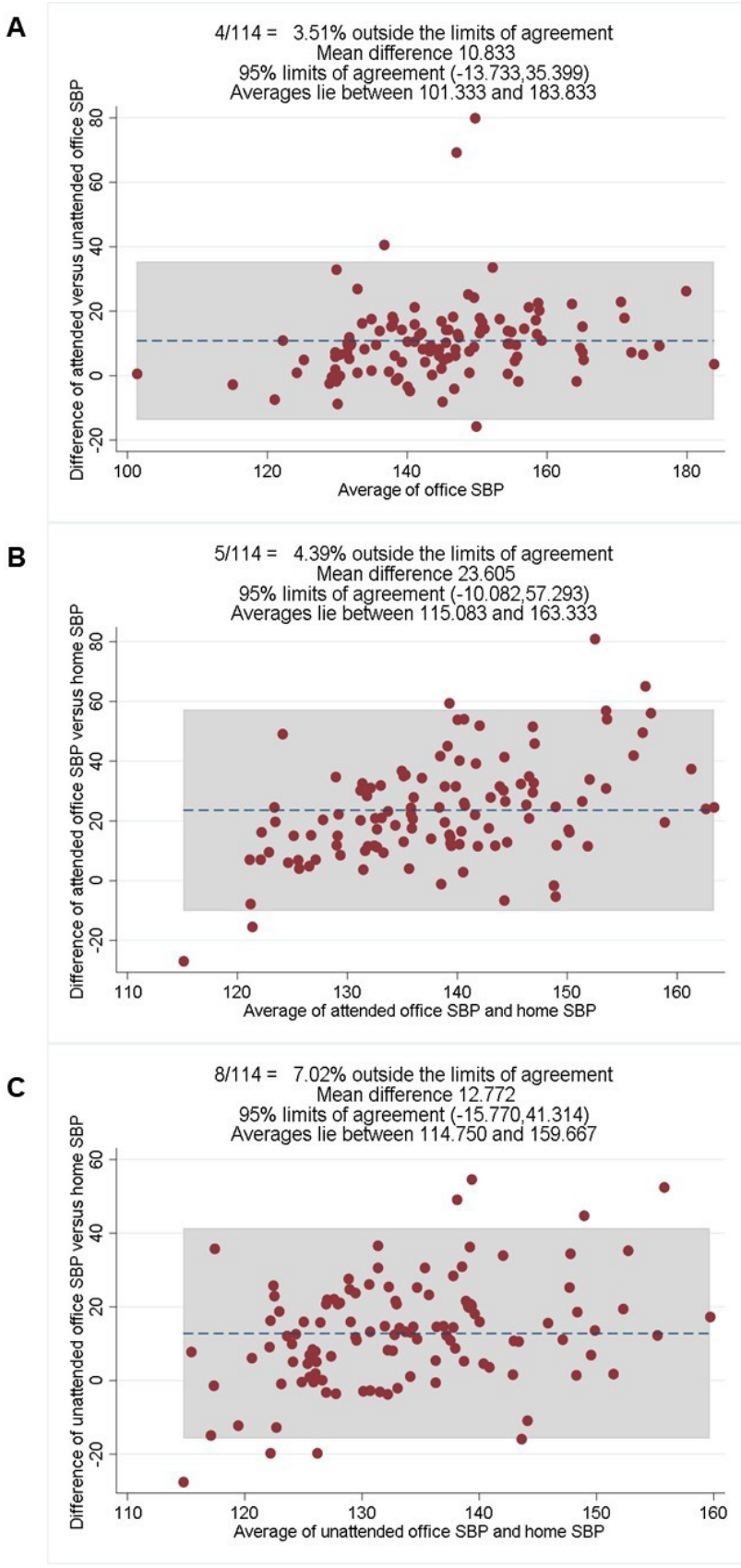

Fig 1. Bland-Altman plot for **(A)** the comparison of attended versus unattended office SBP, **(B)** the comparison of attended office versus home SBP, and **(C)** the comparison of unattended office versus home SBP.

Abbreviation: SBP, systolic blood pressure

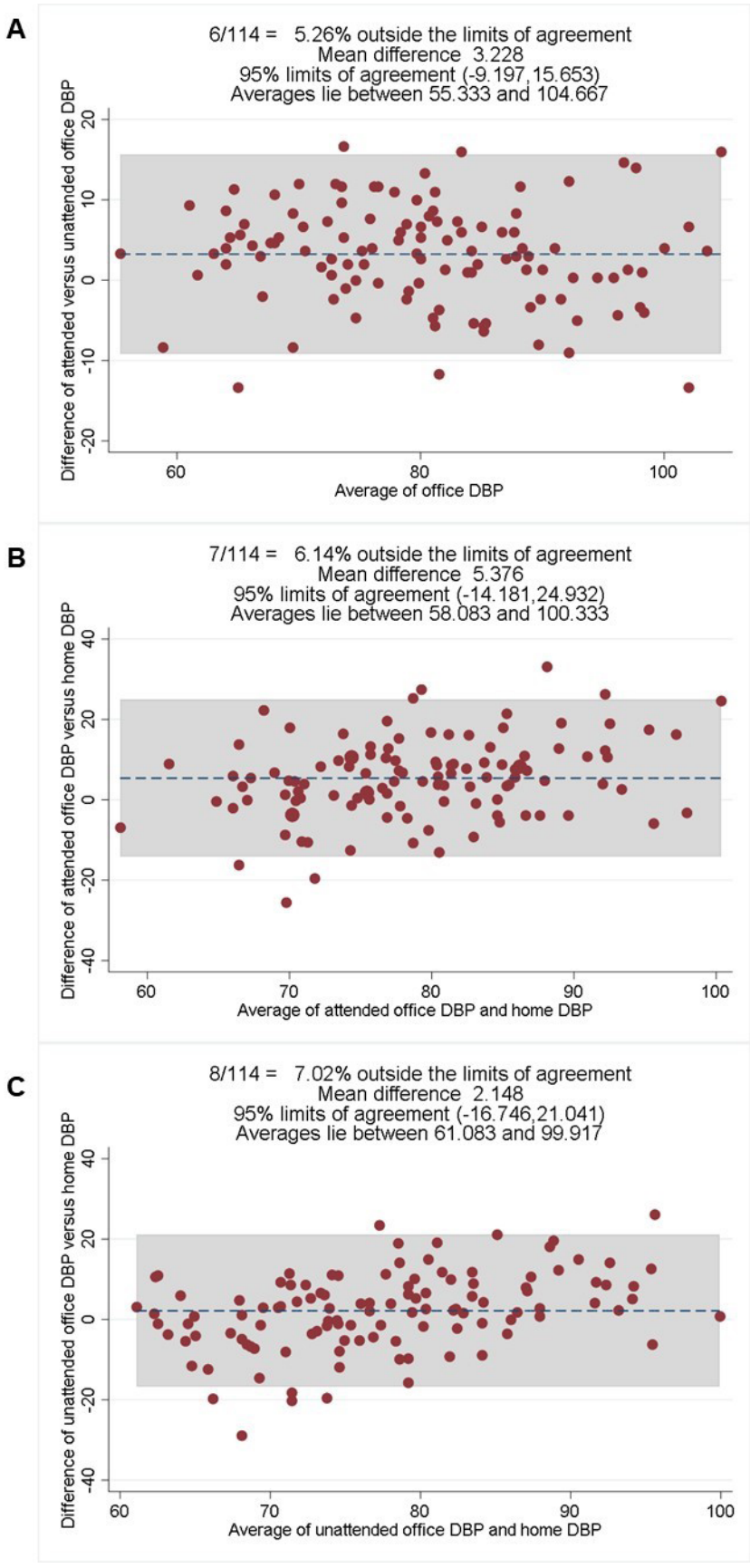

Fig 2. Bland-Altman plot for **(A)** the comparison of attended versus unattended office DBP, **(B)** the comparison of attended office versus home DBP, and **(C)** the comparison of unattended office versus home DBP.

Abbreviation: DBP, diastolic blood pressure

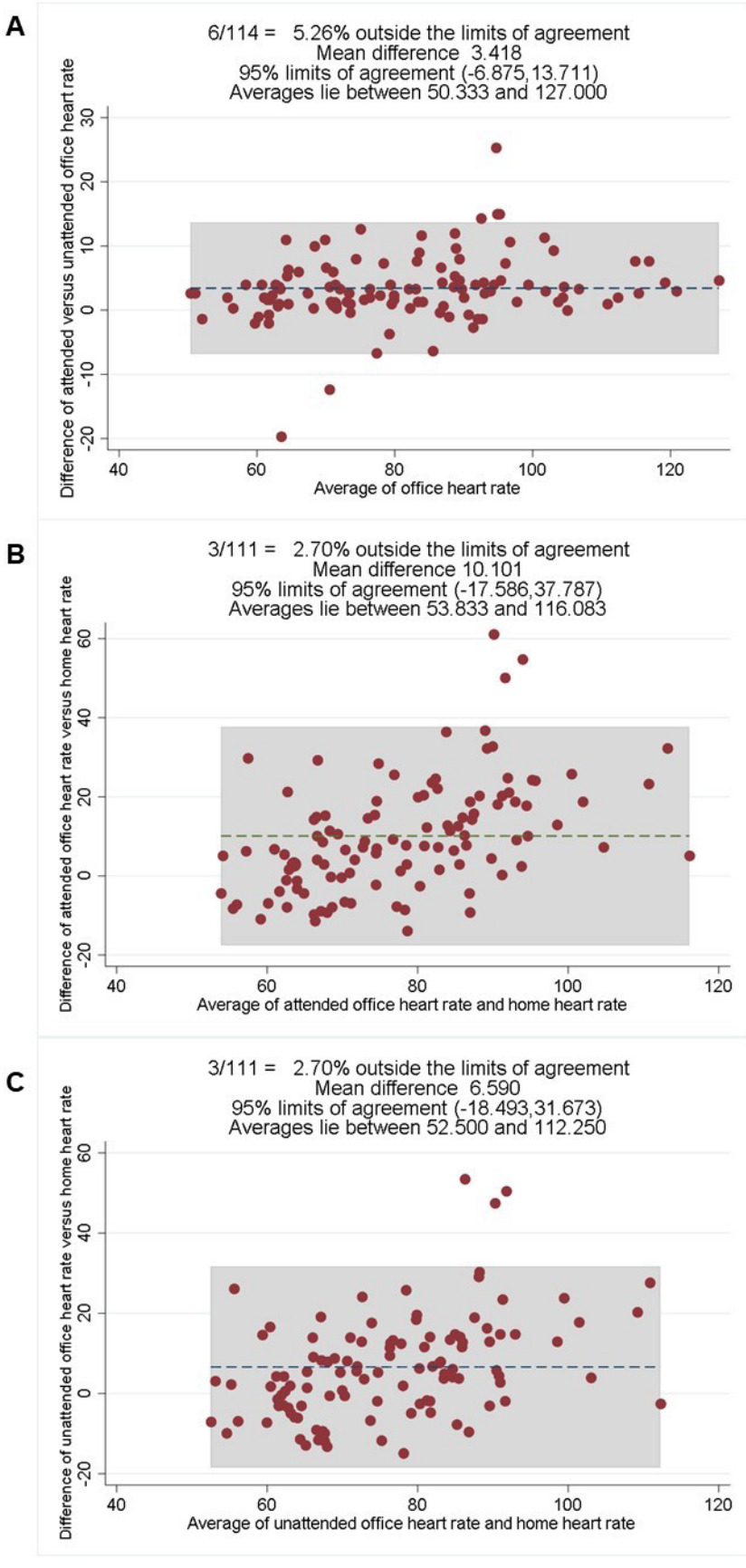

Fig 3. Bland-Altman plot for **(A)** the comparison of attended versus unattended office heart rate, **(B)** the comparison of attended office versus home heart rate, and **(C)** the comparison of unattended office versus home heart rate.

TABLE 4. The correlations of blood pressure and heart rate between the different blood pressure measurement techniques.

Parameters	Pearson's r	P-value
Systolic blood pressure		
Attended versus unattended office BP measurement	0.66	<0.001
Attended office versus home BP measurement	0.19	0.041
Unattended office versus home BP measurement	0.28	0.003
Diastolic blood pressure		
Attended versus unattended office BP measurement	0.85	<0.001
Attended office versus home BP measurement	0.50	<0.001
Unattended office versus home BP measurement	0.58	<0.001
Heart rate		
Attended versus unattended office HR measurement	0.96	<0.001
Attended office versus home HR measurement	0.62	<0.001
Unattended office versus home HR measurement	0.64	<0.001

Abbreviations: BP, blood pressure; HR, heart rate

The classification of BP phenotypes by using the different techniques of AOBPM

The proportions of all patients' BP phenotypes are separately presented according to the different BP thresholds (Table 5). According to the thresholds of normal office and home BPs, which were less than 130/80 mmHg, the proportions of patients with normotension, white-coat hypertension, masked hypertension, and sustained hypertension by attended AOBPM were 5.26%, 50%, 0.88%, and 43.86%, respectively. When unattended AOBPM was performed, the proportions of normotensive, white-coat, masked, and sustained hypertensive patients were changed to 14.91%, 40.35%, 4.39%, and 40.35%, respectively. These results were found to be different when using the other BP thresholds, which consisted of a normal office BP of less than 140/90 mmHg and a normal home BP of less than 135/85 mmHg. Of all patients, the BP phenotypes which were classified by attended AOBPM consisted of 20.18% normotensive patients, 51.75% white-coat hypertensive ones, 1.75% masked

TABLE 5. Classification of blood pressure phenotypes based on the different techniques of office blood pressure measurements and the different blood pressure thresholds of the 2017 ACC/AHA and 2018 ESC/ESH hypertension guidelines in all 114 patients.

BP phenotype Number (%)	2017 ACC/AHA hypertension guideline		P-value*	2018 ESC/ESH hypertension guideline		P-value*
	Attended method	Unattended method		Attended method	Unattended method	
Normotension	6 (5.26)	17 (14.91)	<0.001	23 (20.18)	47 (41.23)	<0.001
White-coat HT	57 (50.00)	46 (40.35)	<0.001	59 (51.75)	35 (30.70)	<0.001
Masked HT	1 (0.88)	5 (4.39)	0.044	2 (1.75)	4 (3.51)	1.000
Sustained HT	50 (43.86)	46 (40.35)	<0.001	30 (26.32)	28 (24.56)	<0.001

*p-value for comparing attended versus unattended method

Abbreviation: ACC/AHA, American College of Cardiology/American Heart Association; ESC/ESH, European Society of Cardiology/European Society of Hypertension; BP, blood pressure; HT, hypertension

hypertensive ones, and 26.32% sustained hypertensive ones. The proportion of the normotensive group was significantly increased in proportions (41.23%; p-value of <0.001) while the proportions of the others (i.e., white-coat and sustained hypertensive groups (30.7%; p-value of <0.001 and 24.56%; p-value of <0.001, respectively)) were significantly decreased in proportion by using the technique of attended AOBPM regardless of BP thresholds. The ratio of identified masked hypertension classified by the two methods of AOBPM was only significantly different as regards the BP threshold of the 2017 American hypertension guideline (p-value of 0.044). Furthermore, we separately reveal the results of the classification of BP phenotypes in patients who were and were not taking antihypertensive medications in Supplementary Table 1 & 2.

DISCUSSION

Since the results of SPRINT were published, there has been strong interest in the methods of BP measurement, especially unattended AOBPM, and such methods have been widely debated. Standardized BP measurement is emphasized in both office and home settings. The observer's effect may confound BP which is measured at the clinic more than that measured at home. The results of this study show a significant difference in office SBP between both techniques of OBPM. SBP measurements from unattended AOBPM were significantly lower than those from attended AOBPM. It indicated that the observer's effect was an important confounding factor of inaccurate OBPM. Our results were concordant with the findings from the previous study of Keeley EC., et al.[18] which showed a significantly higher attended office SBP. Moreover, the study of Fanelli E., et al.[19] highlighted the higher attended office SBP, particularly in patients who initially measured their office BP by attended technique. The sequence of AOBPM techniques might not have affected the results in our study because the process for identifying the initial AOBPM technique in each participant was randomly performed. Although the difference in office DBP and heart rate between both AOBPM techniques did not reach statistical significance, attended office DBP and heart rate tended to be higher than unattended ones. A possible underlying mechanism is more activation of the sympathetic nervous system during attended OBPM compared with unattended OBPM.[20]

The office BP and heart rate from both attended and unattended AOBPMs were statistically higher than home BP and heart rate. This finding supported the presence of the white-coat effect that resulted from patient response to hospital situations, including BP measurement. Office heart rate is still obviously higher than home heart rate despite the fact that some patients took beta-blockers. It implies that the sympathetic nervous system plays a major role in the pathophysiology of the white-coat effect.[21,22] The discrepancies of the biases of office SBP versus home SBP from the Bland-Altman analysis were large in attended AOBPM (23.61 mmHg) and, to a lesser extent, in unattended AOBPM (12.77 mmHg). Our finding indicated unattended AOBPM was not completely devoid of the white-coat effect because office BP, especially SBP, was higher than home BP. This was different from some previous studies.[19,23] The systematic review and meta-analysis of Pappaccogli M., et al.[23] revealed similar BP levels between unattended AOBPM and HBPM. Nevertheless, there should be some caution taken in interpreting this result because of the high heterogeneity of the included studies for meta-analysis. The study of Fanelli E., et al.[19] showed that the BP levels from both AOBPM techniques were lower than home BP. There is a limitation of missing data on the complete home BP of 32 subjects (approximately 22% of the total 118 subjects); therefore, the results may be interfered with by this missing data. In addition, the different baseline characteristics of participants, different methodologies of study, and the environment in each study site may result in different findings. The high correlation of attended and unattended office BP in our study is similar to that found in other studies.[17,18,24,25] Our study showed that BP measured by AOBPM and HBPM was significantly correlated. This is consistent with some previous studies. However, the degree of correlation between office SBP and home SBP was low. The exact reason for the weak relationship between office SBP and home SBP is not well known. A previous study[25] showed similar results of association to our study. Most of the enrolled patients in the previous study (96.4%)[25] and our study (93.86%) were taking at least one antihypertensive medication. We suppose that taking antihypertensive medications[25] and several different drug regimens may result in increased variability of office SBP.[26,27]

Due to the differences in office BP between attended and unattended techniques, we investigated whether the classification of BP phenotypes was affected by them. Our results showed a significant change in the proportion of all BP phenotypes. Unattended AOBPM resulted in decreased numbers of white-coat hypertensive patients because it lowered patients' white-coat effect. The slightly weak correlation between the unattended office and home BP indicated that unattended AOBPM could not replace HBPM. Therefore, there were increased normotensive and masked hypertensive patients. Nevertheless, we

cannot evaluate the diagnostic performance, especially accuracy, for the identification of BP phenotypes because of the lack of ambulatory BP monitoring (ABPM), which is the gold standard for the diagnosis of hypertension.

The strengths of this study consist of using the same standardized protocol of BP measurement for all participants and the randomized order of AOBPM. The measured office BP is not confounded by these factors. The design of our pragmatic study can reflect the real-life outcome in routine clinical practice. There are some limitations in our study. First, most of the participants were taking antihypertensive medications, so their different regimens of such medications including types and numbers may have affected office BP and home BP. Moreover, they may be also affected by the different measured and unmeasured factors of the patients' baseline characteristics, such as age, gender, comorbidities, physical activity and dietary pattern, etc. This limitation may result in high discrepancies in BP parameters and heart rate between the three measured techniques. Second, home BP was collected from the data recorded on paper because the home BP devices used in this study do not send BP data via an online system. Some patients may have failed to record some high BP measurements in their records. Therefore, home BP may not represent actual BP at home. Third, both attended and unattended AOBPM were measured and averaged in a single visit, whereas HBPM was recorded and averaged over 7 days. Given the daily variation of the measurement, the differences between each technique were significant. Finally, ABPM is not performed in our study so there was no gold standard method used to identify abnormal elevated BP, as previously mentioned.

CONCLUSION

Unattended AOBPM results in a lesser white-coat effect than attended AOBPM, however, unattended office BP remains higher than home BP in our study. The office BP measurement method affects the classification of BP phenotypes. The technique of unattended AOBPM can be applied to routine clinical practice.

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Author contributions

Chotruangnapa C created the research question, performed the literature review and then designed the research methodology. All authors conducted and collected the data. The data were statistically analyzed and the manuscript was written by Chotruangnapa C. All authors critically reviewed and approved the final manuscript.

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Efficacy Evaluation of Smartphone-based Stent Tracking Application in Follow-up Patients with Ureteral Stents: A Prospective Study

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ABSTRACT

Objective: Our objective was to determine how effectively our smartphone app improved follow-up compliance in ureteral stent patients.

Materials and Methods: Two groups of patients who underwent double-j stent placement were compared. For the traditional program (i), retrospective data from January 2021 to June 2021 was collected. We randomly selected 72 patients from the overall 121 patient data. For the smartphone-based stent tracking program (ii), a smartphone application was used from July 2022 to January 2023 to track 72 patients.

Result: The rate of poor compliance in group (ii) (4.2%), was significantly lower (p=0.004) than the rate of poor compliance in group (i) (19.4%). Differences in diagnosis between the two groups were not found to be related to the compliance rates. Surprisingly, kidney transplant patients in both groups had perfect compliance.

Conclusion: Smartphone-based stent tracking application increased patient compliance to appointments in patients who underwent double-j stent placement. This study is a demonstration of how technology can assist patients to better health care and can prevent complications.

Keywords: Forgotten ureteral stents; smartphone-based stent tracking application (Siriraj Med J 2023; 75: 466-472)

INTRODUCTION

Ureteral double-J (DJ) stents are routinely used to treat urolithiasis. They are inserted temporarily to relieve blockage of the ureter, prevent ureteral strictures, promote healing, and control urine leakage.[1] The duration of DJ stent placement depends on the material of which the stent is made. To prevent complications, they must be removed, but some patients neglect to follow up for removal. One study found that 12% of DJ stents placed had not been removed as scheduled. As per data collected from patients who were hospitalized at Thammasat University Hospital in the year 2020, 16 out of a total of 134 patients (8.9%) did not come on the appointed date to either change or remove their stents. Another 24 out of 121 patients (20%) missed their appointments between the months of January to June of 2021.

A study by El-faqih found stent encrustation in 9.2% of stents removed within 6 weeks, 47.5% of stents implanted 6 to 12 weeks, and 76.3% of stents older than 12 weeks.[2,3] Indwelling ureteral stents increase the incidence of urinary tract infections, the risk of DJ stent mispositioning, ureteric stone formation encircling the stents, and acute renal failure. These complications may lead to unnecessarily extensive care. Some patients might need further surgical treatment, possibly nephrectomy, especially in those with non-functioning kidney.[2,3] Thus, although DJ stent insertion is advantageous, proper care and punctual stent removal is essential to prevent future morbidity and mortality. Punctual stent removal would also help reduce overall healthcare costs.

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As aforementioned, removing a DJ stent on the appointed date has the advantages of lower healthcare expenses and lower morbidity rates. Past measures to ensure punctual removal include paper based or electronic appointment cards and text messages delivered to mobile devices. However, these media are limited to the hospital grounds and necessitate further medical expenses.[4-6]

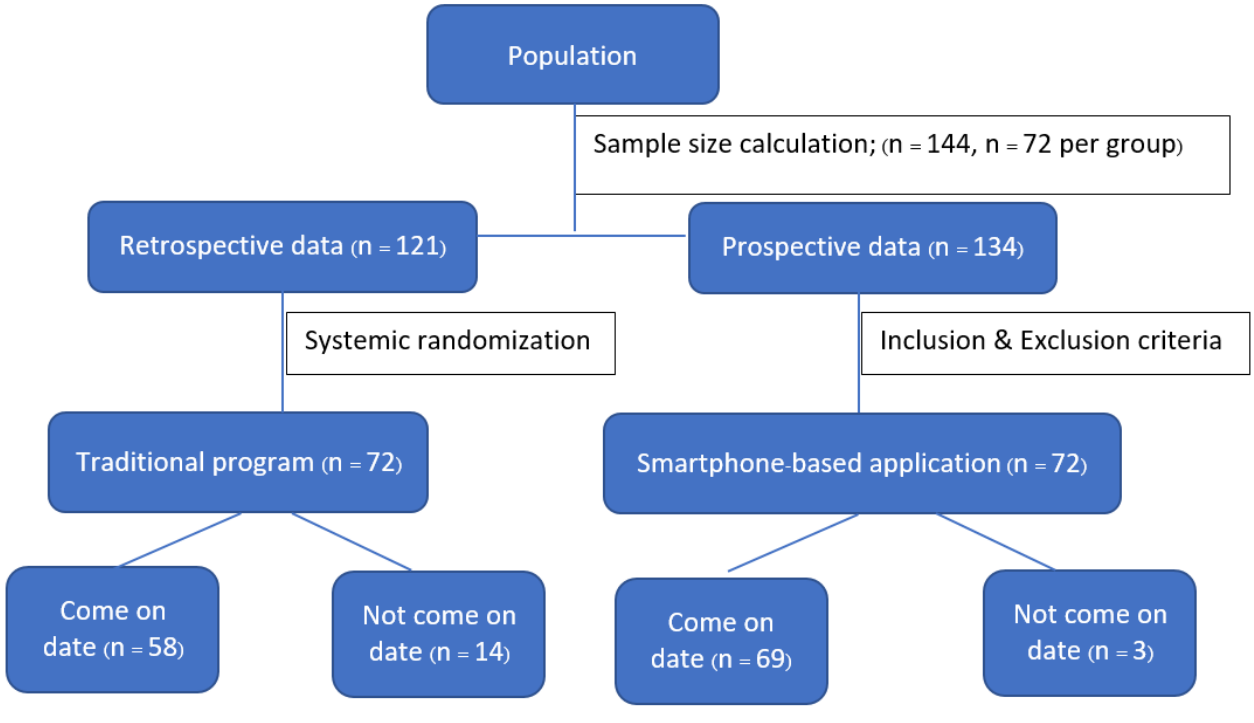
In the present day, as smartphones have become more widespread and globally accessible, several new options to ensure regular hospital visits are available. In the years 2019 to 2021, several studies were conducted to evaluate the efficacy of using applications on smartphones to establish routine follow ups. Results have shown that using tracking applications reduced patients' odds of forgetting to remove their ureteral stents[7,8] and decreased overdue times to scheduled appointments.[9] Research conducted by M. Zeeshan Hameed et al. took advantage of this application to not only track patients' stent placements but also to communicate with them during the pandemic of COVID-19. This tool may provide more than its tracking ability by improving communication between physician and patients. All of these studies reached the same conclusion: smartphone DJ stent tracking applications decrease the likelihood of patients forgetting about their stent insertion, lessening the incidence of retained ureteral stents, which in turn reduces the need for unplanned hospitalizations and medical expenses.[10] DJ stent tracking applications on patients' smartphones can lead to better healthcare. However, a limitation is that these tracking applications are offered only with the English language, limiting their generalizability to other populations. Thus, it was our aim to develop an application in the Thai language for the Thai population. Our assumption is that once patients with inserted DJ stents are using this tracking application, the rates of missing their appointments will be lower when compared to those using traditional appointment methods.

MATERIALS AND METHODS

This study is a prospective cohort study conducted to evaluate the efficacy of a smartphone-based stent tracking application to ensure that patients come for regular follow-ups for stent removal. The ethics committee approval was granted by The Human Research Ethics Committee of Thammasat University (Medicine) (reference MTU-EC-SU-1-286/64). The study population was patients who received double-J ureteral stent placements at Thammasat University Hospital.

Sample size calculation

From retrospective data review on patients hospitalized at Thammasat University Hospital between January and June of 2021, it was seen that 20% of the patients with stent insertion did not come to follow up on the scheduled date. We hypothesized that if patients used our application, it would reduce the proportion of patients with stent insertion who did not come to follow up on the scheduled date to 5%. Our research team set the standard deviation at 5% with the power at 80%. The sample size was 72 patients per group for a total study population of 144 patients.



The first study group was patients who used a traditional appointment program. We collected retrospective data between January 2021 to June 2021 (n = 121), then systematically randomized the data into 72 patients. For the second study group, data from 72 patients who used a smartphone-based stent tracking program were collected. This data was recruited prospectively from July of 2022 and onwards with inclusion and exclusion criteria as follows:

Inclusion criteria: Patients aged above 18 years who underwent DJ stent placement in our clinic from January 2022 onwards

Exclusion criteria: Patients who could not communicate in Thai language or did not use a smartphone android system (version > 5.0)

A total of 72 patients were successfully recruited. There were a total of 134 patients who received DJ stent placement within the designated study time period.

The smartphone-based stent tracking program was developed by the author in Thai language and could be downloaded through Google Play. Registration data included each patient's name, medical record number and telephone number. Appointments for stent removal were set by the physician. (Fig 1).

We collected the patient's data through an electronic website, where the account usernames and passwords were determined by the patients themselves.

After receiving DJ stent placements, the enrolled patients were required to download the application through Google Play. They received a session explaining how to browse and utilize the application. This application allowed users to review their diagnosis, position of stent placement (left or right side or both), appointment date and future care plan after stent placement (Fig 2). Patients could change their telephone numbers by themselves to continuously update their contact information. During their session of using the application, patients were able to contact the author directly to inform about their symptoms or possible complications following stent insertion. The author was always reachable by enrolled patients if they had any inquiries.

After initiating the application, the smartphone-based stent tracking program's visual dashboard was reviewed by the physician on a daily basis (Fig 3). The application reminded patients two days prior to their stent removal appointment. Patients who missed their appointments were contacted by phone, and a new appointment was scheduled within 12 weeks of stent placement. The two study groups were compared in terms of punctuality for appointments.

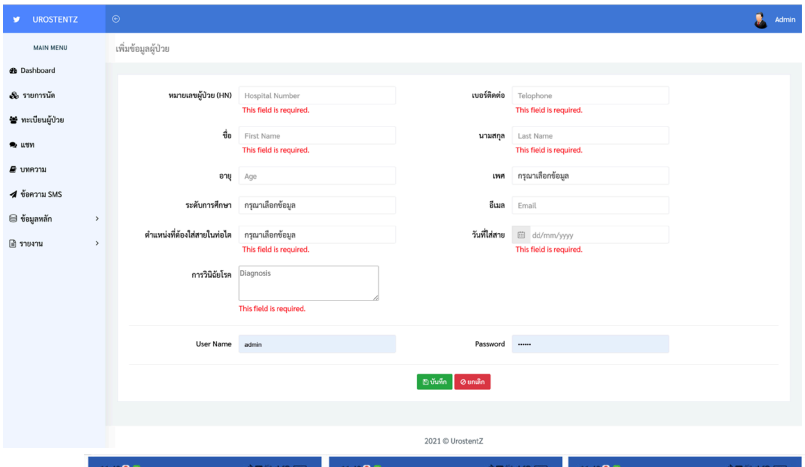


Fig 1. Registration data

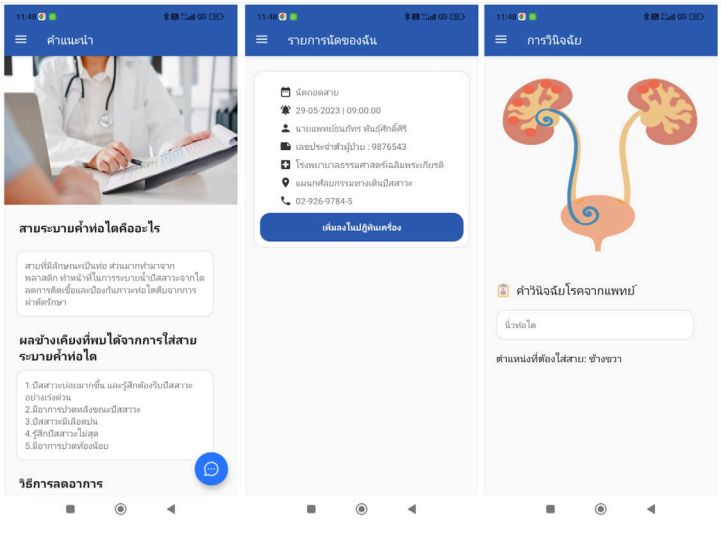


Fig 2. Future care plan, Appointment date and Patient's diagnosis

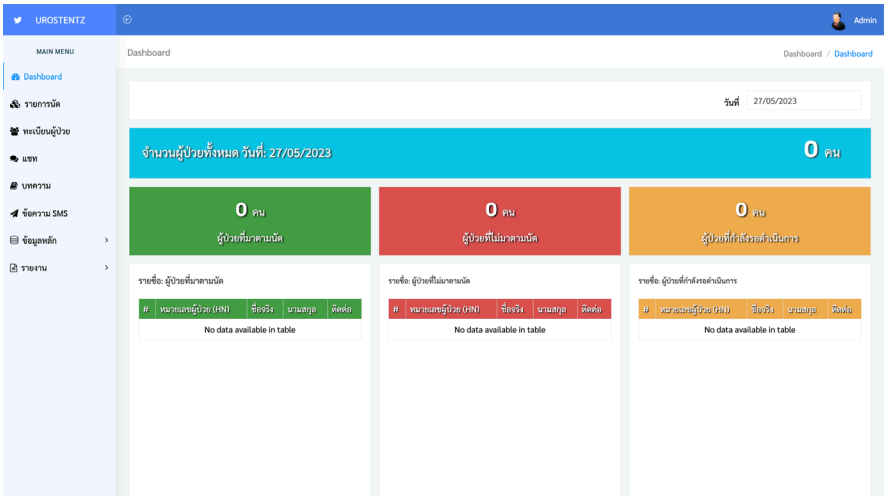


Fig 3. Daily visual dashboard

Statistical analysis

Statistical analysis was performed using STATA software (version 15). For continuous data, we compared the two study groups using T-test. For categorical data, we used Chi-square test and fisher's exact test to analyze patients' characteristics and for dependent variable analyses. Differences were considered statistically significant when the p-value was less than 0.05 ($p < 0.05$)

RESULTS

Group 1 was defined as the traditional program group. Group 2 was defined as the smartphone-based application group. The two groups' characteristics were indistinguishable from each other in terms of age, gender, and educational status. However, the primary diagnoses were different between the two groups, as displayed in Table 1.

TABLE 1. Demographic data.

Characteristic data	Group 1 (n =72)	Group 2 (n =72)	P-value
Age mean(sd)	57.61 (13.50)	52.72 (16.57)	0.054[1]
Sex			0.738[2]
Male	37/72	39/72	
Female	35/72	33/72	
Education level			0.168[2]
Primary school	15/72	11/72	
Secondary school	13/72	10/72	
Vocational certificate	24/72	18/72	
Bachelor or higher	20/72	33/72	
Stent side			0.120[2]
Left	41/72	29/72	
Right	27/72	39/72	
Both	4/72	4/72	
Diagnosis			0.008[2]
Ureteric calculi	22/72	21/72	
Renal calculi	30/72	24/72	
Kidney transplantation	3/72	16/72	
Gynecological condition	5/72	7/72	
Other*	12/72	4/72	

[1]Analyze by independent t-test

[2]Analyze by Chi-square

Comparing punctuality for appointments, 4.2% of Group 2 missed appointments, while a whopping 19.4% of Group 1 missed a follow-up date. This difference was statistically significant (p-value < 0.05), as displayed in Table 2.

In education level of Bachelor or higher, 3% of Group 2 missed appointment and 20% of Group 1 missed appointment. There are not statistically difference between two groups as displayed in Table 3.

When taking the patients' diagnoses into consideration, regardless of whether it was the experimental or the control group, the underlying condition did not influence punctuality, except for patients who had kidney transplants. All kidney transplant patients came to their appointments on schedule, as displayed in Table 4.

Comparing the overdue times between the two study populations, Group 2 had a median delay of seven days and an interquartile range of five days. On the other hand, Group 1 had an overdue median of seven days, but an interquartile range of 96.5 days, as displayed in Table 5.

DISCUSSION

Molina et al. did a retrospective study back in 2017 concerning the usage of a ureteral stent tracking application. Of the 194 patients inspected, 77% presented punctually for stent removal, 9% had not, and 1 patient was lost to follow-up. A subsequent study done by Ziemba et al. reported that three out of 115 patients (3%) who did not return for their scheduled stent removal could be identified only through the UST application. In a similar manner, our research found that characteristics between both study populations were similar in terms of age, gender, education level and side of ureteral stent insertion. The only differences between the two groups were the patients' underlying primary diseases. Complementary to results demonstrated in previous studies, our research has also shown that patients who used a stent tracking application had lower incidences of not returning to scheduled appointments on time when compared to those using traditional appointment methods (4.20% vs. 19.4%, respectively) with the data being statistically significant.

Although, the number of patients with Bachelor or higher in Group 2 was 33, that are higher than Group 1 which were 20 patients. When we compare between the two groups on their punctuality in returning on a scheduled appointment date. There is no statistically significant difference. This indicates that patients placed importance on making appointments to see physicians at all levels of education.

Thus, a presumption that using a tracking application

TABLE 2. Comparison between the two groups on their punctuality in returning on a scheduled appointment date.

Group	Came on appointed date		P-value
	Yes (%)	No (%)	
			0.004[2]
Group 1	58(80.60)	14(19.40)	
Group 2	69(95.80)	3(4.20)	

[2]Analyze by Chi-square test

TABLE 3. Comparison between the two groups on their punctuality in returning on a scheduled appointment date when further classified by Bachelor or higher.

Group	Came on appointed date		P-value
	Yes (%)	No (%)	
Bachelor or higher			0.061[3]
Group 1	16(80.00)	4(20.00)	
Group 2	32(97.00)	1(3.00)	

[3]Analyze by fisher's exact test

TABLE 4. Comparison between the two groups on their punctuality in returning on scheduled appointment dates when further classified by their underlying primary diagnosis.

Diagnosis	Came on to appointed date		P-value
	Yes (%)	No (%)	
Ureteric Calculi			0.512[3]
Group 1	21(95.50)	1(4.5)	
Group 2	21(100.00)	0(0.00)	
Renal Calculi			0.142[2]
Group 1	23(76.70)	7(23.30)	
Group 2	22(91.70)	2(8.30)	
Kidney transplantation			NA*
Group 1	3(100.00)	0(0.00)	
Group 2	16(100.00)	0(0.00)	
Gynecologic condition			0.222[3]
Group 1	2(40.00)	3(60.00)	
Group 2	6(85.70)	1(14.30)	
Other			0.529[3]
Group 1	9(75.00)	3(25.00)	
Group 2	4(100.00)	0(0.00)	

*No one did not come on appointment date

[2]Analyze by Chi-square test

[3]Analyze by fisher's exact test

TABLE 5. Overdue duration between two groups.

Group	Median (days)	Quartile 1 – 3 : (IQR)
Group 1	7 (n = 14)	6.25 – 102.75 : 96.5
Group 2	7 (n = 3)	5 – 10 : 5

can lower the rates of appointment dismissal can be made. A patient's underlying condition did not influence their punctuality for appointments, except for kidney transplant patients, who all came to appointments on schedule. This may be further explained by the pandemic of COVID-19, which reduced the amount of kidney transplantation procedures, which in turn decreased the number of patients who received appointment cards during the study period. On the other hand, the study of patients who utilized the stent tracking application was conducted when the pandemic was on its downward trend. Meanwhile, Thammasat University Hospital recruited a new transplant doctor, increasing the amount of kidney transplant cases within the period of interest. A patient who underwent a kidney transplant typically required a multidisciplinary team to care for the patient. The need to meet several specialists also reiterated the importance of punctuality for follow-up appointments in this group of patient.

Another noteworthy factor to consider is that the overdue duration was significantly shorter in the application usage group when compared to those receiving traditional appointment care (IQR:5 vs. 96.5 days, respectively). This result corresponds to the study done by Ulker et al in 2019, who found that application users had shorter overdue times (Mean 3.5 days, P = 0.001). Phoning patients who missed appointments had reduced the overdue times of application users. Moreover, using their application also allowed them to track each patient's due date for stent removal efficiently, which assists physicians to emphasize the importance of follow up to this group of patients.

Limitations

A limitation of this study is that the study population was small because the application was available only

to Android users.This study did not provided income and residence of the patient that may be risk factor for miss an appointment. Moreover, each patient's personal information and clinical data had to be manually transferred from the hospital database into the software, causing possible technical errors and excessive time consumption. Retrospectively collected data was compared to newly collected information, so the comparison was presumptive, not prospective, possibly causing bias during data collection.

Future direction

This tracking application was designed specifically for Thai users. A similar iOS version is planned. In addition to improving punctuality for appointments, this tracking device assists closer patient follow-up. Further potential may be revealed in future studies.

CONCLUSION

The usage of a mobile tracking application device for patients with indwelling ureteral stents has decreased the tendency of these patients to miss their appointments and reduced overdue time. The stent tracking application is superior to traditional follow up methods for ensuring punctual outpatient visits with this group of patients.

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Conflict of interest: We have no conflict of interest.

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Long-Term Outcomes After Right Ventricular Outflow Tract Conduit Placement

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ABSTRACT

Objective: Our aim was to report on the long-term outcomes of patients who underwent RV-PA conduit placement at our institute.

Materials and Methods: We retrospectively reviewed 407 RV-PA conduit placements from January 1997 to December 2018. The primary outcomes were freedom from and risk factor(s) for conduit re-operation. The secondary outcomes were survival, freedom from conduit dysfunction and conduit-related catheter intervention.

Results: Of all the included patients, 209 were male (51.4%) and the median age at the operation was nine years (IQR 6, 18 years). The most commonly used conduit types were bovine jugular vein conduit (125, 30.7%), pulmonary homograft (122, 30.0%), and aortic homograft (76, 18.7%). The median follow-up time was 5.1 years (IQR 0.9, 9.2 years). The overall survival was 92.2% at 5 years. Freedom from re-operation was 95.4% and 84.2%, at 5 and 10 years. Factors related to conduit reoperation were age at operation less than 1 year, diagnosis rather than pulmonary atresia or stenosis, conduit size less than 18 mm, and conduit z-score greater than 3 (all $p<0.01$). In multivariate analysis, a significant contributing factor for re-operation was small conduit size (13 mm or smaller; HR 6.87 (95%CI 2.36, 20.01); $p<0.001$, 14–17 mm; HR 3.20 (95%CI 1.28, 8.00); $p=0.013$). Freedom from conduit dysfunction was 84.4 and 61.6% at 5 and 10 years. Freedom from conduit intervention was 94.4% and 89.3% at 5 and 10 years.

Conclusion: Our study showed that patients had excellent survival with acceptable freedom from re-operation despite deteriorated conduit function. Small conduit size is associated with re-operation.

Keywords: Allografts; heterografts; reoperation; survival analysis; ventricular outflow obstruction (Siriraj Med J 2023; 75: 473-480)

Presentation: The Asian Society for Cardiovascular & Thoracic Surgery (ASCVTS) 2020, Chiang Mai, Thailand, 7-10 February 2020

INTRODUCTION

The placement of a valved conduit between the right ventricle (RV) and pulmonary artery (PA) is a crucial part of congenital heart defect repairs. It is usually performed in patients with discontinuity between the right ventricle and branch pulmonary arteries, or in patients with significant pulmonary stenosis or insufficiency. Despite the initial success of these procedures, long-term outcomes are affected by hemodynamic sequelae of conduit dysfunction with subsequent need for re-intervention and re-operation.[1,2] Several options are available, and the advantages, limitations, and associated factors of each have previously been described.[1,3,4] However, comparison of different valved conduit materials and sizes in the right ventricular outflow position in large cohorts is scarce.

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Many types of conduit material have been used at our institute for decades.[5] The placement of homografts, xenografts and institutional-developed synthetic valved conduits in recent years has made up one of the largest registries in this region with high follow-up rates at our grown-up congenital heart clinic.

Our objectives were to describe long-term outcomes of right ventricular-pulmonary artery (RV-PA) conduit placement at our institute and to identify factors associated with conduit re-operation.

MATERIALS AND METHODS

Study design

We retrospectively examined clinical outcomes of all RV to PA conduit placements in congenital cardiac defects between January 1997 and December 2018 at the Faculty of Medicine Siriraj Hospital, Thailand. Patients with anatomic left ventricle to PA conduit and patients with inaccessible records were excluded. This study was approved by the Siriraj Institutional Review Board (COA no. Si 004/2019). Patient consent was waived as there were minimal risks for the subjects.

Study parameters and outcomes

Study parameters included demographics, primary cardiac diagnosis and surgical indications, previous operation(s), type and size of the conduit, concomitant procedure(s), postoperative clinical outcomes, re-intervention and re-operation, and status at the last follow-up.

Conduit function was assessed using transthoracic echocardiography, cardiac magnetic resonance imaging, and/or cardiac catheterization performed by paediatric cardiologists per standard guidelines. Conduit dysfunction was defined by evidence of aneurysmal change, conduit dehiscence, moderate or greater valve incompetence and/or moderate or greater conduit stenosis. Conduit re-operation was indicated in symptomatic patients with moderate or severe conduit stenosis or regurgitation, in an asymptomatic patient with severe conduit stenosis or regurgitation accompanied by right ventricular dysfunction or dilatation, and in a patient with conduit aneurysm or dehiscence.

The primary outcomes were freedom from conduit reoperation and independent factors associated with it. Secondary outcomes included overall survival, freedom from conduit dysfunction, and transcatheter intervention of the conduit.

Statistical analysis

Data was described in frequencies, medians with interquartile ranges, or means with standard deviations. The variables between the two study groups were compared using independent T-test samples or Pearson Chi-Square test (or non-parametric equivalents where appropriate), with statistical significance defined as a p-value of less than 0.05. The continuous variables (age, conduit size, conduit Z score, operative era) and categorical variables with multiple subcategories (morphologic indication, conduit type, type of operation) were grouped into no more than three subgroups for analysis. Survival rates were calculated using the Kaplan–Meier method and the log-rank test for adjusting the differences between subgroups. The Cox proportionate hazard model was used to determine both univariable and multivariable relationships between time-to-conduit re-operation and associated variables. Data analysis was carried out using SPSS™ software version 20.0 (SPSS Inc., IBM Company, Chicago, Illinois, USA).

RESULTS

Baseline characteristics (Table 1 and study flow diagram)

A total of 415 RV to PA conduit placements were performed in 382 patients during the study period with 8 of them being excluded from the analysis due to a lack of follow-up data. Of the remaining 407 conduits, the median age at the time of conduit placement was 9 years (interquartile range 6 to 18 years) with an average conduit size of 20.56±4.15 mm.

Operative detail (Table 1 and Fig 1)

Indications for surgery were pulmonary atresia or stenosis in 341 patients (83.8%) and truncus arteriosus in 56 patients (13.8%). A total of 289 conduits (71.0%) were used as part of the primary total repair. The conduit material in 201 patients (49.4%) was a homograft and xenograft in 185 patients (45.5%). The trend of conduits used has changed over time as homografts were mostly used in the 1990s and 2000s, but bovine jugular vein conduits have become more common since 2011.

Overall outcomes (Fig 2)

Of the 407 patients with available follow-up data, the median follow-up duration was 5.1 years (interquartile range 0.9 to 9.2, maximum 23.3 years), with 33 deaths (8.1%), 103 instances of conduit dysfunction (25.3%), 26 conduit transcatheter interventions (6.4%), and 44 conduit re-operations (10.8%).

The overall survival was 92.2% at 5 years and remained plateaued over 20 years. The overall freedom from reoperation was 95.4% and 84.2% at 5 years and 10 years, respectively. Overall freedom from transcatheter

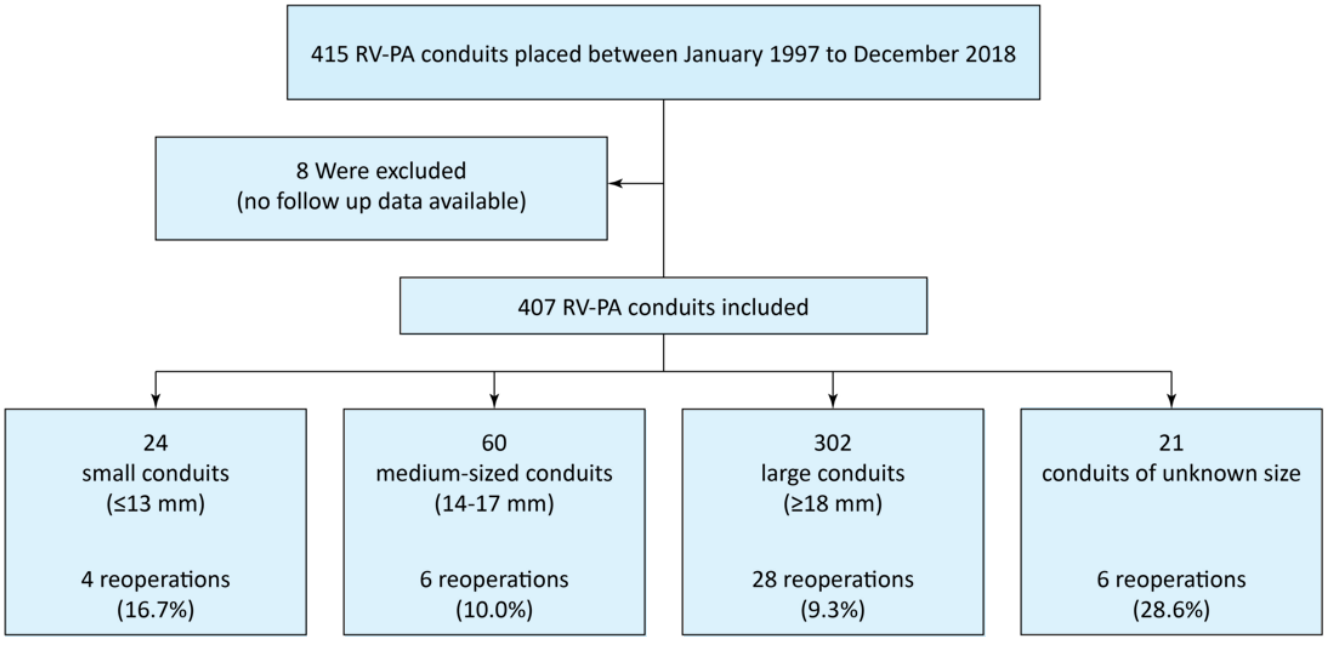
TABLE 1. Baseline characteristics and operation details.

Demographic data (n=407)	N	%	Number (%)		P-value
			Re-operation	No re-operation	
Sex					0.159
Male	209	51.4	27 (12.9)	182 (87.1)	
Female	198	48.6	17 (8.6)	181 (91.4)	
Age (year) Median 9 (IQR 6,18)					0.222
<1	42	10.3	8 (19)	34 (81)	
1–10	184	45.2	18 (9.8)	166 (90.2)	
>10	181	44.5	18 (9.9)	163 (90.1)	
Indication for conduit placement					**0.026**
PA group	164	40.3	14 (8.5)	150 (91.5)	
PS group	177	43.5	18 (10.2)	159 (89.8)	
Truncus arteriosus	56	13.8	12 (21.4)	44 (78.6)	
Ross procedure	8	2.0	0 (0)	8 (100)	
Conduit dysfunction	1	0.2	0 (0)	1 (100)	
Other	1	0.2	0 (0)	1 (100)	
Surgery type					0.820
Primary conduit placement	289	71.0	33 (11.4)	256 (88.6)	
Conduit placement after total repair	73	17.9	7 (9.6)	66 (90.4)	
Conduit replacement	45	11.1	4 (0.8)	41 (99.2)	
Conduit position					0.504
Heterotopic	278	68.3	32 (11.5)	246 (88.5)	
Orthotopic	129	31.7	12 (9.3)	117 (90.7)	
Conduit type					**<0.001**
Aortic homograft	76	18.7	12 (15.8)	64 (84.2)	
Pulmonic homograft	122	30.0	18 (14.8)	104 (85.2)	
Edward porcine valved conduit	4	1.0	0 (0)	4 (100)	
Stentless porcine valve conduit	40	9.8	3 (7.5)	37 (92.5)	
Hancock valve conduit	11	2.7	5 (45.5)	6 (54.5)	
Bovine jugular vein conduit	125	30.7	3 (2.4)	122 (97.6)	
Goretex tube with 0.1 mm GoreTex trileaflet valve	15	3.7	0 (0)	15 (100)	
Autologous pericardial tube with pericardial valve	2	0.5	1 (50)	1 (50)	
Freestyle porcine aortic root valve	3	0.7	0 (0)	3 (100)	
Dacron graft	2	0.5	0 (0)	2 (100)	
Unspecified homograft	3	0.7	0 (0)	3 (100)	
Unspecified conduit	4	1.0	2 (50)	2 (50)	
Conduit materials					**0.002**
Homograft	201	49.4	30 (14.9)	171 (85.1)	
Xenograft	185	45.5	12 (6.5)	173 (93.5)	
Synthetic	17	4.2	0 (0)	17 (100)	
Other	4	1.0	2 (50)	2 (50)	

TABLE 1. Baseline characteristics and operation details. (Continued)

Demographic data (n=407)	N	%	Number (%)		P-value
			Re-operation	No re-operation	
Conduit size (mm) Mean 20.56 (SD 4.15)					**0.042**
Small size (≤ 13 mm)	24	5.9	4 (16.7)	20 (83.3)	
Medium size (14–17 mm)	60	14.7	6 (10.0)	54 (90.0)	
Large size (≥ 18 mm)	302	74.2	28 (9.3)	274 (90.7)	
Missing data	21	5.2	6 (28.6)	15 (71.4)	
Conduit z-score Median 0.90 (IQR 0.07,1.61)					**0.001**
<1	207	50.9	13 (6.3)	194 (93.7)	
1-3	151	37.1	18 (11.9)	133 (88.1)	
>3	26	6.4	7 (26.9)	19 (73.1)	
Missing data	23	5.7	6 (26.1)	17 (73.9)	

PA group = pulmonary atresia group; PS group = pulmonary stenosis group;
Homograft group = aortic homograft, and pulmonic homograft;
Xenografts group = Edward porcine valved conduit, Stentless porcine valve conduit, Hancock valve conduit, Freestyle porcine aortic root valve, and bovine jugular vein conduit;
Synthetic group = GoreTex tube with 0.1 mm GoreTex trileaflet valve



Study flow diagram

intervention was 94.4% at 5 years and 89.3% at 10 years. The overall freedom from conduit dysfunction was 84.4% at 5 years, and 61.6% at 10 years.

Factor associated with conduit reoperations (Table 2 and Fig 3)

In univariate analysis, the infantile age group witnessed the worst freedom from reoperation (67.1% at 10 years versus 84.6% for 1 – 10 years and 86.9% for the older than 10 years group). Diagnosis of truncus arteriosus was also associated with reoperation (40.6% at 10 years versus 12.5% for pulmonary atresia and pulmonary stenosis group). The conduit size of 13 mm or smaller had the lowest freedom from reoperation (36.7% at 10 years versus 61.5% for 14 – 17 mm and 88.5% for 18 mm or larger).

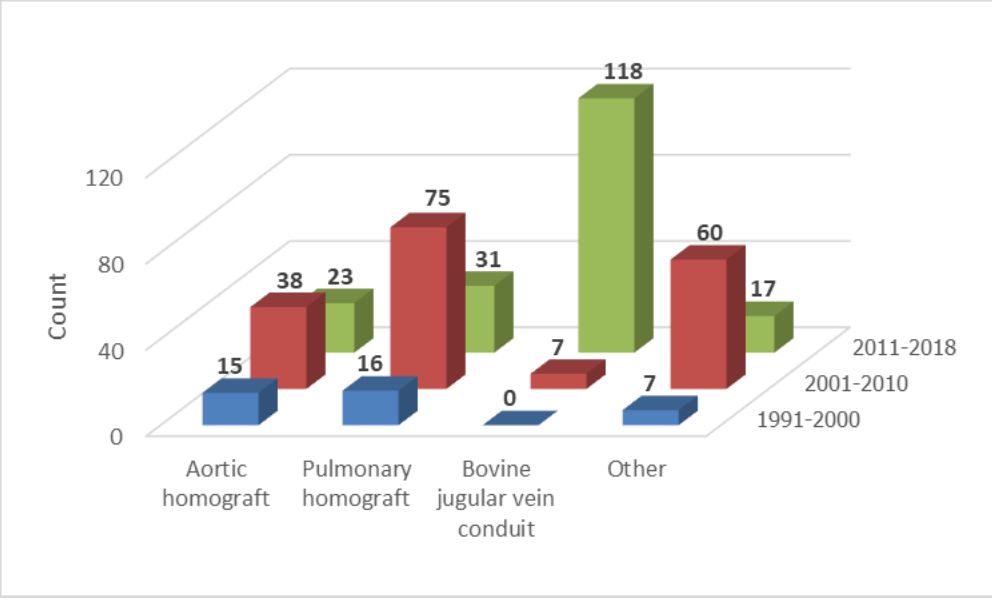


Fig 1. Type of conduit by operation era

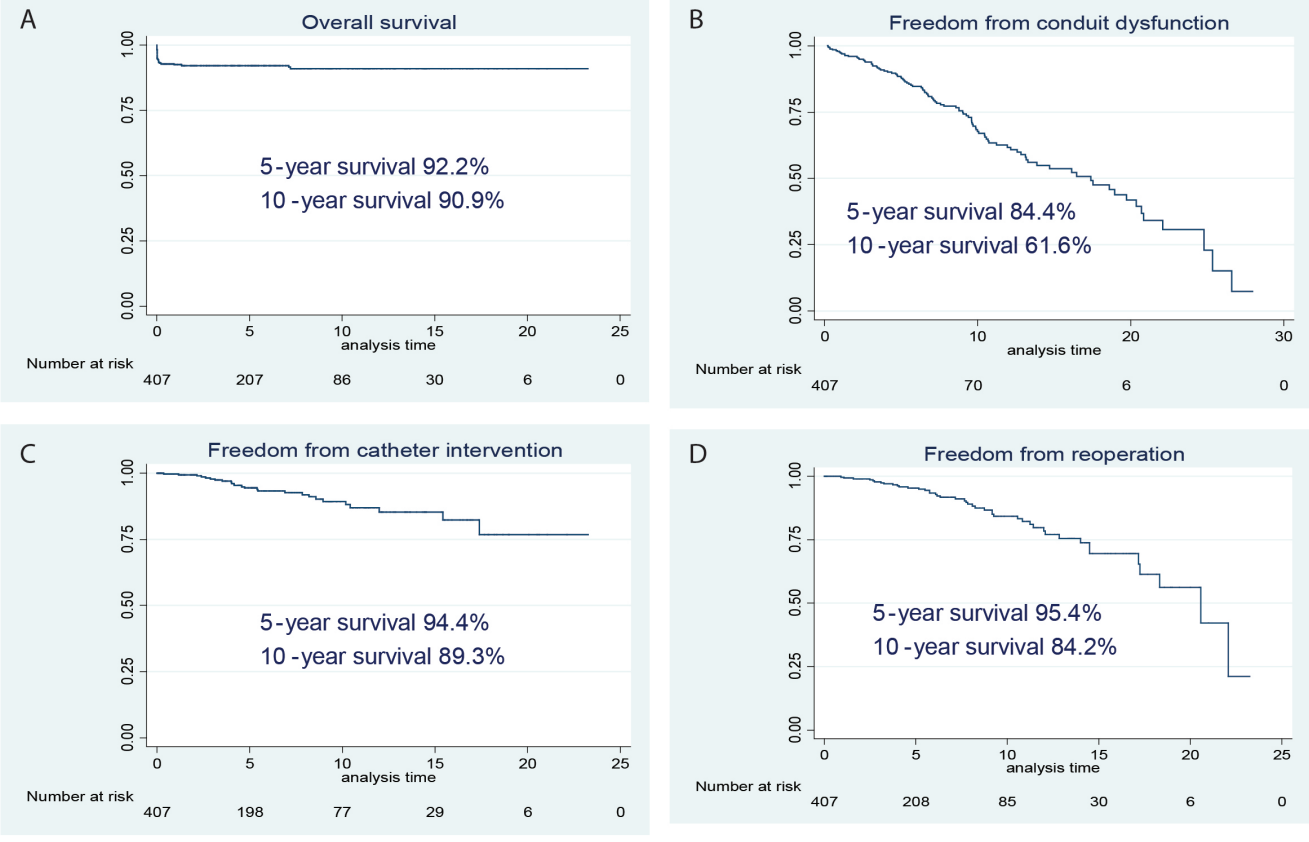


Fig 2. Overall long-term outcomes

Only having small- or medium-sized conduits remained significant in the multivariate model at an adjusted hazard ratio of 6.87 (95%CI 2.36, 20.1, p<0.001) and 3.20 (95%CI 1.29, 8.00, p=0.013) reference to large-sized conduits.

DISCUSSION

We found that even with good long-term survival outcomes, most RV to PA conduits deteriorated over time and at some point, would require re-intervention and/or re-operation. The smaller the implanted conduit, the higher risk for re-operation, with up to a 6.87 times adjusted hazard ratio when compared with large conduits.

This is consistent with studies from other groups that demonstrated small conduits as an independent risk for conduit re-operation.[2,4,6,7] Other risk factors for

TABLE 2. Factors associated with conduit re-operation.

Factors	Crude HR	Univariate (95%CI)		P-value	Adjusted HR	Multivariate (95%CI)		P-value
Sex								
Male	1.681	0.91	3.103	0.097				
Female	1							
Age (year)								
<1 year	3.627	1.55	8.488	**0.003**	0.553	0.101	3.034	0.496
1–10 years	0.977	0.505	1.888	0.944	0.666	0.281	1.577	0.355
>10 years	1				1			
Primary diagnosis								
PA group	1				1			
PS group	1.059	0.52	2.155	0.875	0.932	0.428	2.028	0.859
Others	4.154	1.903	9.069	**<0.001**	1.62	0.393	6.677	0.504
Surgery Type								
Primary conduit placement	1							
Conduit placement post-total repair	1.035	0.45	2.378	0.936				
Conduit replacement	1.483	0.518	4.244	0.463				
Position of Conduit								
Heterotopic	1.127	0.564	2.255	0.735				
Orthotopic	1							
Type of conduit								
Aortic homograft	1.284	0.333	4.942	0.717				
Pulmonic homograft	1.207	0.331	4.396	0.776				
Bovine jugular vein conduit	1							
Material of conduit								
Homograft	1							
Xenografts	1.019	0.493	2.11	0.959				
Conduit size								
Small (≤13 mm)	6.725	2.306	19.611	**<0.001**	6.869	2.359	20.004	**<0.001**
Medium (14-17 mm)	3.197	1.278	7.993	**0.013**	3.204	1.283	8	**0.013**
Large (≥18 mm)	1				1			
Conduit z-score								
<1	1				1			
1–3	1.321	0.645	2.707	0.447	1.096	0.495	2.429	0.821
>3	3.033	1.191	7.721	**0.02**	2.435	0.661	8.978	0.181

PA group = pulmonary atresia group; PS group = pulmonary stenosis group;
Homograft group = aortic homograft, and pulmonic homograft;
Xenografts group = Edward porcine valved conduit, Stentless porcine valve conduit, Hancock valve conduit, Freestyle porcine aortic root valve, and bovine jugular vein conduit;

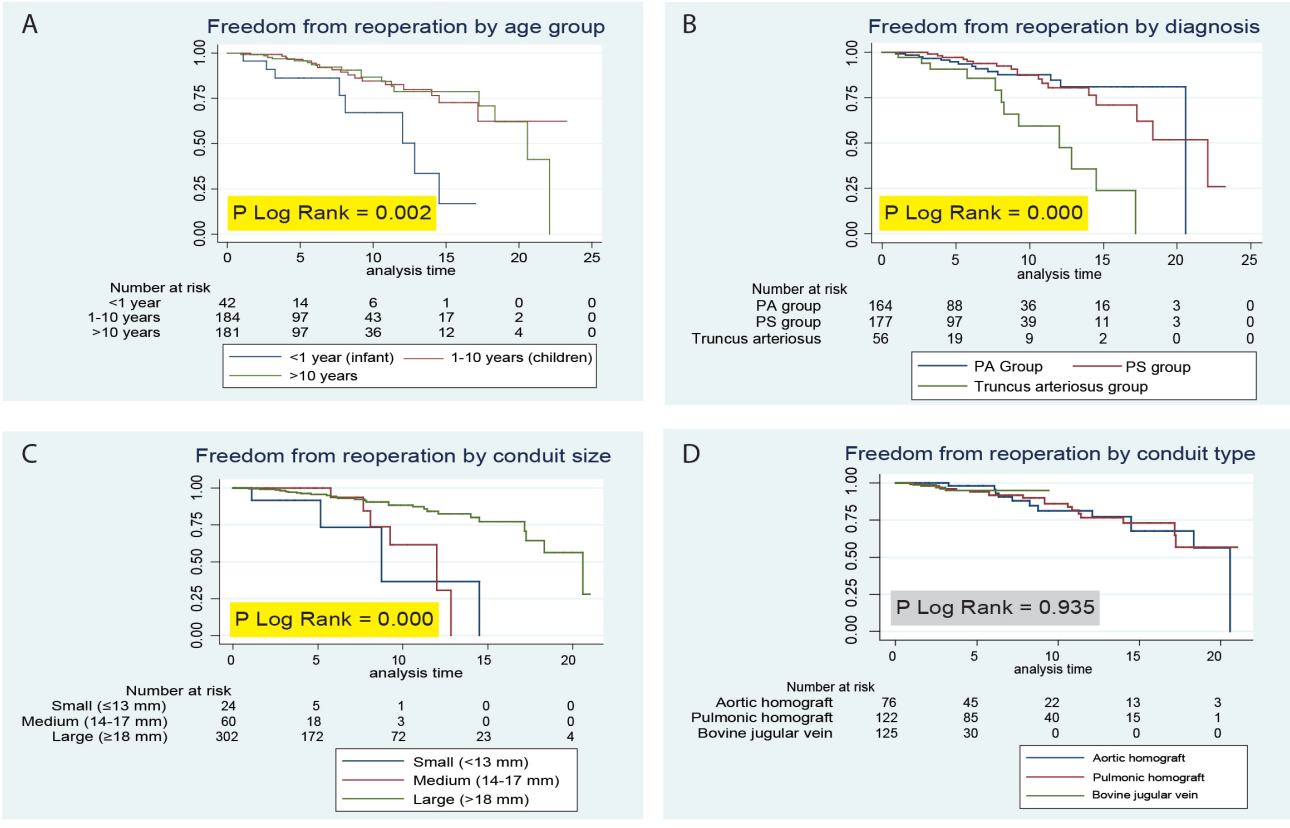


Fig 3. Freedom from conduit re-operation

re-operation include younger age and diagnosis of truncus arteriosus in other studies[4,8] failing to achieve statistical significance in our multivariate analysis. The diagnosis of truncus arteriosus and younger age at conduit placement could easily confound the outcomes as both almost always need small conduits. The type of conduit and position of conduit (i.e. orthotopic versus heterotopic) are associated with conduit longevity in other studies[9,10] showed no difference in this study. The reason for these findings might be due to the limited follow-up time and heterogeneity of our patients. One interesting finding in the univariate model is that oversizing the conduit (z score of more than 3) seems to jeopardise the durability of the conduit as opposed to lengthening it. This finding is consistent with other studies.[11-13]

Our study is by far the largest series of RV to PA conduit in this region with a long follow-up time of up to 20 years and contains multiple conduit types. However, several limitations exist, such as recent advances in conduit re-intervention, especially transcatheter pulmonary valve implantation,[14] which allows deferment or even avoidant re-operation that may lead to an overestimation of the longevity of conduits implants in the recent era. Also, despite evidence in several studies,[15,16] the durability of polytetrafluoroethylene over other biologic conduits cannot be demonstrated in this cohort as it was just introduced at our institute in 2018.[17] A further study is warranted to compare this promising conduit with the pulmonary homograft.

CONCLUSION

Our study demonstrates excellent long-term survival following RV to PA conduit placement with acceptable freedom from re-operation and catheter re-intervention despite the deterioration of conduit function over time. The use of a small conduit is an independent risk factor for conduit re-operation.

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Declarations

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Conflicting interests: None declared

Abbreviations

PA = pulmonary artery
PA group = pulmonary atresia group
PS group = pulmonary stenosis group

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