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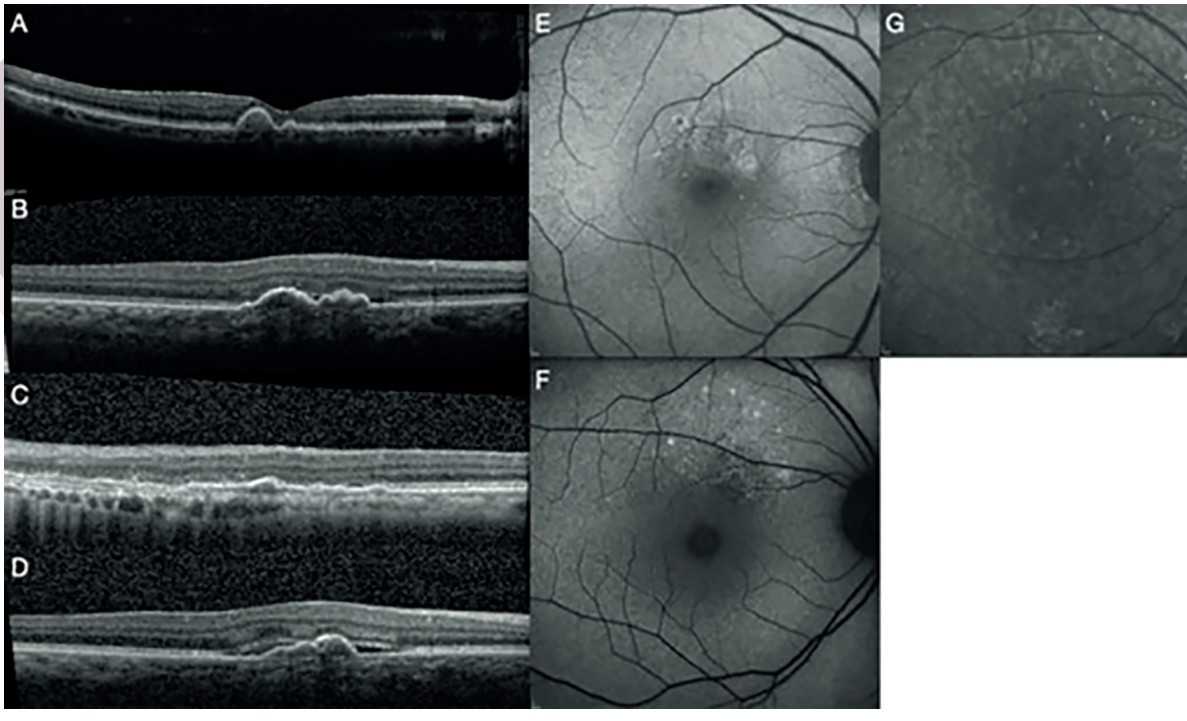
EDITORIAL



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Innovative Device for Enhancing Physical Distancing in the COVID-19 Situation

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ABSTRACT

Objective: During the COVID-19 pandemic, physical distancing is one of the non-pharmaceutical measures that was recommended to reduce COVID-19 spread. Studies regarding physical distancing intervention and its effectiveness in Thailand have rarely been reported. This study aimed to evaluate physical distancing compliance among newly developed media interventions.

Methods: We used accidental sampling and the data collection method was observation via CCTV, at the university canteen. Three interventions, including an attractive picture, a flashing red-light, a speech alarm sound and the conventional intervention were employed to 400 customers. Each intervention was monitored in non-prime hours.

Results: The quasi-experimental study of 400 participants, the success rate of developed intervention including a flashing red light (6.0%, p = 0.279), an attractive picture (5.0%, p = 0.445) and a speech alarm sound (4.0%, p = 0.683) in promoting physical distancing compliance was not statistically significant from conventional intervention (2.0%). However, there was a statistically significant enhancement of physical compliance in some marking positions in our intervention.

Conclusion: The effectiveness of the innovative device was not statistically significant to enhance physical distancing compliance among customers of the university canteen. The compliance statistically significantly enhances in some marking points. The integration of the use of media into conventional interventions provides an alternative for enhancing physical distancing.

Keywords: Physical distancing; COVID-19; innovative device (Siriraj Med J 2021; 73: 69-76)

INTRODUCTION

The COVID-19 pandemic has confronted an unprecedented challenge to the world, our societies, health care systems, and economies. Within six months (from January to June 2020), 210 countries and territories around the world have reported more than seven million confirmed cases including almost four hundred thousand deaths as of 8th June, 2020.[1] The SARS-CoV2, a highly infective pathogen, causes moderate to severe clinical outcomes in about 20% of all recognized infected individuals leading to the risk of health system collapse due to overwhelming medical resources.[2] In addition to the global health care system threat, it also contributes to the risk of economic recession (e.g., an 8.1% contraction of this year gross domestic product according to the Bank of Thailand forecast, Thailand's biggest GDP decline ever.).[3]

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In the absence of a vaccine, public health responses have posed the use of varying level of non-pharmaceutical interventions (e.g., hand hygiene, wearing face mask, and physical distancing) to mitigate the impact of the COVID-19 pandemic.[4] Physical distancing was recommended to reduce COVID-19 spread.[5] The Thai government has correspondingly implemented social distancing measures including stay at home, the closure of schools, restaurants, and other public places since March 2020. When stringently applied and perpetuated, these measures profoundly provoke societal and economic disruption.[6] Thus, individual physical distancing is the most effective way to balance competing risks between health system collapse and economic risks.

Although there have been several previous studies on effectiveness of non-pharmaceutical intervention and factors affecting physical distancing compliance, studies regarding physical distancing intervention and its effectiveness in Thailand during this ongoing COVID-19 pandemic have rarely been reported. Our study developed media interventions based on behavioral change theory. The study aimed to evaluate physical distancing compliance among interventions.

MATERIALS AND METHODS

Setting and sample

This is a quasi-experimental study. The sampling technique used is an accidental sampling by the first 100 participants starting at 11.00 AM. The study was conducted in the university canteen at Prince of Songkla University, where there was conventional intervention as a footprint standing sign to encourage people to keep physical distancing (Fig 1A).

Measurement of key variables

Independent variable: innovative device

We developed three different media interventions to be used in the university canteen setting. (1) An attractive picture developed from original concept[7], then designed in a colorful adorable coronavirus graphic with a crying-face and "COVID-19" text (Fig 1B). (2) A flashing red-light developed from color psychology[8] and attention theory[9-12] composed of flexible 10 W flashing red LED strip lights which are waterproof, silicone-coated and battery-powered. The light strip was stuck in front of the conventional marking standing positions and covered with transparent adhesive tape (Fig 1C). (3) A speech alarm sound based on attention theory[13,14], "Please keep at least 1-meter distance apart" in Thai, delivered by 12-inch speaker within normal hearing intensity every 30 seconds (Fig 1D).

Each intervention was monitored over lunchtime for four days in early August, 2020 until four interventions were completed. The study outcome was physical distancing compliance.

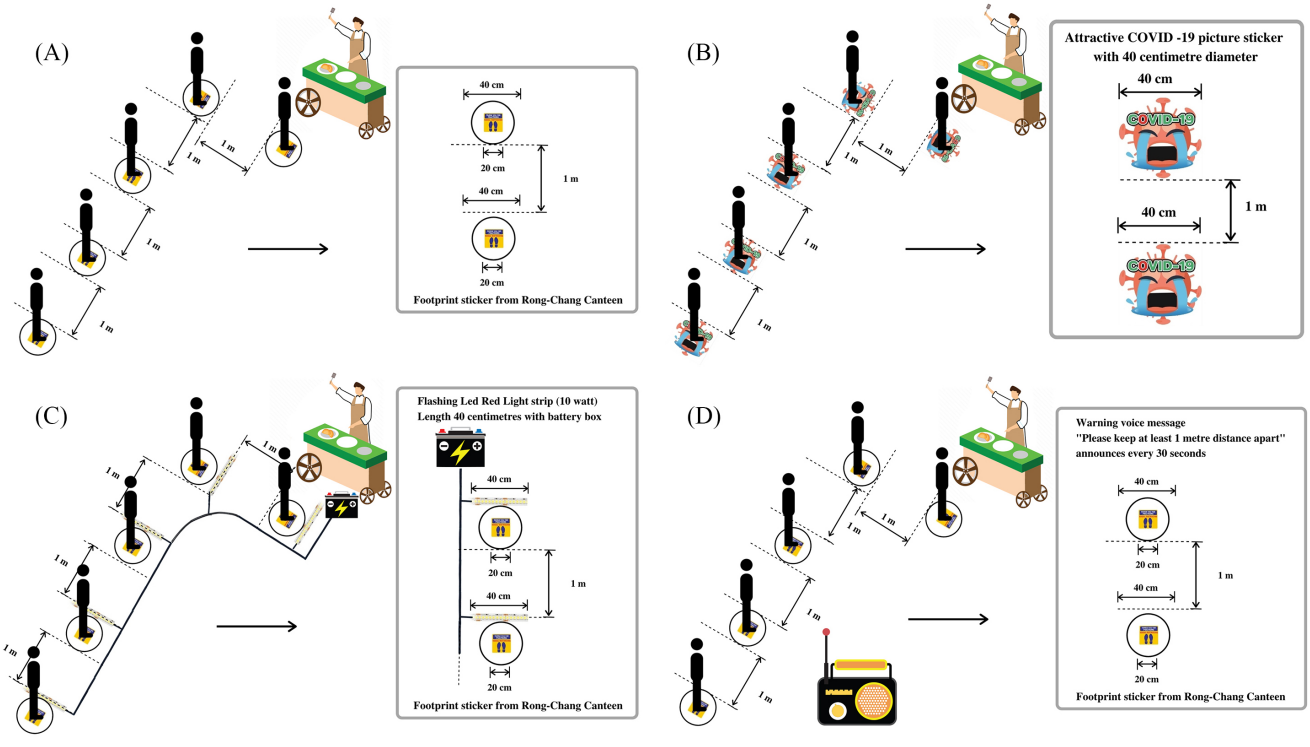

Fig 1. **(A)** Control **(B)** An attractive picture **(C)** A red flashing-light **(D)** A speech alarm sound.

Dependent variable: physical distancing

Physical distancing is defined as at least 1-meter distance among people.[5] Successful physical distancing was defined according to the following criteria:

(1) Standing within the 40-centemeter-length marking position along the process of queueing.

(2) Moving out of the marked position 3 seconds and less each time is acceptable.

Other conditions which do not meet these criteria above are defined as a failure to keep physical distancing.

Factors affecting physical distancing

This study is a comparative behavioral observation study via CCTV. We established the protocol for CCTV data collection. After piloting the protocol for CCTV record, observers revised the established protocol to validate inconclusive situations. The revised protocol was applied in the data collection. We observed the characteristics of participants including age group (by observation), gender, university uniform, companion, and carrying item. The accessibility of the records is limited to our research team only at the study location and the records will not be published. These do not contain personal identification and will be deleted within 7 days according to the organization's security policy. All analyses were carried out on anonymized data and will be analyzed in aggregates. Moreover, the publication will not mention the dates and specific places. Therefore, we guarantee the confidentiality and the privacy of the participants and communities.

Statistical analysis

The statistical analysis included both continuous and categorized variables for physical distancing. The median and interquartile range (IQR) were used to describe the physical distancing as the data were not normally distributed. The Wilcoxon signed-rank test was used to compare the physical distancing regarding different interventions within the same cluster. Categorical variables were analyzed using a Chi-square or Fisher's exact test. The analysis was computed by R® 4.0.0.

The study was conducted in line with the Belmont Report and was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University (REC.63-272-9-1).

RESULTS

There was a total of 400 participants observed over 4 interventions including the conventional one, an attractive picture, a flashing red-light, and a speech alarm sound. One quarter of the participants engaged in each intervention. The participant demographic data was recorded in Table 1 as gender, age group (by observation), uniform wearing, coming with companion, and carrying items categorized in number and types. Considering characteristics, gender was solely not statistically different in an attractive picture ($p = 1.00$), a flashing red-light ($p = 0.764$), and a speech alarm sound ($p = 0.114$).

Comparing each intervention with the control group, there was no significant effect of all interventions on physical distancing compliance (Table 2). The highest average number of failures of physical distancing was an attractive picture (3 times). The number of failures of physical distancing of the other three interventions was 2 on average.

According to Table 3 and Fig 2, the failure of physical distancing at the first two marking points in all interventions were approximately 80% while the rest were apparently lower. In the attractive picture intervention, the failure of physical distancing went in an upward trend at marking point 3, 4 and 5. The flashing red-light intervention could significantly decrease 25.4% failure of physical distancing comparing to the control group at marking point 3 ($p = 0.011$). At the latter marking points, the failure of physical distancing in the speech alarm sound intervention continuously attenuated, demonstrating a similar trend to the control group. At the marking point 5, the failure of physical distancing declined. The decline was statistically significant ($p = 0.044$).

DISCUSSION

Our results demonstrated that failure of physical distancing compliance in all interventions declined compared to the control group. However, findings did not have enough strength to support the effectiveness of interventions on delivering the encouragement of behavioral change. Considering each marking point in all interventions, the first two positions bore noticeably high percentage of failure of physical distancing due to the distraction from menu selection. In position 3, 4 and 5 of the attractive picture intervention, there was an increasing failure of physical distancing (Fig 3). A message from an attractive picture might not efficiently be delivered to the participants. Failure of physical distancing at marking point 3 of the flashing red-light intervention decreased significantly since the intervention could establish an effect to draw attention.[10–12] The speech alarm sound intervention could improve behavior of participants in maintaining physical distance, especially at the latter marking points. Despite the fact that physical distancing, one of non-pharmaceutical interventions, is key to preventing spread of respiratory

TABLE 1. Background information of participant on the interventions (n=400).

Characteristics	Control (n=100)	An attractive picture (n=100)	*P*-value	A flashing red-light (n=100)	*P*-value	A speech alarm sound (n=100)	*P*-value
Gender, n (%)							
Male	65 (65)	66 (66)	1_a	68 (68)	0.764_a	53 (53)	0.114_a
Female	35 (35)	34 (34)		32 (32)		47 (47)	
Age group by observation, n (%)							
Wearing university uniform	2 (2)	39 (39)	$< 0.001_{a*}$	39 (39)	$<0.001_{a*}$	8 (8)	0.105_a
Not wearing university uniform	98 (98)	61 (61)		61 (61)		92 (92)	
Children (est. 0-11 years)	1 (1)	0 (0)	0.003_{b*}	0 (0)	0.608_b	0 (0)	$< 0.001_{b*}$
Adolescences (est. 12-18 years)	12 (12.4)	0 (0)		4 (6.6)		1 (1.1)	
Adult (est. 19-64 years)	83 (84.6)	61 (100)		56 (91.8)		91 (98.9)	
Elderly (est. ≥65 years)	2 (2.1)	0 (0)		1 (1.6)		0 (0)	
With companion, n (%)							
No	66 (66)	86 (86)	0.002_{a*}	82 (82)	0.016_a	72 (72)	0.445_a
Yes	34 (34)	14 (14)		18 (18)		28 (28)	
Carrying items, n (%)							
No carrying item	38 (38)	78 (78)	$< 0.001_{a*}$	70 (70)	$< 0.001_{a*}$	82 (82)	$< 0.001_{a*}$
Carrying items	62 (62)	22 (22)		30 (30)		18 (18)	
Number and type of items,	1 [1,2]	1 [1,1]	0.093_c	1 [1,1]	0.005_{c*}	1 [1,1]	0.06_c
Median, [IQR]							
1	41 (66.1)	19 (86.4)	0.09_b	28 (93.3)	0.01_{b*}	16 (88.9)	0.202_b
2	19 (30.6)	2 (9.1)		2 (6.7)		2 (11.1)	
3	2 (3.2)	1 (4.5)		0		0	
Type of items, n							
Container	3	0		0		0	
Book	0	0		1		0	
Bag	44	12		20		12	
Mobile	26	7		7		5	
Other	7	6		3		2	

Abbreviation: IQR = interquartile range

* P-value < 0.05, compared with control group, [a] Chi-squared test, [b] Fisher's exact test, [c]Wilcoxon rank-sum test

TABLE 2. Effects of the interventions on failure of physical distancing practice (n=400).

	Failure of physical distancing (n = 100)		Number of failure of physical distancing	
	n (%)	*P*-value	Median (IQR)	*P*-value
Control	98 (98.0)	-	2 (2,3)	-
An attractive picture	95 (95.0)	0.445_a	3 (2,3)	0.293_b
A flashing red-light	94 (94.0)	0.279_a	2 (2,3)	0.866_b
A speech alarm sound	96 (96.0)	0.638_a	2 (2,2,2)	0.006^*_b

Abbreviation: IQR = interquartile range

*P-value < 0.05, compared with control group, [a] Chi-square test, [b] Wilcoxon rank-sum test

TABLE 3. Failure of physical distancing practice by the marking point.

	Failure of physical distancing						
Marking point	Control	An attractive picture		A flashing red-light		A speech alarm sound	
	No. of failure/total (%)	No. of failure/total (%)	*P*-value[a]	No. of failure/total (%)	*P*-value[a]	No. of failure/total (%)	*P*-value[a]
1	87/99 (87.9)	76/99 (76.8)	0.062	85/97 (87.6)	1	80/95 (84.2)	0.596
2	81/99 (81.8)	84/100 (84.0)	0.825	85/99 (85.9)	0.562	81/98 (82.7)	1
3	22/42 (52.4)	32/71 (45.1)	0.578	20/74 (27.0)	**0.011***	11/36 (30.6)	0.086
4	8/24 (33.3)	24/50 (48.0)	0.346	17/54 (31.5)	1	4/16 (25.0)	0.729
5	6/12 (50.0)	17/26 (65.4)	0.481	13/36 (36.1)	0.501	0/7 (0)	**0.044***

*P-value < 0.05, compared with control group, [a] Pearson's Chi-squared test

diseases including COVID-19 as reported in previous studies[15–19] interventions on physical distancing are scarce as a limited number of studies additionally investigated the factors affecting physical distancing.

When assessing the compliance on physical distancing at marking point 3, flashing red- light (73.0%, p-value = 0.011) could significantly increase customers practicing physical distancing compared to the control (47.6%). There were studies on the effect of flashing lights on behavioral change. The results supported that flashing lights were highly visible to draw enough attention with the potential to induce positive attitudes and a level of behavioral change, and attention.[10–12] Moreover, Hill and Barton (2005) described the mechanism of the red effect, is that dressing red increases one's dominance, aggressiveness and testosterone and finally improves competitive outcome.[9]

The use of flashing red-light was appropriate with the university canteen setting. The red color was in contrast to the floor and the flashing light could draw attentions since there was ambient light without any stronger light within the setting.

In the speech alarm intervention, the compliance on physical distancing significantly increased 2.0% compared

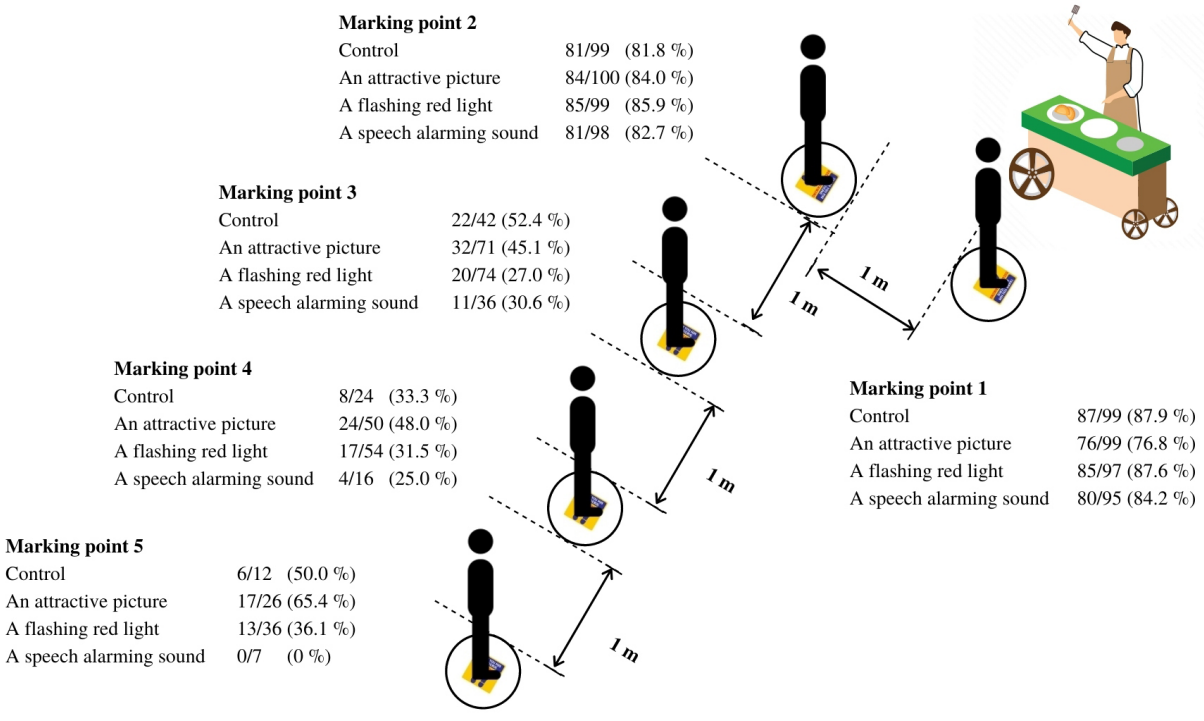

Fig 2. Overall failure of physical distancing compliance.

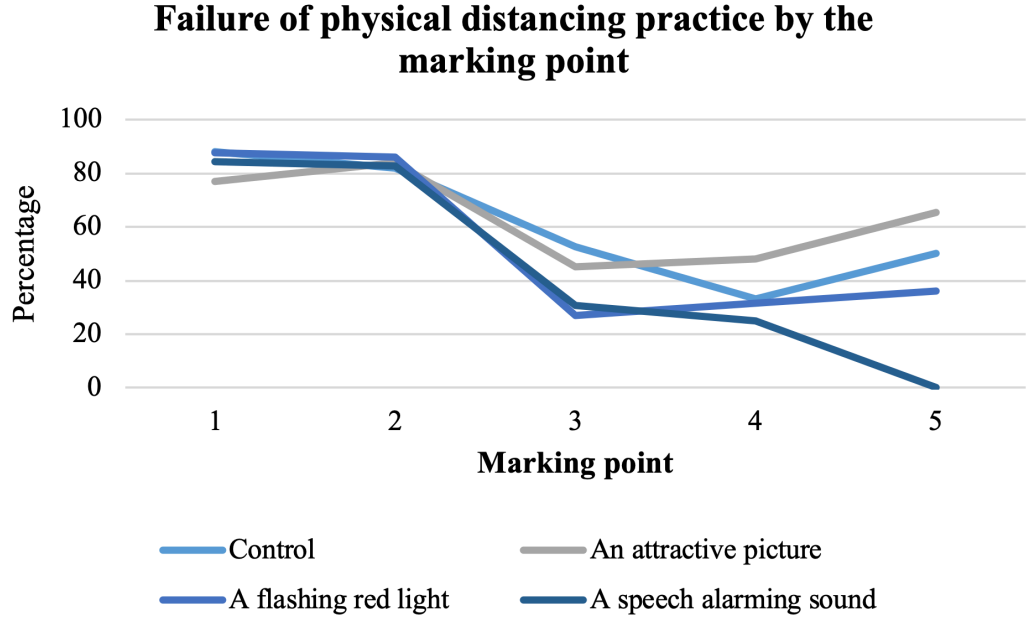

Fig 3. Failure of physical distancing practice by the marking point.

to the conventional one. There were two studies on the effect of using auditory modality on compliance. The results demonstrated that presenting warning information using auditory modality may also lead to greater warning attention and compliance.[13,14]

In the attractive picture intervention, the compliance in physical distancing improved 3.0%. The crying-face of an adorable COVID-19 picture painted in pink could bring out the cute emotion of customers. Jones et al.[7] recorded and written about the cute-emotion is mainly a response to neotenic or baby-animal characteristics, such as big round eyes, small size, and softness. Commercial enterprises intentionally utilize adorable characteristics to generate cute-emotion responses by their customers

as it is such a powerful and effective approach. As in our setting, with the use of cute-emotion approach, the majority of adult customers could consequently perceive and positively respond to an attractive picture. Besides the control, the COVID-19 Figure tended to enhance the level of self-awareness by reinforcing the correlation between practicing physical distancing and the prevention of ongoing COVID-19 pandemic.

Limitations

Our largest limitation was the inadequate sample size since our study was part of the family medicine course, which had a short timeline for performing this study and the data collection from CCTV was a time-consuming process. However, our research team could not reach an adequate sample size regarding the marking point 4 and 5. This interfered with the validity of data interpretation. In addition, the results could be influenced by the researcher's personal judgement contributing to information bias, even though there were valid data collection protocol for observers and inclusion criteria documented to diminish this bias. Regarding to the small sample size at some marking points, and the period of data collection during zero COVID-19 cases, we dictate caution in the interpretation of these findings. In future studies, it would be advisable to increase number of times for each intervention exposure and extend the data collection period to obtain adequate sample size, in which subsequent subgroup analysis may provide a more significant outcome.

The second limitation was the inappropriate period of study. The study was held during the period with zero new COVID-19 infection reported in Thailand so that the participants' level of awareness altered. The researcher provided intervention correlating between COVID-19 situation and disease prevention. Though, it was inadequately promoting a behavioral change. Therefore, the result from our interventions might not characterize the participants' behavior during high incidence rate of infection episode. With time restriction, our interventions were not employed on scheduled workdays so that the characteristics of participants in the control group were varying and could not entirely be used to describe the effect of factors affecting physical distancing compliance. Lastly, the study was conducted at university canteen, mainly composed of university students. The result of physical distancing compliance among general population in this setting might not be widely applicable. Our interventions were simple and affordable to install and used locally available materials. Henceforward, future studies should be performed in other settings among general population and containing a large number of participants would compare the behavioral impact of our interventions. Another explanation for limited generalizability of the outcomes is the pattern of queueing process which is unique in each setting. According to the size of intervention and a criterion to keep 1-meter distance apart, the previous compatible pattern of marking points was changed. The customers were not accustomed to the provided interventions. In consideration with the battery capacity, the extended period of data collection might not be practical for flashing red-light. Moreover, there was a need of experts to create further interventions.

CONCLUSION

In this quasi-experimental study of 400 participants over the effectiveness of innovative device on physical distancing compliance in the university canteen setting, the data suggests that innovative devices were statistically insignificant to enhance physical distancing compliance. The compliance was statistically significant to enhance at some marking points. Future studies containing a large number of participants would compare the behavioral impact of our interventions. The integration of the use of media into conventional interventions provides an alternative way of enhancing physical distancing.

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Conflict of interest: The authors do not have any conflicts of interest to declare.

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Sudden Sensorineural Hearing Loss among COVID-19 Patients-Our Experiences at an Indian Teaching Hospital

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ABSTRACT

Objective: To study the sudden sensorineural hearing loss (SSNHL) in patients with COVID-19 infections.

Methods: This is a retrospective descriptive study. There were 16 COVID-19 patients participated in this study those presented with sudden sensorineural hearing loss (SSNHL). The study was done between March 2020 to August 2020. All these patients were diagnosed with SARS-CoV-2 infection with help of the reverse transcription polymerase chain reaction (RT-PCR) testing.

Results: Out of 652 COVID-19 patients, 16 (2.45%) patients diagnosed with SSNHL. Out of 16 patients with SSNHL, 11 (68.75%) were male and 5 (31.25%) were female with male to female ratio of 2.2:1. The age ranges of the participants were 38 to 72 years with a mean age of 48.42 years. There were 14 (87.50%) patients were presented with unilateral and 2 (12.50%) were presented with bilateral SSNHL. There were left sided SSNHL in 9 patients (56.25%) and right side SSNHL in 5 patients (31.25%).

Conclusion: There should be continuous monitoring of the SSNHL. Tracing COVID-19 infection is needed to ensure a detailed understanding of this inner ear pathogenesis.

Keywords: COVID-19 patients; SARS-CoV-2; sudden sensorineural hearing loss (Siriraj Med J 2021; 73: 77-83)

INTRODUCTION

Hearing loss has a vital role in speech and communication and can cause an invisible handicap of the affected person and psychological solitary confinement. The World health organization (WHO) has documented that around 360 million people with disabling hearing loss in the world which proved that more than half of the persons with a hearing handicap can be prevented by early diagnosis and treatment.[1] The association between the COVID-19 infection and sudden sensorineural hearing loss makes intuitive sense, given the neuropathic manifestations of the inner ear and auditory nerve. Although certain viral infections cause hearing loss, there is still unknown whether COVID-19 infection leads to auditory dysfunction or not. COVID-19 infection is highly contagious and seen in the respiratory system due to the novel virus SARS-CoV-2 (Fig 1).[2] There are several causes for hearing loss in clinical practice. Viral etiology is often ignored during assessing hearing loss. Viral infections like cytomegalovirus (CMV) cause congenitally acquired hearing loss and many other

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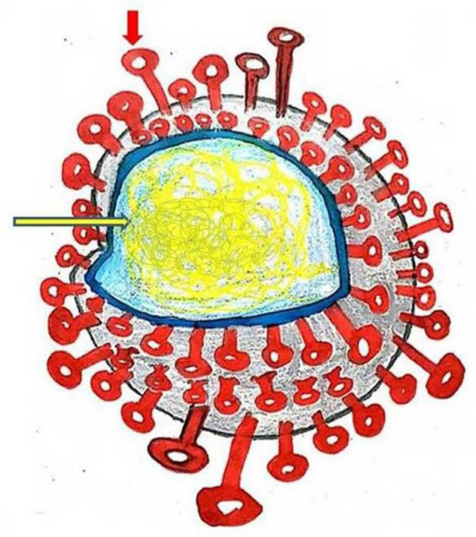

Fig 1. Structure of the COVID-19 virus (Red arrow is spike protein over lipid membrane, yellow arrow indicates RNA).

viruses are also associated with congenital or acquired hearing loss.[3] Typically viruses cause sensorineural hearing loss. The viral etiology is often proposed for the etiology of otosclerosis.[4] HIV infection can cause conductive hearing loss through fungal and bacterial infections which are frequent after immunosuppression by the virus. The hearing loss by viral etiology can be mild or severe to profound, unilateral or bilateral. In COVID-19 infections, the development of the SSNHL is rare and the exact etiopathology is difficult to explain in this current pandemic. Here this study is relating to the impact or incidence of the novel corona virus infection on the auditory system with the manifestation of SSNHL.

MATERIALS AND METHODS

This retrospective study was conducted at a tertiary care teaching hospital. The study was done during the period between March 2020 to August 2020. This study was approved by the Institutional ethical committee (IEC) with reference number IEC/IMS/SOA/21/12.3.2020. The COVID-19 patients with sudden sensorineural hearing loss (SSNHL) were participated in this study. The patient details were collected from the patient files of the hospital. Informed consent was obtained from the patients those participated in this study. The audiological symptoms were searched from 652 COVID-19 patients at COVID-19 hospital. The eligible candidates were presented with SSNHL. SSNHL was defined as a hearing loss of more than 30 decibel at three consecutive frequencies at least over a period of less than 3 days.[5] Audiological assessments were done by tuning fork test, pure tone audiometry and tympanometry. All the COVID-19 patients those complained of sudden hearing loss were evaluated by otolaryngologists. Those patients discharged from the COVID hospital with a history of SSNHL and confirmed with investigations were also included in this study. All the patients those participated in this study were tested positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 before admission to the COVID hospital. COVID-19 patients with a previous history of hearing loss and any association such as a history of the ototoxic drugs, noise exposure, age related hearing loss, measles, mumps, rubella, meningitis, syphilis, hypertension, thyroid diseases, diabetes mellitus and kidney diseases were excluded from this study. COVID-19 patients with a history of oral hydroxychloroquine taken previously were excluded from this study. Proper history taking and otological examinations including tuning fork tests were done in all the participants before audiological testing. All the participating patients were underwent pure tone audiometry testing, tympanometry and Otoacoustic emissions (OAE) which were done by an audiologist in a soundproof room. The pure tone audiometry was performed with all safety protocols for the COVID-19 pandemic. Pure tone audiometry findings were done with frequency at 250, 500, 100, 2000, 4000 and 8000Hz using Telephonics TDH39 earphones. The audiometric assessment was conducted in a sound treated room, using GSI 61 clinical audiometer. The average value for the hearing threshold at 500Hz, 1000Hz and 2000Hz was calculated. The pure tone average greater than 25 decibels was considered as hearing loss. Tympanometry was carried out with help of the amplaid 775 middle ear analyzer to rule out middle ear pathology. Before performing the pure tone audiometry, tuning fork tests were done by using 256,512 and 1024 Hz tuning forks. Transient evoked otoacoustic emissions (TEOAEs) were recorded in all participating patients with help of the Madsen Capella Analyzer. The stimuli in TEOAEs were a nonlinear click of about 80 dB peak SPL in the ear canal. The spectrum analyzer was stimulated as 4ms after the presentation of the stimuli for avoiding the ringing of the input stimuli and the temporal window was set at 20ms. Magnetic resonance imaging (MRI) of the brain was done in all the cases with SSNHL to find out the status of the inner ear. In this study, all the data were recorded and analyzed by using Statistical Package for Social Science (SPSS) software, v20.

RESULTS

In this study, 652 COVID-19 patients were evaluated to find out hearing loss. Out of 652 patients, 16 (2.45%) patients were diagnosed with SSNHL. These 16 patients underwent an audiological assessment at the otolaryngology

department. All the sixteen patients presented with SSNHL after confirmation with pure tone audiometry. There were 11 (68.75%) were male and 5 (31.25%) were females with male to female ratio of 2.2:1. The age ranges of the participating patients were 38 years to 72 years of age with a mean age of the study patients was 48.42 years. There were 7 patients (43.75%) in the age range of 38 to 50 years and 9 patients (56.25%) in the age range of 51 to 72 years (Table 1). All of these patients were positive with RT-PCR for SARS-CoV-2. There were 9 patients (46.42%) with SSNHL in the left ear, 5 patients (31.25%) with SSNHL in the right ear and 2 patients (12.50%) had bilateral sudden SSNHL. All these patients were presented with symptoms of sudden hearing loss and heaviness in the affected ear. Out of 16 patients, 5 (31.25%) presented with tinnitus and 3 (18.75%) presented with vertigo (Table 1). In this study, 13 patients (81.25%) presented with SSNHL along with respiratory symptoms such fever, cough, throat pain, rhinorrhea, loss of smell, dysgeusia and hearing loss whereas 3 patients(18.75%) were presented with only hearing loss and heaviness in the ear during stay at the COVID hospital. There were no respiratory symptoms among 3 patients (Table 1). Tuning fork tests were performed in all cases. In tuning fork test with 512 Hz tuning fork, the Weber test showed lateralization towards the right side with patients with left sided hearing loss and towards the left side in case of right sided hearing loss. The tympanometry test revealed a type-A tympanogram in 13 patients (81.25%), indicating normal middle ear whereas the type-C tympanogram was found in 3 patients (18.75%) which indicates eustachian tube dysfunction. In this study, 14 (87.50%) showed unilateral SSNHL and 2 (12.50%) showed bilateral SSNHL. In this study, 11 patients (68.75%) showed high frequency hearing loss in pure tone audiometry whereas the rest 5 (31.25%) showed low frequency hearing loss. Out of the 16 patients, 15 (93.75%) showed reduced amplitude of the TEOAEs (Table 2). In 10 patients (62.50%) with SSNHL, MRI with contrast showed enhancement of the cochlea on the affected side (Fig 2). All the diagnosed cases of SSNHL were treated with oral prednisolone 1mg/kg/day in the tapering dose for 3 weeks. Along with oral prednisolone, oral vitamin-B with folic acid complex and with proton pump inhibitor was taken by patients daily. As all these patients were at the COVID hospital and isolation in the home, proper evaluation and follow up were not done properly. The hearing status of the patients was obtained by a telephonic conversation with the patient. There was the recovery of the hearing in 9 patients (56.25%) after appropriate and prompt treatment. The recovery of hearing loss to normal was confirmed by pure tone audiometry.

DISCUSSION

COVID-19 is an infection of the respiratory tract caused by a novel virus called severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).[2] Corona viruses causing COVID-19 are encapsulated or enveloped positive strand RNA virus which can be classified into four genera such as alpha, beta, delta and gamma. Out of these four types, alpha and beta are known to infect human beings.[6] The first case of COVID-19 infection was reported in Wuhan, China in late December 2019 which now covered all over the world.[7] By 27th February 2020, more than 82,000 COVID-19 positive cases with death more than 2800 have been reported of which approximately 95% the positive cases and 97% of deaths were in China.[8] By March 26th, 2020, there were 462,684 patients with COVID-19 infections reported in 199 countries.[9] By the 16th August 2020, over 1.8 million new cases of COVID-19 and 39000 new death were reported by WHO and this gives the cumulative total to 21.2 million confirmed cases of COVID-19 including 761000 deaths.[10] The novel SARS-CoV-2 virus is transmitted from one person to

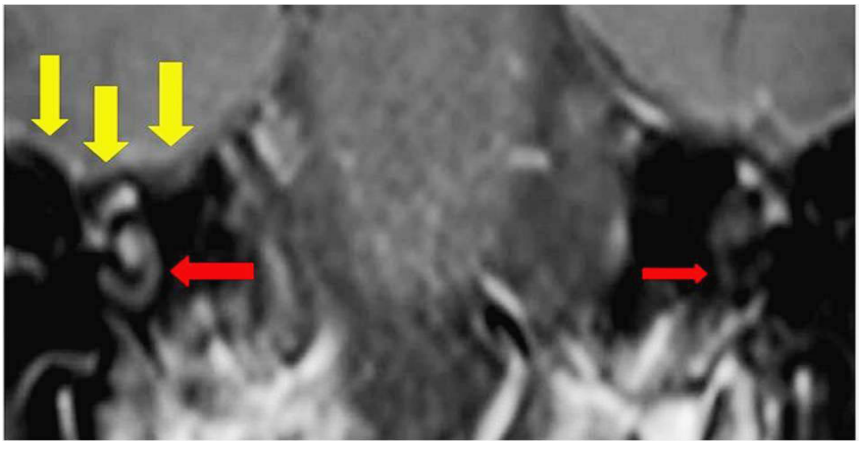

Fig 2. MRI with coronal view in T1 post-contrast sequence showing increased contrast enhancement of the right side cochlea (thick red arrow) and the left side cochlea (thin red arrow) showing normal enhancement. Meninges at the base of the temporal lobe at the right side showing linear enhancement (yellow arrows).

TABLE 1. Outcomes of RAI therapy at the 6 to 9-month follow-up.

Characteristics	n=16	Percentage (%)
Gender		
Male	11	68.75
Female	5	31.25
Age group		
38-50	7	43.75
51-72	9	56.25
Sudden sensorineural hearing loss (SSNHL)	16	100
SSNHL in right ear	5	31.25
SSNHL in left ear	9	56.25
SSNHL in both ear	2	12.5
Tinnitus	5	31.25
Vertigo	3	18.75
Sudden hearing loss with respiratory infections (Fever, cough, throat pain, throat pain, cough, rhinorrhea, loss of smell and dysgeusia)	13	81.25
No respiratory symptoms but with hearing loss and heaviness in the ear	3	18.75

TABLE 2. Audiological profile of the COVID-19 patients.

Parameters	Number of the patients (n=16)	Percentage (%)
Pure tone audiometry		
Unilateral SNHL	14	87.50
Bilateral SNHL	2	12.50
Tympanogram		
Type A	13	81.25
Type C	3	18.75
TEOAE		
Reduced amplitude	15	93.75

another by respiratory droplets or contact with an infected person. The symptoms of the COVID-19 infection may appear after 2 to 14 days following the exposure (based on the incubation period of COVID-19 virus). The clinical presentations of the COVID-19 patients are fever, cough, fatigue, gastrointestinal symptoms, sore throat, headache, olfactory and taste dysfunctions.[11] In this study, 13 patients (81.25%) presented with SSNHL with respiratory symptoms such as fever, cough, throat pain, cough, rhinorrhea, loss of smell and dysgeusia whereas 3 patients (18.75%) were presented with only hearing loss and heaviness in the ear without any respiratory symptoms. The elderly patients and the persons with co-morbid conditions or immunocompromised conditions are prone to serious outcomes such as acute respiratory syndrome (ARDS) and cytokine storm.[11] The neurological manifestations associated with SARS-CoV-2 infections are nonspecific symptoms such as loss of smell, loss of taste, dizziness, ataxia and peripheral nerve involvement. The etiopathology for SSNHL includes neuritis of the cochlear nerve by the virus, inflammation of the cochlea by viral infection and the perilymphatic tissues. The evidence of sensorineural hearing loss (SNHL) was also documented with infections of certain viruses such as herpes simplex virus, measles virus, hepatitis virus, rubella virus, mumps virus, human immunodeficiency virus (HIV), Lassa virus and enteroviruses.[12] Incidence of SNHL is 12 to 19% cases in rubella infections, up to 33% in infections with herpes simplex virus, 0.1 to 3.4% in measles, 0.005 to 4% in mumps,6 to 23% (asymptomatic patients) to 22- 65% (symptomatic patients in cytomegalovirus infections and 27.5 to 33.5% in HIV infections.[13] Certain viruses like rubella and cytomegalovirus infections cause congenital SNHL which are not documented in case of COVID-19 infections. There are three mechanisms associated with the incidence of SSNHL in viral infections such as: (1) neuritis caused by viral infection of auditory nerves or cochlea; (2) viral involvement of the perilymphatic tissues; (3) Stress response occurred by cross reactions of the antigens of the inner ear.[14] Study on the animal was showing viral infections causing hearing loss through directly affecting labyrinth or indirectly through cerebrospinal fluid.[15,16] If any patients develop the SSNHL and seek consultations at the outpatient department of Otorhinolaryngology, they should require RT-PCR testing to rule out SARS-CoV-2 infection. There are several reports regarding the neurological involvement by the SARS-CoV-2 infection but not much report with SSNHL. One study reported with non-specific neurological symptoms ataxia, dizziness, olfactory or gustatory dysfunctions and neuralgia due to peripheral nerve involvement by SARS-CoV-2.[17] This study tried to find out the specific SSNHL among the COVID-19 patients. The better way to study the etiology is autopsy which seems to provide definite evidence towards a better understanding of the nerve involvement by the virus. In past SARS-CoV and Middle East respiratory syndrome corona virus (MERS-CoV) outbreak, cerebrospinal fluid studies revealed the presence of the nucleic acid and neural involvement in an autopsy study.[18,19] Autopsy studies of the patients with SARS-CoV-2 had shown the hyperemic and edematous brain tissue along with degeneration of the nerves.[20]

The SARS-CoV-2 enters the airways and invade the cell by penetrating the angiotensin-converting enzyme 2 (ACE2) receptors at the lungs. Once the cytosolic pH decreases, the binding of the ACE 2 to the virus will be easier.[21] As the cytosolic pH decreases with the increase of age, the virus can lead to easy and heavy infections in elderly persons.[21] The SARS-CoV-2 can attach to the hemoglobin and penetrate the red blood cell/erythrocyte.[22] Then this virus can be transported with erythrocyte or vascular endothelium and affect all the tissues with ACE2. There are abundant ACE2 at the brain and medulla oblongata.[23] The auditory center is situated at the temporal lobe of the brain where ACE2 is present. Over expression of ACE2 in the brain except at the medulla oblongata has a positive effect like anti-oxidant and anti-inflammatory and regulator of the blood pressure.[23] But, if the cytosolic pH is less, raised ACE2 leads to an increase in the viral load.[21] So, the SARS-CoV-2 infection may progress to more severity. The virus release excess cytokines at the auditory center of the brain and its surroundings. So, it can cause permanent damage to the auditory center of the brain by raising oxidative damage. If there is excessive activation of the virus at the auditory center, can cause it hypoxic and lead to damage. The virus has also nature to cause an increase in thrombosis risk. SARS-Cov-2 can infect the veins which drain the auditory center so can make a clot of these vessels. This clot blocks the blood vessels and affects the hearing center, leading to ischemic damage. Because of the impaired vascularity and susceptibility for thrombosis in elderly age people, hearing problems may happen by this above mechanism. There may be associated with inner ear symptoms like tinnitus and vertigo may be found. In this study, 5 patients (31.25%) presented with tinnitus and 3 patients (18.75%) presented with vertigo.

Tuning fork tests, pure tone audiometry, tympanometry and Otoacoustic emissions (OAE) were done to evaluate the SSNHL in our study patients with COVID-19 infection. The type and degree of hearing loss were assessed by

the tuning fork test and pure tone audiometry. In this study majority of the cases of SSNHL (68.75%) show high frequency hearing loss in pure tone audiometry. In this study, 87.50% patients showed unilateral SSNHL and 12.50% cases showed bilateral SSNHL. In this study, 11(68.75%) showed high frequency hearing loss in pure tone audiometry. Tympanometry was done to assess the middle ear pathology. In this study, 13 patients (81.25%) showed type-A tympanogram and 3 patients (18.75%) showed type-C tympanogram. Type-A tympanogram indicates normal middle ear whereas type-C indicates eustachian tube dysfunction. The airway infections in COVID-19 patients specifically infections or inflammations at the nasopharynx cause Eustachian dysfunction and responsible for type-C tympanogram. Otoacoustic emissions represent a form of energy produced from the outer hair cells of the cochlea. Otoacoustic emissions can be spontaneous (SOAEs), evoked by transient stimuli like clicks or tone bursts (TEOAEs). TEOAEs are not invasive and can be easily performed. For performing TEOAEs, the time is short, low cost and high sensitivity.[24] In this study, 15 patients (93.75%) showed reduced amplitude in TEOAE which indicates subtle deterioration of the outer hair cell functions of the cochlea. The magnetic resonance imaging (MRI) with the contrast of the brain and inner ear may show the inflammatory changes at the cochlea and auditory center. Even cochlear ossification may be found because of the inflammation. In this study, 62.50% of patients showed signs of inflammation at the cochlea in MRI. Thorough investigations should be done to find out the exact etiology of the SSNHL and using other treatment options in COVID-19 positive patients can prevent such undesirable complications.

It is challenging for a clinician to identify the etiology as COVID-19 infections for SSNHL and start appropriate treatment to get maximum clinical recovery with minimal side effects and complications. Corticosteroid is an important first line drug for the treatment of the SSNHL.[25] In this study, all the diagnosed cases of SSNHL were treated with oral prednisolone in the tapering dose and vitamin-B with folic acid complex and with proton pump inhibitor daily. However, the use of the corticosteroids in the SARS-CoV-2 infections as in other viral infections, can lead to increased severity of the infection and cause delayed clearance of the viral infections.[26] In this study 9 patients (56.25%) showed complete resolution of hearing loss/normal hearing and became normal with treatment by corticosteroids. In non-COVID patients, the rate of recovery from SSNHL after treatment in the first week of disease onset, within 2 weeks and beyond 3 months is 87%,52% and <10% respectively.[27,28]

CONCLUSION

Patients with COVID-19 infections have a chance of hearing loss specifically sudden sensorineural hearing loss. In our study, the incidence of SSNHL among COVID-19 patients was 2.45%, where the majority of them were associated with respiratory symptoms. The exact role of the pathogenesis of the SSNHL in COVID-19 infections is not well defined. We would like to recommend routine screening of all the COVID-19 positive cases with pure tone audiometry, tympanometry and otoacoustic emission for early diagnosis of the SSNHL and prompt treatment or rehabilitation. In our study, 56.25% patients with SSNHL recovered with prompt and appropriate treatment. Awareness regarding SSNHL in COVID-19 patients is often crucial in the current pandemic. Early identification of the COVID-19 patients with isolation and early initiation of the targeted treatment for the patients helps to reduce the incidence of the SNHL. A high level of vigilance and assessment of the sudden sensorineural hearing loss in COVID-19 patients require urgent treatment for the revival of hearing. The sudden SNHL may be the only symptom in COVID-19 patients. Awareness of this presentation in COVID-19 patients is often crucial in this current pandemic. Isolation ad early treatment for COVID-19 patients may give a good outcome. This study surely brings awareness among the clinicians and researchers to look for SARS-CoV-2 infections in patients with SSNHL.

Study limitation

This study has a relatively small sample size due to the rarity of the clinical outcome (sudden sensorineural hearing loss) in COVID-19 infections which may limit the outcome of the above interpretation. Although the sample size is small, the result of this study is an important message for the public health point of view to isolate the SSNHL with COVID-19 patients. However, the development of the SSNHL in COVID-19 patients in this study will surely encourage further research.

Conflict of interest: NIL

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Comparison of Adjunctive Treatment with IgM-Enriched IVIG and Antibiotics Alone in Treatment of Neonatal Sepsis

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ABSTRACT

Objective: The primary objective of this study was to compare the clinical and laboratory outcomes and the mortality rate of neonatal sepsis treated with antibiotics and IgM-enriched IVIG as adjunctive therapy versus antibiotic alone. In addition, the secondary objective was to determine the morbidities and safety following the IgM-enriched IVIG treatment and the duration of mechanical ventilation and length of hospital stay.

Methods: A retrospective cohort study was conducted between January 2016 to December 2018 in Naresuan University Hospital, Thailand. All eligible neonates were divided into 2 groups. The control group received antibiotics alone. The intervention group received both antibiotics and IgM-enriched IVIG. The clinical, laboratory parameters and morbidities were collected and compared.

Results: There were 28 neonates enrolled in the study. There were 14 in each group. In the intervention group, after receiving the 3-day course of IgM-enriched IVIG concurrently with antibiotics, the patients had significantly decreased respiratory rates (p=0.022), increased mean arterial pressure (p=0.049) and increased serum pH (p=0.017). The incidence of intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia and patent ductus arteriosus in preterm neonates were not found to be significantly changed in both control and intervention groups. No adverse effects recorded.

Conclusion: The use of IgM-enriched IVIG as adjunctive treatment in neonatal sepsis showed evidence of improvement in some clinical and laboratory parameters in neonates presented with hypotension and DIC. The mortality rate improvement was inconclusive and the use of IgM-enriched IVIG was not found to reduce morbidities in preterm neonates.

Keywords: Neonatal sepsis; intravenous IgM-enriched IVIG; intravenous immunoglobulin; antibiotics (Siriraj Med J 2021; 73: 84-91)

INTRODUCTION

In 2015, the World Health Organization (WHO) reported that there were almost 2.6 million newborn deaths per year and most of them were caused by neonatal sepsis.[1] The Expert Meeting on Neonatal and Pediatric Sepsis in 2010 defined that neonatal sepsis is a condition of which clinical manifestations and laboratory investigations compatible with infection, although no evidence of infection (through microbiological cultures or polymerase chain reaction (PCR).[1] Premature birth and newborn with extremely low birthweight are prone to have a severe infection. Moreover, premature neonates are susceptible to pathogens especially from gram-negative bacteria requiring maternal serum immunoglobulin G (IgG) for opsonization to activate phagocytic activity. However, maternal serum IgG is inadequate in premature neonates and the immune system,

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integumentary system, and thymus glands are not fully developed.[2] There were some evidence reported that the use of intravenous immunoglobulins (IVIG) can enhance immunity functions such as opsonization, complement activity, antibody dependent-cytotoxicity, and neutrophil chemoluminescence.[3-6] The newer studies found that the IgM- enriched IVIG have a higher opsonization activity, specific complement activation and phagocytic activity, and more potent agglutination strength than IVIG.[5,7]

The diagnosis of neonatal sepsis is through comprehensive assessment when a newborn exhibits at least two clinical manifestations and two main laboratory findings. Clinical manifestations involve temperature instability, cardiovascular instability, skin and subcutaneous lesions (petechial rash, sclerema), respiratory instability, gastrointestinal disturbances, and other non-specific symptoms such as irritability and hypotonia. The main laboratory findings include but not limited to leukopenia or leukocytosis, increased immature to total neutrophil (I/T) ratio, thrombocytopenia, increased serum C- reactive protein (CRP) or procalcitonin, glucose intolerance and metabolic acidosis.[1]

Timely antibiotic therapy of neonatal sepsis is necessary without the need for positive microbiological cultures to reduce the delay of treatment. Antibiotics are still the most important specific treatment of neonatal sepsis. Various studies reported substantial outcome improvement, especially in severe cases who received intravenous immunoglobulin (IVIG), and IgM-enriched IVIG as adjunctive treatment.[2,4-6,8-19] However, in 2015, the International Neonatal Immunology Study Group (INIS Collaborative Group) and Cochrane Review published that certain studies showed no distinction in mortality rates between newborns with neonatal sepsis treated with antibiotics alone compared to those treated with both IVIG and antibiotics.[20] In contrast, IgM-enriched IVIG proved to considerably reduce the mortality rate of neonatal sepsis when incorporated as a concomitant to antibiotics.[2-3,5,10-11,13,21-22] Newer studies reported positive changes in symptoms and laboratory results among severely underweight newborns with suspected or confirmed neonatal sepsis after receiving IgM-enriched IVIG. IgM-enriched IVIG also found to decrease mortality rates on day 7 and day 28.[13,21-23] Currently, there are very few studies involving the effectiveness of IgM-enriched IVIG with antibiotics for treatment of neonatal sepsis in Thailand.

The primary objective of this study was to compare the clinical and laboratory outcomes and the mortality rate of neonatal sepsis treated with antibiotics and IgM-enriched IVIG as adjunctive therapy versus antibiotic alone. In addition, the secondary objective was to determine the morbidities and safety following the IgM-enriched IVIG treatment and the duration of mechanical ventilation and length of hospital stay.

MATERIALS AND METHODS

The retrospective cohort study was conducted between January 2016 to December 2018. Data were collected from all infants in Naresuan University Hospital, Phitsanulok, Thailand. The Institutional Review Board of Naresuan University (COA No. 296/2019 IRBNo. 0364/2020) approved this study. The inclusion criteria were neonates with a gestational age of 24 to 40 weeks and 500 to 4,000 grams birthweight diagnosed with neonatal sepsis by ICD-10 and admitted in NICU. The exclusion criteria were neonates with prenatal diagnosis of chromosomal abnormalities, congenital anomalies and congenital infections (TORCH). Neonates included in the study received the standard antibiotic treatment whereas some eligible neonates were given intravenous IgM-enriched IVIG (Pentaglobin®) 5 ml/kg per day for three consecutive days as an adjunctive treatment. The subjects were divided into 2 groups. The first group (the intervention group) comprised of neonates who received antibiotics and IgM-enriched IVIG as an adjunctive treatment while the second group (the control group) consisted of neonates who received antibiotics alone. The decision to prescribe an adjunctive treatment depended on the physician's assessment and the family's financial capability. Data records collected contains the demographic details of the infants (gestational age, sex, birth weight, mode of delivery, age at diagnosis of sepsis and age at treatment initiated), maternal antenatal corticosteroid and antibiotic uses, timing of membrane ruptured and maternal chorioamnionitis. The clinical characteristics collected at time of the sepsis diagnosis consists of feeding intolerance, respiratory distress, hypotension and Disseminated Intravascular Coagulation (DIC). The data collected were analyzed according to the source of infection, clinical and laboratory parameters, culture results before and after the treatment in both groups. The clinical and laboratory information obtained from the control group were 48-72 hours after antibiotic administration, whereas, data gathered in the intervention group were 24 hours after the 3-day course IgM-enriched IVIG infusion. Other comorbidities and complications recorded were grade 2 intraventricular hemorrhage, necrotizing enterocolitis, periventricular leukomalacia, and patent ductus arteriosus. Additional data monitored were the duration of mechanical ventilation, length of hospital stay, and mortality rate on the 7th day and 28th

day. The notable IgM-enriched IVIG adverse effects evaluated were hypotension, anaphylaxis, and rashes.

Statistical analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY). Continuous data were shown as mean ± standard deviation (SD). Categorical data were shown as frequency and percentage. The pair t-test was used to compare the results before and after treatment. Independent T-test, Chi-square tests and Fisher's exact test were used to compare data between control and intervention groups. The comparison of changes of parameters between the two groups was performed by mixed linear regression. The absolute differences between the two groups of treatment with the p- value < 0.05 are considered to be statistically significant.

RESULTS

There were 166 neonates diagnosed with neonatal sepsis from 1,860 infants born between January 2016 and December 2018. There were 14 neonates in the intervention group given IgM-enriched IVIG as an adjunctive treatment while the other 152 received antibiotic alone. The 14 neonates in control group were taken from the 152 neonates through by blocked randomization. Table 1 provides the demographic details and information of each group. After comparing between the two study groups, there were no differences found related to patient characteristics and timing of antibiotic received.

Table 2 shows the clinical characteristics at the time of neonatal sepsis diagnosis. These clinical characteristics were quite similar between these two groups. 9 out of 14 (64.3%) patients in the intervention group had hypotension, whereas 2 out of 14 (14.3%) in the control group (p-value 0.007). Disseminated intravascular coagulation (DIC) was frequently found in the intervention group (9 vs. 0 with P-value <0.001). Necrotizing enterocolitis (NEC) and hospital-acquired pneumonia (HAP) were found to be the source of infection in the intervention group (5 vs. 0 with P-value 0.014). Early neonatal sepsis was found more in the control group (9 vs. 14 with P-value 0.014).

After the 3-day course of IgM-enriched IVIG along with antibiotics, patients in the intervention group had significantly decreased respiratory rates (68.18±10.94 vs. 60.80±4.13 with p-value 0.022), increased mean arterial pressure (MAP) (40.36±15.36 vs. 46.43±15.04 with p-value 0.049) and serum pH (7.28±0.11 vs. 7.36±0.09 with p-value 0.017) comparable to the value prior to treatment. In the control group, white blood cell count was significantly decreased after antibiotic treatment (15,709.29±1,601.15 vs. 10,792±1,206.88 with p-value 0.041) as shown in Table 3.

There was no remarkable difference in microbiological culture values after treatment was administered in both study groups (Table 4).

Duration of mechanical ventilation and length of hospital stay in the intervention group were found to be longer than those in the control group (50.85±12.62 vs. 8.14±5.71 with P- value 0.007, 97.00±16.93 vs. 21.79±8.80 with P-value 0.001). No difference in mortality rate at day 7 and day 28 was recorded in both groups (0(0%) vs. 0(0%)). After the mixed linear regression analysis, the estimated difference between the intervention and control groups on account of the duration of mechanical ventilation and length of hospital stay (adjusted for changes in respiratory rate, mean arterial pressure, and pH) was 29.03 days (95%CI -7.10 to 65.17, p = 0.108) and 42.98 days (95%CI -1.99 to 87.95, p = 0.060) respectively, resulting to insignificant change between groups as shown in Table 5.

After performing subgroup analysis, the results of morbidities in preterm neonates were shown in Table 6. The incidence of intraventricular hemorrhage at least grade 2, necrotizing enterocolitis, periventricular leukomalacia and patent ductus arteriosus were not found to be significantly changed in both groups.

No adverse effects consisting of hypotension, anaphylaxis and rash found during and 24 hours after IgM- enriched IVIG therapy.

DISCUSSION

This study was initiated to evaluate the efficacy of IgM-enriched IVIG as adjunctive treatment for neonatal sepsis in Thailand. A previous study conducted by Kola E, et al. showed that neonates with sepsis who received IgM-enriched IVIG had a significant increase in survival rate and a significant reduction in length of hospital stay as compared to neonates who were given antibiotics and placebo.[12] In Capasso et al. study, similar findings were also reported regarding the IgM-enriched IVIG therapy in infants and showed a reduction in short - term mortality in neonates (OR 0.16; 95% CI 0.3-0.7).[2,13,21] In the meta-analytical study conducted by Kreymann et al., they found that from 12 trials on 710 neonates, polyvalent immunoglobulins (IgGAM) had a significant effect on mortality in sepsis and septic shock.[5] On the other hand, Ohlsson A and Lacy JB reported no evidence for the reduction of mortality or other relevant outcomes of 3,973 neonates who received IVIG. In addition, subgroup analysis for IgM- enriched IVIG from this study was performed (N = 266) and there was no indication that

TABLE 1. Demographic data.

Characteristics	Intervention n=14 (%)	Control n=14 (%)	P-value
Gestational age (week)			
< 37	12 (85.7)	10 (71.4)	0.357
≥ 37	2 (14.3)	4 (28.6)	
Sex			0.131
Male	9 (64.3)	5 (35.7)	
Female	5 (35.7)	9 (64.3)	
Birth weight (gram)			0.115
< 2,500	11 (78.6)	7 (50.0)	
≥ 2,500	3 (21.4)	7 (50.0)	
Mode of delivery			0.303
Normal labor	3 (21.4)	1 (7.1)	
Cesarean section	10 (71.4)	13 (92.9)	
Vacuum extraction	1 (7.2)	0 (0.0)	
Antenatal corticosteroid received	7 (50.0)	2 (14.3)	0.103
Maternal prolonged PROM (>18 hour)	1 (7.1)	5 (35.7)	0.065
Maternal received antibiotic	2 (14.3)	6 (42.9)	0.094
Maternal chorioamnionitis	2 (14.3)	0 (0.0)	0.142
Timing of antibiotic received (hour)	7.77±2.85	8.43±2.87	0.871

its use would significantly reduce mortality in infants with suspected infection (Risk ratio 0.68; 95% CI 0.39-1.20).[20] However, the results of this study only revealed the mortality outcome.

Our study did not find a difference in the mortality rate as there were no recorded deaths on day 7 and day 28. The length of hospital stay was longer in the intervention group. This may be caused by the more severity (hypotension and DIC) in the intervention group at time of sepsis. However, the duration of mechanical ventilation and the length of hospital stay were insignificant between groups as revealed in the mixed linear regression analysis.

In a study conducted by Salihoglu O, et al., I/T ratio and CRP level were significantly decreased and a substantial increase in the pH and base excess were recorded following IgM- enriched IVIG therapy.[22] This result is similar to this study as the intervention group had significantly decreased respiratory rates, increased mean arterial pressure (MAP) and serum pH after treatment. Whereas no significant decline in preterm morbidities was observed in both groups.

It is inconclusive to state that IgM-enriched IVIG provides benefits to any specific microbial organism as presented in this current study. Furthermore, randomization between groups could not be performed because of the retrospective nature of the study. Thus, it may be difficult to compare the baseline characteristics such as severity of neonatal sepsis between groups. Further prospective study with precise protocols should be conducted to substantiate the results of this current study.

This research study was designed to offer information about the new adjunctive treatment for neonatal sepsis, therefore providing physicians feasible treatment alternatives in the care of patients with neonatal sepsis.

TABLE 2. Clinical characteristics at time of neonatal sepsis diagnosis and source of infection.

	Intervention n=14 (%)	Control n=14 (%)	P value
Clinical characteristics at time of neonatal sepsis diagnosis			
Feeding intolerance	7 (50.0)	5 (35.7)	0.445
Respiratory distress	12 (85.7)	13 (92.9)	0.541
Cyanosis/desaturation	6 (42.9)	5 (35.7)	0.699
Hypotension	9 (64.3)	2 (14.3)	0.007*
Apnea	2 (14.3)	2 (14.3)	1.000
Abdominal distension	6 (42.9)	2 (14.3)	0.094
Jaundice	3 (21.4)	3 (21.4)	1.000
Bradycardia	1 (7.1)	1 (7.1)	1.000
Lethargy	2 (14.3)	1 (7.1)	0.541
Disseminated intravascular coagulation (DIC)	9 (64.3)	0 (0.0)	<0.001*
Source of infection			
Necrotizing enterocolitis (NEC)	5 (35.7)	0 (0.0)	0.014*
Early neonatal sepsis	9 (64.3)	14 (100.0)	0.014*
Septicemia (hemoculture positive)	3 (21.4)	0 (0.0)	0.067
Congenital pneumonia	5 (35.7)	4 (28.6)	0.686
Hospital acquired pneumonia (HAP)	5 (35.7)	0 (0.0)	0.014*

TABLE 3. Clinical and laboratory parameters.

Clinical and laboratory parameters	IgM- enriched IVIG treatment (n=14)			Control (n=14)		
	Before	After	P-value	Before	After	P value
Body temperature (°C)	37.16± 0.78	37.09±0.78	0.727	37.16±0.44	37.29±0.31	0.334
Respiratory rate (bpm)	68.18±10.94	60.80±4.13	0.022*	61.21±10.14	55.79±9.74	0.150
Heart rate (bpm)	169.79±34.22	164.21±12.53	0.520	157.00±22.87	143.00±27.22	0.198
Systolic blood pressure (mmHg)	57.14±17.83	62.43±17.39	0.111	60.14±8.18	60.36±8.88	0.928
Mean arterial pressure (mmHg)	40.36±15.36	46.43±15.04	0.049*	46.29±9.24	45.07±9.64	0.666
Diastolic blood pressure (mmHg)	32.36±14.90	37.43±14.68	0.068	38.50±10.18	36.36±9.60	0.494
SpO_2 (%)	87.79±12.78	91.86±6.32	0.286	95.57±9.20	95.86±8.01	0.923
pH	7.28±0.11	7.36±0.09	0.017*	7.28±0.06	7.34±0.09	0.135
pO_2	41.65±19.40	41.22±14.13	0.940	74.30±18.63	51.60±6.30	0.296
pCO_2	56.43±17.59	46.29±11.00	0.093	42.87±5.62	51.60±19.92	0.146
HCO_3 (mEq/L)	26.36±7.18	25.56±4.07	0.560	20.54±3.28	22.89±4.59	0.182
Base excess	-0.31±2.22	0.77±1.41	0.538	-6.00±3.97	-2.40±4.67	0.062
WBC count (/mm^3)	12,012.14 ±1,897.50	8,472.14 ±2,155.73	0.133	15,709.29 ±1,601.15	10,792 ±1,206.88	0.041*
Platelet count (/mm^3)	191,321.43 ±25,912.66	199,071.43 ±29,303.35	0.812	259,714.29 ±23,819.47	257,555.56 ±42,699.89	0.884
Hemoglobin (g/dL)	12.59±0.50	12.26±0.45	0.658	17.06±2.21	17.23±1.97	0.428
I:T ratio	0.37±0.07	0.17±0.09	0.127	0.25±0.08	0.14	NA
C- reactive protein (mg/dL)	7.83±5.02	11.30±5.70	0.645	1.79±0.89	2.89±0.24	0.401

TABLE 4. Microbiological cultures.

Laboratory	IgM- enriched IVIG treatment (n=14)			Control (n=14)		
	Before n (%)	After n (%)	P value	Before n (%)	After n (%)	P value
Hemoculture			1.000	0 (0.0)	0 (0.0)	NA
Staphylococcus aureus	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Staphylococcus spp.	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Gram negative bacilli	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Sputum culture			0.376			NA
Acinetobacter baumannii	3 (21.4)	4 (28.5)		0 (0.0)	1 (7.1)	
Enterococci spp.	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Pseudomonas aeruginosa	2 (14.3)	1 (7.1)		0 (0.0)	0 (0.0)	
Stenotrophomonas maltophilia	1 (7.1)	1 (7.1)		0 (0.0)	0 (0.0)	
Staphylococcus coagulation negative				1 (7.1)	0 (0.0)	
Urine culture	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Cerebrospinal fluid culture	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Fungus				0 (0.0)	0 (0.0)	NA
Hemoculture for fungus	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Sputum for fungus	0 (0.0)	1 (7.1)	0.733	0 (0.0)	0 (0.0)	NA
Urine for fungus	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

TABLE 5. Outcome measurement.

Outcome measurement	IgM-enriched IVIG treatment (n=14)	Control (n=14)	P- value
Duration of mechanical ventilation (day)	40.33 ±15.82	11.30 ± 7.89	0.108[a]
Length of hospital stay (day)	70.78 ±18.17	27.80 ±11.93	0.060[a]
Mortality rate			
At day 7 (n (%))	0 (0.0)	0 (0.0)	NA
At day 28 (n (%))	0 (0.0)	0 (0.0)	NA

[a] adjusted for changes in respiratory rate, mean arterial pressure, pH

TABLE 6. Morbidities in preterm.

Morbidity	IgM- enriched IVIG treatment (n=12)			Control (n=10)		
	Before n (%)	After n (%)	P value	Before n (%)	After n (%)	P value
Intraventricular hemorrhage grade ≥ 2	6 (50.0)	6 (50.0)	1.000	0 (0.0)	1 (10.0)	0.305
Necrotizing enterocolitis	5 (41.7)	5 (41.7)	1.000	0 (0.0)	1 (10.0)	0.305
Periventricular leukomalacia	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Patent ductus arteriosus	6 (50.0)	5 (41.7)	0.682	0 (0.0)	1(10.0)	0.305

CONCLUSION

Following a 3-day course of IgM-enriched IVIG concurrently with antibiotics, improvements in clinical and laboratory parameters were recorded. Mortality rate was inconclusive as there was no reported patient death on day 7 and day 28. However, improvements on respiratory rates, mean arterial pressure (MAP) and serum pH are beneficial indicators to monitor sepsis in neonates and there were found to be improved after using IgM-enriched IVIG as adjunctive treatment in the neonates presented with hypotension and DIC. Nevertheless, the use of IgM-enriched IVIG was not found to reduce morbidities in preterm neonates.

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Falls among Older Adults with Type 2 Diabetes Mellitus with Peripheral Neuropathy

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ABSTRACT

Objective: The high incidence and prevalence of falls among older people with type 2 diabetes mellitus (ODM) have been documented. The risk factors of falls among ODM were identified as poor diabetic control, diabetic peripheral neuropathy (DPN) and balance impairment. This study aimed to investigate the contribution of DPN to history of falls. The differences of balance performance and lower limb muscle strength among ODM with and without DPN were also explored.

Methods: This cross-sectional study interviewed 112 ODM for their falls occurrences within the previous 6 months. DPN was determined by the score of the Michigan Neuropathy Screening Instrument. Balance performance tests included Clinical Test of Sensory Interaction and Balance (mCTSIB), Functional Reach Test (FRT) and Timed Up and Go Test (TUG). Leg muscle strength was also measured. The logistic regression analysis was performed.

Results: The history of falls was reported 30.6% of ODM with DPN and 10.4% of ODM without DPN. Presenting of DPN influenced falls with odds ratio of 3.46 among ODM. Differences were found of mCTSIB in the condition of eyes closed on firm and foam surfaces, FRT, and TUG between those with and without DPN. Knee extensor strength differed between those with and without DPN.

Conclusion: DPN was more prominent among fallers. Balance performance and leg strength were lower in ones with DPN. Falls prevention programs including balance training and therapeutic exercise to improve balance performance and muscle strength should be emphasized among ODM, especially before the onset of DPN.

Keywords: Balance; diabetic peripheral neuropathy; elderly; falls; type 2 diabetes mellitus (Siriraj Med J 2021; 73: 92-98)

INTRODUCTION

Diabetes mellitus (DM) is a major metabolic condition with several complications causing disabilities among older adults i.e., people with age greater than 60 years. High prevalence of older adults with Type 2 diabetes mellitus (ODM) has been reported globally, 15-22% worldwide[1] and 17.2% in Thailand.[2] Compared with a nondiabetic group, older adults with Type 2 diabetes mellitus (ODM) reported greater falls occurrence[3] and risk of falls.[4] Other important risk factors of falls among ODM include balance impairments and reduced muscle strength.[5] However, studies regarding falls risk among ODM showed inconsistent findings which might be associated with the complications, duration of disease, cognitive function, age and sex differences.[4]

Diabetic peripheral neuropathy (DPN) is a major complication known to be associated with increasing falls and reduced quality of life among ODM.[6] The overall prevalence of DPN among ODM was 28% in the US[7] and 2.82% in Thailand.[8] ODM with DPN exhibited significant deficits in sensory-motor function, postural instability and gait imbalance leading to a high fall incidence.[9] The presence of DPN was associated with poorer balance performance including the Berg Balance

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score (BBS), single leg stance test (SLS) and Timed Up and Go Test (TUG). The severity of DPN reflected by MNSI score was reversely correlated with BBS score and SLS time.[10] Although DPN affects both sensory and motor functions,[11] the sensory deficits specifically exteroception and proprioception are usually more prominent than muscle dysfunction among ODM with DPN.[12] The early clinical picture typically involves altered somatosensory functions, while motor involvement usually manifests in the later stages of DPN.[13] In more severe stages, the motor deterioration presents as unilateral or bilateral muscle weakness and atrophy of the proximal thigh muscles.[14]

The functional fallouts of sensory and motor impairments such as postural instability, unsteady gait and frequent falls were evident among ODM.[10,12,15] These adverse consequences could be inflated in cases of ODM with DPN. However, the effects of DPN concerning falls among ODM still require more evidences. Therefore, this study aimed to determine the contribution of DPN on the history of falls. Balance performance and lower limb muscle strength were also compared between ODM with and without DPN.

MATERIALS AND METHODS

This study employed a cross-sectional, comparative design. The research settings were eight community hospitals in the Mueang, Phuttamonthon, Nakornchaisri and Sampran districts, Nakornpathom province. The inclusion criteria were community dwellers, aged over 60 years and diagnosed with type 2 DM by medical doctors for at least five years. Two hundred and forty-eight (n=247) ODM who were followed up in the diabetes clinics of hospitals nearby their residents were enrolled in the study. All participants were informed about the study procedures and signed informed consent before participating. This study was approved by the Mahidol University Central Institutional Review Board (MU-CIRB 2015/035.0303).

The participants were included if their vital signs including heart rate, blood pressure and respiratory rate were in normal range. The letter chart and visual acuity conversation was used to confirm that all participants had normal vision. They also had no complaints of vertigo and dizziness, could understand and follow verbal instruction and could walk independently at least 10 meters. The exclusion criteria were a history of central nervous system dysfunction, cognitive impairment, lower limb amputation or joint replacement and symptoms affecting walking. One hundred and thirteen ODM were finally included in the study and divided into ODM with DPN (n=36) and ODM without DPN (n=77) groups for analysis. Fig 1 presents the flow of participants.

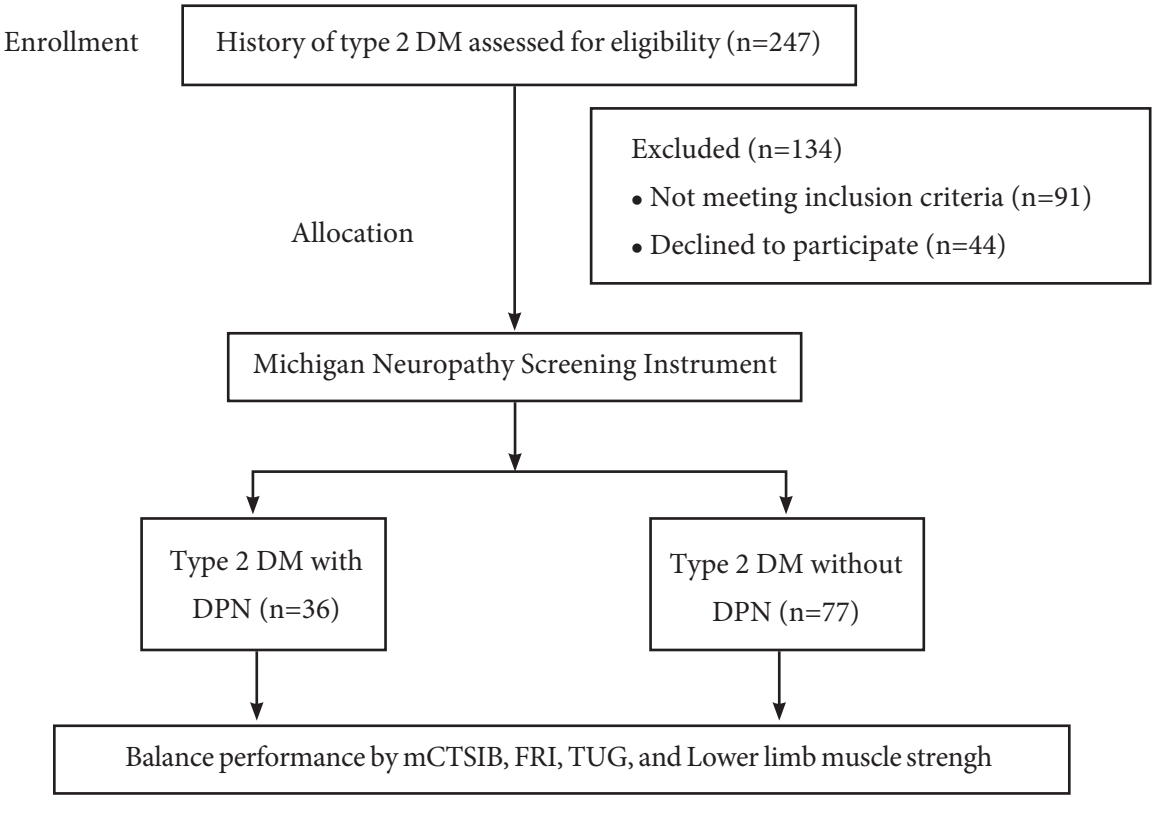

Fig 1. Flow of Participants

Procedures

An experienced physical therapist recruited and screened all participants. The data collection was undertaken by four physical therapists trained by the investigators. A handout for interview and assessment protocols was used to ensure the consistency. Before collecting data, the reliability was monitored using the participants aged 60 and over. A minimum of 0.75 was achieved for the values of Intraclass Correlation Coefficient (ICC) intertester and intratester reliability for all tests.

Participants' information regarding age, sex, history of type 2 DM and duration of DM exposure were recorded. Venous blood was drawn on the day of testing to determine fasting blood sugar (FBS) and hemoglobin A1c (HbA1c).

History of falls within the previous six months based on participant recollection was monitored. Falls was defined as an event resulting to a person coming to rest inadvertently on the ground or floor or other lower level.[16] The Thai version of the Montreal cognitive assessment (MOCA) was used for screening cognitive impairment. This tool had good criterion validity and good internal consistency (cronbach's alpha = 0.914).[17]

The Michigan Neuropathy Screening Instrument (MNSI) Thai version, was used to identify DPN.[18] This instruments has good test-retest reliability (ICC=0.830) and intertester reliability (ICC=0.780-0.869).[18] Positive DPN was determined in cases scoring greater than 2 of 8 of the physical examination part, not including the monofilament test.[19]

Balance performances were evaluated by the modified Clinical Test of Sensory Interaction and Balance (mCTSIB), Functional Reach Test (FRT) and TUG test. The procedures of all measurements were also described as following.

The mCTSIB involves observing a participant's attempt to maintain static balance for 30 seconds. Participants were asked to stand with feet together and hands at sides in four conditions including eyes open (EO) on a firm surface, eyes closed (EC) on a firm surface, EO on a foam surface, and EC on a foam surface. The foam was medium density, 24 inches in width and length and 4 inches in height (SunMate Dynamic System Inc., Leicester, USA). Three trials were performed under each condition.[20] The participants were allowed 60 seconds rest between each condition to diminish the effects of fatigue. Sway was defined as inability to stand with feet together, moving upper extremity, opening eyes, flexing one or both knees, toes, or heels raised from the floor and attempting to hold onto the tester during test execution. This test had good interrater agreements (Kappa = 0.57-0.72).[21]

For the FRT, barefoot participants stood with their right side close to a wall. The feet were apart at shoulder width. The right shoulder was flexed at 90 degrees with the elbow extended. The 3rd metacarpal bone was the landmark used to measure the distance between starting and ending points. The participants were asked to reach forward as far as possible without taking a step. They were allowed to practice once and performed the FRT twice. The reaching distance comprised the averaged value.[22] The FRT had been reported excellent test-retest reliability (ICC=0.89-0.92) in community dwelling older adults.[23]

For the TUG, the participants sat on a 46-cm height armchair with their back contacting the chair back support. They were asked to stand up, walk 3 meters as quickly and safely as possible, turn around, walk back and sit down. They were allowed to use a gait assistive device as preferred. The timing was started at the instruction "go" and stopped when the participants sat with their back touching back support. They performed the TUG twice, as a practice session and the latter as the test.[24] This test has been reported excellent test-retest reliability (ICC = 0:96-0.98).[25]

For muscle strength, knee extensors, knee flexors, ankle plantar flexors and ankle dorsiflexors were measured using a hand-held dynamometer (Lafayette Instrument Company, IN, USA). All muscle groups were tested in midrange of joint motion. One practice trial was given before measuring each movement. The average of three trials was recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 18 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov Goodness of Fit test was used to test the distribution of the data. Demographic data and health information were compared between groups. The Mann-Whitney U test was used to examine differences of non-normal distributed data, while the independent t-test was used to determine differences of the normal distributed data. The value of $p<0.05$ was considered statistically significant.

The univariate logistic regression model was constructed to identify the association between DPN and the history of falls among ODM. The association of categorical independent variables with balance impairment was assessed using the Chi-square test, and the calibration was performed using the Hosmer-Lemeshow goodness of fit test. Discrimination was determined using the area under the receiver operating characteristics (AUROC) to evaluate overall predictive accuracy of the model.

RESULTS

The characteristics of participants with and without DPN are presented in Table 1. They did not differ in terms of age, proportion of sex, duration of DM, levels of FBS and HbA1C and cognitive function scores. The overall prevalence of falls among ODM was 17.7%. The prevalence of falls in the groups with and without DPN was 30.6% and 11.7%, respectively (Table 1). Statistically, the DPN had contribution on the fall occurrences among ODM with Odds ratio of 3.46 (95% CI: 1.28-9.38, p = 0.015) with the AUROC value of 0.645.

Differences between ODM with and without DPN were observed in two conditions of the mCTSIB, eye close on a firm surface ($p < 0.001$) and eye close on a foam surface ($p = 0.039$), as well as the FRT ($p = 0.022$) and TUG ($p< 0.001$) (Table 2). Of all lower limb muscles tested, only knee extensors strength differed between groups ($p = 0.031$) (Table 2).

DISCUSSION

This study aimed to explore the contribution of DPN on the occurrence of falls and to compare the balance performances and lower limb strengths among ODM with and without DPN. The results showed that DPN was a contributing factor of the history of falls. Poorer balance performances and less knee extensor strength were also observed among ODM with DPN compared with those without DPN.

The history of falls within the previous six months differed between ODM with and without DPN. Statistically, DPN was a significant predictor of falls. ODM with DPN had the odds of having history of falls 3.46 times more than the odds for ODM without DPN with 64.5% prediction accuracy. The results agreed with a previous longitudinal study reporting higher falls occurrences among older adults with neuropathy compared with a matched nonneuropathy group.[26] Other than DPN, patients with diabetes usually developed retinopathy, vestibular dysfunction, cognitive impairment and hypoglycemic events with insulin use which might also contribute to falls.[4] However, the participants in our study had normal visual acuity, no cognitive impairment and did not complain of vertigo and dizziness. Therefore, falls prevalence and balance impairment would be associated with their DPN condition. The phenomenon of increased falls also reportedly presented 3 to 5 years before the neuropathy diagnosis and worsened rapidly over time, rising from 23 to 56% over the course of a longitudinal study.[26] Thus, falls is a crucial problem which should be addressed in the management plan of ODM.

TABLE 1. Characteristics of older adults with type 2 DM with and without DPN (n=113).

	DPN	
Parameters	**Yes (n=36)**	**No (n=77)**
Age (years)	70.42 ± 5.96	68.42 ± 7.10
Sex: male	12 (33.3%)	21 (27.3%)
female	24 (66.7%)	56 (72.7%)
Duration of DM (years)	12.44 ± 6.39	10.68 ± 5.98
FBS (mg/dL)	153.78 ± 64.95	141.38 ± 40.86
HbA1C (%)	8.10 ± 1.63	7.50 ± 1.43
MOCA	20.22 ± 4.329	18.69 ± 3.345
History of falls: Yes	11 (30.6%)	9 (11.7%)
No	25 (69.4%)	68 (88.3%)

Values are presented as mean ± standard deviation or numbers and percentage. *p-value <0.05 significant difference pairwise comparison without DPN group.

Abbreviations: DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; FBS, fasting blood sugar; HBA1c, hemoglobin A1c (glycated hemoglobin); MOCA, Montreal cognitive assessment score

TABLE 2. Lower limb muscle strength and balance performance among older adults with Type 2 DM with and without DPN (n=113).

	DPN	
Parameters	**Yes (n=36)**	**No (n=77)**
Muscle strength (kg)		
Knee extensors	15.01 ± 5.02*	16.93 ± 5.07
Knee flexors	11.06 ± 2.94	10.92 ± 3.36
Ankle plantar flexors	15.51 ± 3.57	16.90 ± 4.87
Ankle dorsiflexors	11.33 ± 2.88	11.78 ± 3.26
Balance performance		
mCTSIB (s)		
Condition 1	28.72 ± 4.90	29.91 ± 0.75
Condition 2	22.39 ± 11.26**	28.93 ± 4.47
Condition 3	22.37 ± 11.37	25.44 ± 8.43
Condition 4	10.15 ± 11.75*	14.63 ± 11.92
FRT (inches)	8.99 ± 2.79*	10.38 ± 3.06
TUG (s)	16.14 ± 6.59**	11.76 ± 3.45

Values are presented as mean ± standard deviation. *p-value <0.05 significant difference pairwise comparison without DPN group. **p-value <0.001 significant difference pairwise comparison without DPN group.

Abbreviations: DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; mCTSIB, modified Clinical Test of Sensory Interaction and Balance; FRT, Functional Reach Test; TUG, Timed Up and Go Test.

Sensory impairment and lower limb muscle weakness are possibly the underlying causes of increased falls in DPN. Somatosensory, visual function and vestibular inputs play an important role in balance control.[27] Due to impaired somatosensory and motor outputs, patients with DPN demonstrated postural instability and gait imbalance leading to higher fall incidence.[9,28] The nerve damage in DPN is characterized by the development of vascular abnormalities with a subsequent decline in oxygen tension and hypoxia.[11] The mutilation progressively alters the sensory and autonomic axons, and later the motor axons, leading to sensory, autonomic as well as motor losses.[11] Other than falls, patients with DPN could also injure themselves from the reduced sensitivity of touch and pain leading to foot ulceration, which could become infected and lead to amputation.[10] However, the diagnosis of DPN is often delayed by the fact that neuropathy often develops slowly over time.[26] Consistent monitoring of glycemic control and the complications are therefore crucial concerns in ODM.

The ODM with DPN in this study also exhibited less knee extensor strength compared with those without DPN. The declined muscle strength of the knee and ankle were reported among people with T2DM with and without DPN compared with the nonDM control group.[29] The isometric performance of the knee extensors was also suggested to be an assessment for fall risk among ODM.[30]

Poorer static and functional balance was observed among ODM with DPN identified by mCTSIB, FRT and TUG. These impairments might also contribute to the increased prevalence of falls in this study. During the mCTSIB, differences in dependency on sensory inputs were identified, i.e., somatosensory during EO and EC on a foam surface,[31] visual during EC on firm and foam surfaces[32] and vestibular by EC standing on a foam

surface.[33] ODM were found to be somatosensory dependent because they presented impaired postural control during somatosensory disruption[34,35] while ODM with DPN lost their balance during deprived visual input.[34] Our results implied an assumption similar to related studies,[34,36] i.e., ODM with DPN were visual dependent because they tended to rely more on visual inputs to compensate for their declined somatosensory inputs. These patients might be able to achieve acceptable postural control using an appropriate compensatory strategy.[37] However, in cases of the other sensory input limitations such as dim light, an irregular trail or presenting of retinopathy and vestibulopathy, the risk of fall among these patients would be even higher.

The static balance reflected by the FRT significantly differed between ODM with and without DPN. Lower FRT values were observed among ODM with somatosensory impairment.[38] The sensory threshold of hallux was reported to be a predictor of reach distance and center of mass displacement among patients with DM.[38] Considering the manner of FRT performance, the strength of lower limb muscles would also influence the test results. In this study, knee extensor muscle strength was reduced among ODM with DPN. The ankle plantar flexors, reported to significantly contribute to the center of mass displacement during forward reach, also had a trend of decreased strength among ODM with DPN.[38]

In this study, the TUG significantly differed between groups. The TUG is a gait-based functional test with the purpose to measure mobility, balance, walking ability, locomotor performance and falls risk among older people.[24] In addition to the reduced proprioception, the dynamic balance impairment among the participants with DPN might have been associated with lower limb muscle weakness reflected by the reduced strength of knee extensors. The correlation of TUG and knee extensor muscle strength has been highlighted among older people.[35]

In conclusion, this study presented the contribution of DNP on higher fall occurrence among ODM with DPN. The poorer performances of static and dynamic balance as well as less knee extensor strength were also found among ODM with DPN. The results suggested that clinicians should systematically monitor and control these impairments as an approach to prevent falls among ODM.

This study had some limitations. The fall occurrence data in this study was based on the interviews. Recall bias is likely especially regarding self-reported falls among ODM. Other factors reported to affect balance and falls in DM including body mass index, medications, depression and fear of falling were not assessed. We also did not monitor the occurrence of hypoglycaemia and the severity of the neuropathic pain. These DM associated conditions were postulated to lead to falls among individuals with DM due to their effects on the attention deficit, slow psychomotor speed as well as orthostatic hypotension.

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Development and Effectiveness Testing of "Punsook": A Smartphone Application for Intermittent Urinary Catheter Users with Spinal Cord Injury

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ABSTRACT

Objective: To develop and evaluate effectiveness of a smartphone application to assist the self-management of intermittent urinary catheter users

Methods: This is experimental clinical research as part of a medical device trial. In phase 1, 10 intermittent urinary catheter users were recruited from spinal cord injury (SCI) patients who had been admitted to a rehabilitation ward at Siriraj Hospital. They used the preliminary version of "Punsook", a web-based application (app) for a smartphone, alongside usual intermittent urinary catheterization (IC), and gave feedback on their experiences. Their qualitative opinions were used to further develop a second version of the "Punsook" app. In phase 2, the new version was used by 35 participants, who were asked to complete an effectiveness questionaire after using the app, including providing details on their history of urinary tract infection (UTI), urinary leakage, and catheterization-related pain. This information was gathered at the end of first and third months in the second phase of the study.

Results: More than half the participants agreed at the end of the first month that every part of the app was acceptably pleasant. They liked the simplicity and ease of use of the app, accessibility, ease of return to use, and interest in the program. No statistically significant changes in urinary leakage, UTI, or pain were found.

Conclusion: The app was considered effective in terms of the positive user satisfaction with all aspects of the app. However, despite this positive reception, the app may not have contributed to an improvement in participant bladder control.

Keywords: Mobile application; intermittent urinary catheterization; spinal cord injuries; neurogenic bladder (Siriraj Med J 2021; 73: 99-107)

INTRODUCTION

World Health Organization (WHO) estimates from 2013 suggest that the incidence of global spinal cord injury (SCI) is 40 to 80 new cases per million of population per year. This means that every year, between 250,000 and 500,000 people suffer spinal cord injuries.[1] The average yearly expenses and lifetime costs for patients with paraplegia are about USD 526,066,[2] with sufferers experiencing a 2- to 5-fold higher mortality rate than healthy people.[1] In Thailand, the incidence of SCI is approximately 23 cases per million people per year, with an economic loss of more than THB 2.6 million per case where disability occurs.[3]

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Constrained mobility, the reduction of self-care performance, and limitation of the patient's vocation and social life can occur due to neurological dysfunction in SCI. These are also key determinants of various systemic complications in SCI that increase the morbidity and mortality rates. Urinary tract infection (UTI) is the important source of hospital re-admission in developed countries and can be a cause of mortality, even in developing countries.[1] Around 62% of people with SCI will experience an infection in their urinary tract within 1 year after a SCI and 95% will have suffered this within 20 years of the SCI.[4]

Severe problems of the urinary tract, for instance, infection, retention, leakage, stones, and reflux, may result from inappropriate bladder management. Prolonged exposure to such problems can lead to fatal renal failure.[1] Accordingly, certain bladder management methods can be applied. The individual treatment method for a patient is selected depending on many factors, for example, their sex, bladder, sphincter function, hand function, mobility competence, and sitting balance. Intermittent catheterization (IC) is one possible option. This involves the insertion of a urinary catheter into the bladder and its removal after completed urination using a clean or sterile technique. This method carries the least risk of urinary tract complications.[1] A study in the United States of America (USA) reported an educational program as a treatment option, comprising nursing observation, medical consultation, and the instruction of basic knowledge about UTI, and follow-up. Using this educational program coupled with regular IC was capable to decrease the rate of UTI and antibiotics treatment in the study cohort.[5] This indicated that IC is safe, effective, and worth applying.[6]

Currently, mobile phones (or smartphones) are commonly used to facilitate communication among SCI patients and whoever. Various health problems can be widely discussed and advice provided through internet networking for the benefit of patients' self-care, such as for smoking cessation, diabetic care, and body weight control. Nevertheless, there is currently little information shared about IC. To address this, a web-based self-management intervention was developed in English,[7] which included an online voiding diary, a journal, educational material, calls with a nurse, a forum, and smartphone app. It is clear that communication and information sharing between provider and the patient population is purposeful and warranted. Based on the success of that development, a web-based mobile phone application (app) was developed in the Thai language with the purpose of supporting self-management of IC users with SCI. Satisfaction with the app and effectiveness were evaluated.

MATERIAL AND METHODS

This study was part of an experimental clinical research project and medical device trial. In phase 1 of study, we investigated the effectiveness of a new web-based app called Punsook, on a mobile phone for IC users. Qualitative remarks from users about the app were collected 1 month after the end of the first phase. The gathered data were sent to the Punsook application developers to guide further development of the app in a new updated version. However, problems arising during use the app were solved and minor changes in the app were done throughout the duration of the initial phase. In phase 2, the effectiveness of the new version of the app was evaluated (Fig 1).

Participants

SCI patients, both inpatients and outpatients, of the Department of Rehabilitation Medicine, Siriraj Hospital, during 2017-2019 who were IC users were invited to participate in this study by direct contact or in a phone call. The inclusion and exclusion criteria were outlined to each possible participant to identify the patients who were able to comprehend the issues and decide about their bladder management themselves. The participants were informed about the study rationale and their role should they choose to join the study. Researchers asked for written informed consent from these patients. If they agreed to join the study and provided this consent, they were then given access to the app.

Inclusion criteria

- At least 18 years old
- Had the ability to access the web-based smartphone app
- Understood Thai language

Exclusion criteria

- Had communication problems
- Had cognitive impairment.

Furthermore, patients who had never done catheterization by themselves were able to participate in the study if they met the other qualifying conditions.

At the beginning of both phases of the study, the participants' demographic data were collected. This included their diagnosis, patient characteristics, daily living function abilities, and their medication. Further information about the catheterization procedures and patient care was also gathered, including the frequency

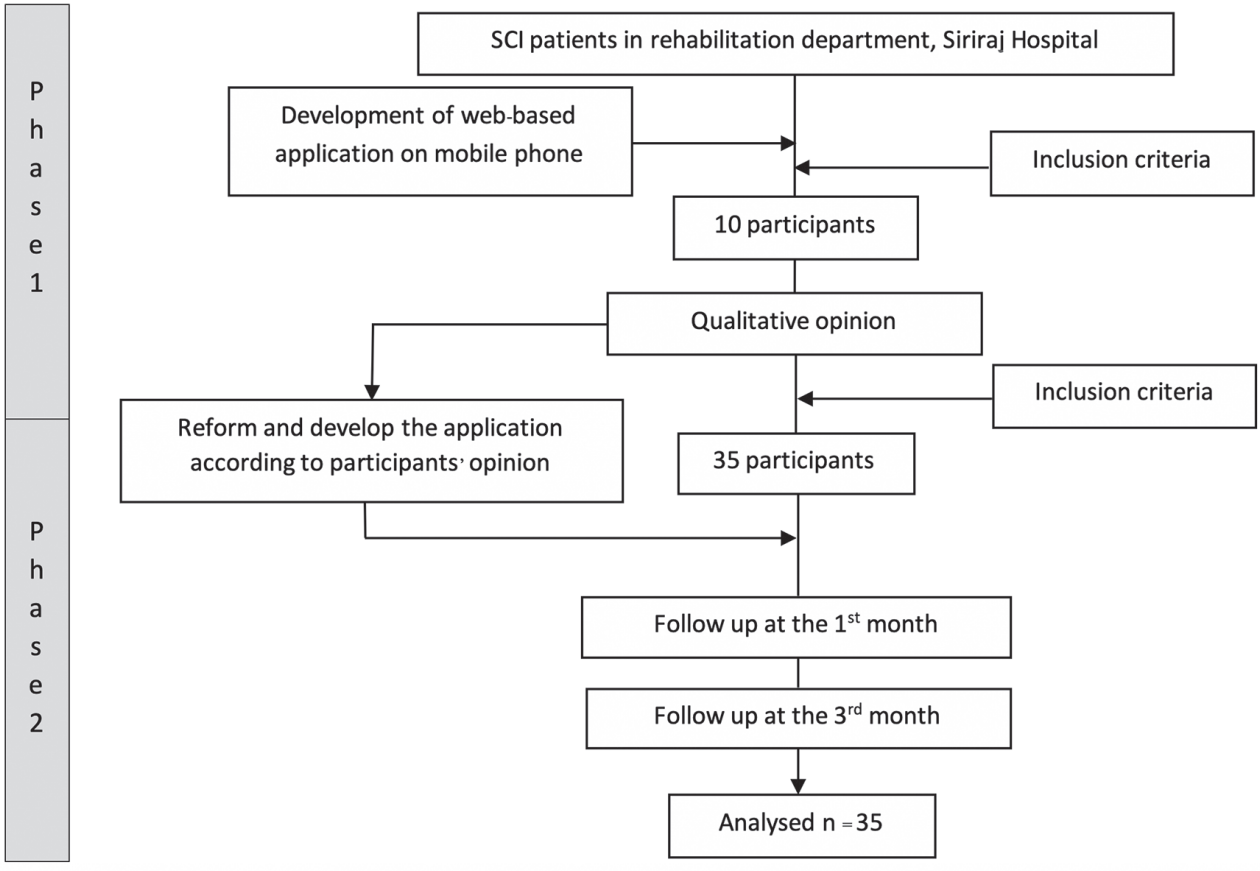

Fig 1. Flow chart of research process.

and interval of catheterizing, estimated urine output, and catheter-related adverse events (e.g., UTI, leakage, pain).

Sample size

Initially, 10 participants joined in phase 1 of the study to test the initial app and to give feedback and/or comments to aid the further development of the app in a new updated version. The power analysis was based on a similar study[8] that showed a confidence level of 95% for adequate bladder control, which was the most important objective in its usability questionnaire. However, our study inferred a slightly lower rate for the effectiveness of the app as 90% with an allowable error of 10%. Consequently, it was calculated that 35 patients were needed to participate in the second part of study (phase 2).

Intervention

In phase 1 of the study, the web-based smartphone app "Punsook" was developed in a collaboration between physiatrists and the Computer Engineering Department of King Mongkut's University of Technology Thonburi (KMUTT). The app consists of four parts: an electronic basic knowledge guidebook, frequently asked questions (FAQ), online voiding diary, and possible contact with a doctor. The FAQ was presented in a chatbot format. The questions covered elementary self-care management around urinary catheterization and other related conditions. The online voiding diary was useful for IC users to record their volumes of water intake and urine output. Also, voiding sensations and any abnormality of concern could be recorded. The application administrator was able to check the real-time records from the app and provide feedback to patients. The participants were asked to use this app alongside their usual regular IC practices. Besides, if they needed medical counsel, they could directly contact a doctor via the app.

One month after using the app, qualitative opinions were obtained from the participants as feedback. Most comments suggested improving the FAQ chatbot, e.g., by increasing the number of common questions and by making the answers easier to understand. In addition, some participants complained about the registration methods. Therefore, we reformed the homepage and modified the chatbot in the new version and then evaluated these updates in phase 2 of the study (Fig 2).

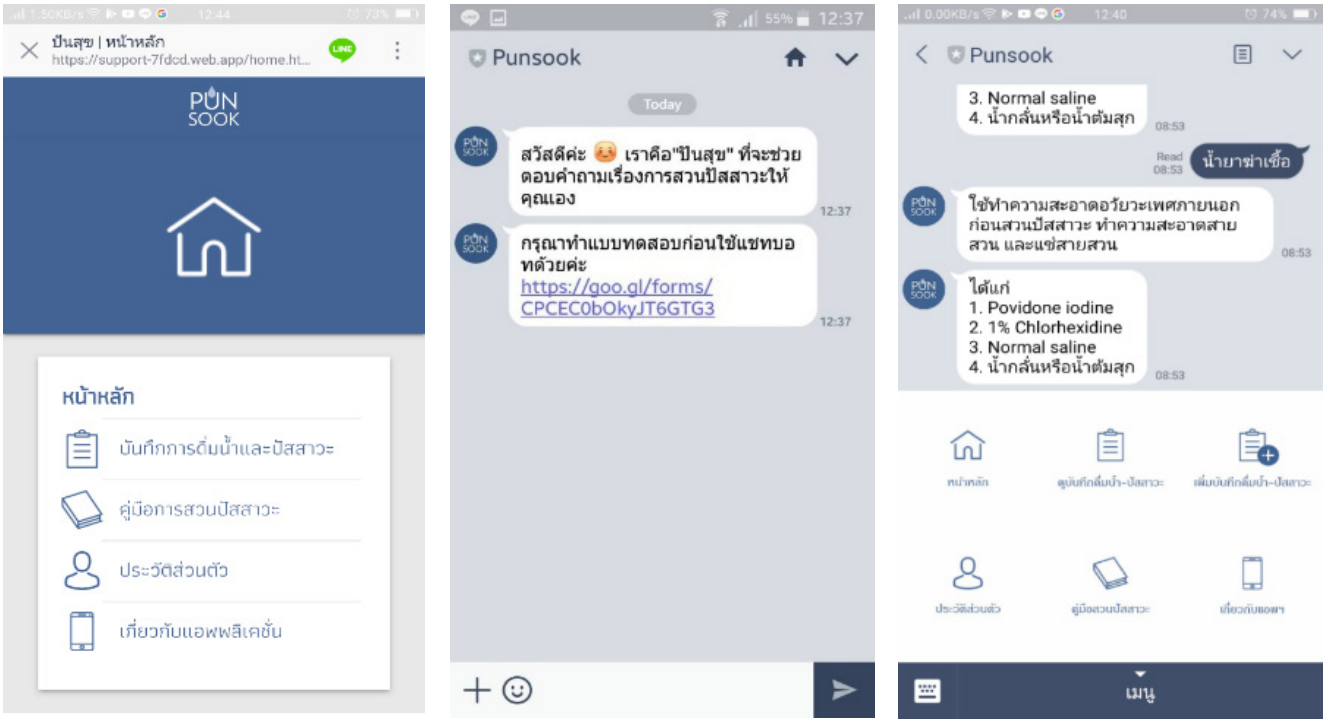

Fig 2. Features of web-based application

Measurement

Assessing the effectiveness of the smartphone app consisted of measuring user satisfaction and their views on its usability, and its ability to decrease the incidence of urinary complications. We hoped that satisfaction with the educational materials, active interaction with an expert, and regular diary recording might influence appropriate bladder management, improve bladder control, and decrease the incidence of urinary complications. We tried to develop the program based on the comments from phase 1 of the study. Then the effectiveness of the new app was measured in phase 2 of the study. Participants were asked to take part in a survey at the end of first month for assessing the effectiveness of the app and additionally at the end of the third month to evaluate their adherence to using the app.

The primary outcome was the satisfaction and applicability of the app. We assessed the user satisfaction toward each part of the program through a feasibility questionnaire, which was divided into 2 parts: user opinions on the information provided and user satisfaction with the whole program. There were 5 scales for the user rating: "strongly agree", "agree", "neutral", "disagree", "strongly disagree". In addition, if the participants did not use a certain part of the application, they could answer with "did not use". The answers "agree" and "strongly agree" represented acceptable satisfaction. The usability questionnaire evaluated the applicability of the program. Usability was evaluated in 5 aspects: ease of use, accessibility, ease upon return to use, interest, and improved ability to control their bladder. The choices were related to the duration of use for the participants' condition, and the options were: "All of the time", "most of the time", "a good bit of time", which were passable times, and "some of the time", "a little bit of the time", and "none of the time", which meant it did not meet expectations. The users were asked to complete the questionnaires after they had been using the application for 1 month and 3 months.

The secondary outcome was related to the app's ability to decrease the incidence of urinary complications. Catheter-related adverse events could be reported at the same time when the participants completed the feasibility and usability questionnaires. Scores based on the VAS were used to indicate the user's pain from catheterization. The number of UTI events and leakage rates during the last 3 months were accumulated.

Statistical analysis

Data were analyzed by PASW (SPSS) Statistics for Windows version 18. Descriptive statistics were used for the subject characteristics. Qualitative data are presented herein by the percentage and quantitative data by the mean and standard deviation (SD). The paired t-test was used to compare quantitative data, while the chi-square test was used for qualitative data. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Table 1 presents the participants' characteristics and their urinary complications. In total, 35 patients were recruited in the study. Everyone completed the initial survey and no one was lost to follow-up. All of the patients used an IC until the end of study. The study cohort comprised 18 males (51.4%). The average age of the participants was 41.86 ± 15.1 years. Most were diagnosed with incomplete SCI (65.7%). Considering the duration of SCI, 77.1% were diagnosed as having SCI for more than one year. Most participants were independent in terms of performing the activities of daily living. The most commonly used medications were baclofen (54.3%) and oxybutynin (45.7%), with solifenacin and trospium chloride also reported in some cases. Some participants used other methods for bladder management along with IC; for example, some participants used an indwelling catheter when traveling, a condom at night, or sometimes they self-voided. Around 60% of all participants catheterized 4-6 times per day, with an interval of 4-6 hours between each time. However, 20–30% irregularly catheterized and did not measure the volume of urine output.

Feasibility

In the 1-month feasibility survey, the participants mostly commented that they were quite satisfied and thought that every part of the app was useful. The evaluation at the end of the third month found that the number of participants who did not use the program was still the same as in the first month, implying a good adherence to the app use by the users (Table 2). Also, the patients still used most parts of the app, except for the FAQ chatbot. In terms of the FAQ chatbot, 48% thought the information in it was useful, and 51.4% were in favor of keeping the FAQ chatbot (Table 2). Overall, the comparison between the users' opinions at the end of the first and the third month showed no statistically significant difference in opinion ($p = 0.47$ concerning the information in the app, $p = 0.63$ concerning the program itself) (Table 2).

Usability

By the end of the first month, most participants could access the different parts of the program and thought the app was easy to use. Likewise, they could return to use it quite efficiently even after leaving it for a while. Half the participants regarded the app as interesting. However, only 40% were able to control their bladder better even with using the advice from the app (Table 3). Two months later at the end of month 3, they still proficiently use the app, even if they had not used it for a while. A larger number of participants, however, stated that using the app was difficult. Controlling their bladder was the main issue that they had never managed to achieve.

Catheter-related pain

The averaged catheter-related pain score was collected by the visual analogue scale (VAS). The baseline pain score was 1.66 ± 1.8 (Table 4); whereas at 1 month and 3 months later, the pain intensity had increased to 1.8 ± 2.1 and 2 ± 2.2, respectively (Table 4). However, there was no significant difference between the scores after a longer duration of the study ($p = 0.74$ at the 1-month survey, $p = 0.44$ at the 3-month survey) (Table 4).

Leakage

Overall, 74% of the participants reported rarely suffering leakage (Table 4). We compared this parameter with the baseline result. There was no statistically significant difference at either the 1-month or 3-month survey points ($p = 0.79$) (Table 4).

Urinary tract infection (UTI)

Information on the history of UTI in the previous 3 months was gathered from the participants. Before joining the study, about 30% of the participants had previously experienced UTI (Table 4). The number of patients who had UTI was still the same as at baseline as reported in the first-month and the third-month surveys.

DISCUSSION

A web-based smartphone app for IC users with spinal cord injury (SCI) was developed for the first time in the Thai language for Thai patients. This app was intended to aid patients' self-management. Our preliminary reports had indicated that the views of the medical practitioners and the engineers who developed the app might have been different from the views and needs of the patients as end users. Therefore, the present study was carried out to assess the effectiveness of this app from the patients' point of view to determine their satisfaction level with the app.

Feasibility and usability surveys were performed and the findings fell in the form of a bimodal distribution. Most respondents expressed either satisfaction or rejection of the app. There were a number of reasons why some participants rejected using the app. At the beginning of the study, the knowledge guidebook and FAQ chatbot were launched before the online voiding diary. Accordingly, some participants in the first phase of the study spent too little time with this online voiding diary. At the

TABLE 1. Demographic data.

Characteristics	n = 35
Sex n (%)	
Male	18 (51.4)
Female	17 (48.6)
Age Year, mean (SD)	41.86 (15.1)
Education level n (%)	
Below high school	8 (22.9)
High school	7 (20)
Bachelor's	16 (45.7)
Master's / Doctor's	4 (11.4)
Completeness of lesion n (%)	
SCI Complete	8 (22.9)
SCI Incomplete	23 (65.7)
Unknown	4 (11.4)
Duration of SCI n (%)	
Less than 1 year	8 (22.9)
≥ 1 year	27 (77.1)
Level of SCI n (%)	
Cervical	6 (17.1)
Thoracic	9 (25.7)
Lumbar	17 (48.6)
Sacral	3 (8.6)
ADL bathing n (%)	
Dependent	5 (14.3)
Independent	30 (85.7)
ADL dressing n (%)	
Dependent	5 (14.3)
Independent	30 (85.7)
ADL toileting n (%)	
Dependent	7 (20)
Independent	28 (80)
ADL ambulation and transfer n (%)	
Dependent	8 (22.9)
Independent	27 (77.1)
ADL eating n (%)	
Dependent	2 (5.7)
Independent	33 (94.3)

Trospium chloride = 2, Solifenacin = 1, Gabapentin = 1

TABLE 1. Demographic data. (Continue)

Characteristics	n = 35
Medication n (%)	
Baclofen	19 (54.3)
Oxybutynin	16 (45.7)
Antibiotics	2 (5.7)
Amitriptyline	2 (5.7)
Not use	7 (20)
Other	4 (11.4) #
Other bladder management methods n (%)	
Indwelling	7 (20)
Condom	1 (2.9)
Absorbent product	1 (2.9)
Credé	1 (2.9)
Self-voiding	7 (20)
No other method	18 (51.4)
Frequency of catheterizing per day n (%)	
1–3 times	4 (11.4)
4–6 times	23 (65.7)
7 times or more than	8 (22.9)
Catheterizing intervals n (%)	
2-3 hours	4 (11.4)
4-6 hours	21 (60)
7-9 hours	0 (0)
10-12 hours	2 (5.7)
Varies	8 (22.9)
Urine output n (%)	
Less than 100 ml	3 (8.6)
100-399 ml	19 (54.3)
400 ml or more than	4 (11.4)
Unknown	9 (25.7)
Leakage n (%)	
Every day	9 (25.7)
Less than every day	26 (74.3)
UTI in last 3-month n (%)	
Never	22 (62.9)
1-2 times	11 (31.4)
3-4 times	2 (5.7)
5 times or more	0 (0)
Pain mean (SD)	1.69 (1.9)

Trospium chloride = 2, Solifenacin = 1, Gabapentin = 1

TABLE 2. Result of feasibility questionnaire.

	Did not use		Strongly disagree		disagree		Neutral		Agree		Strongly agree	
	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month
Was the information useful?												
Voiding diary	8 (22.9)	9 (25.7)	0 (0)	0 (0)	0 (0)	0 (0)	5 (14.3)	3 (8.6)	12 (34.3)	14 (40)	10 (28.6)	9 (25.7)
Knowledge	7 (20)	8 (22.9)	0 (0)	0 (0)	2 (5.7)	2 (5.7)	5 (14.3)	7 (20)	12 (34.3)	13 (37.1)	9 (25.7)	5 (14.3)
Contact with doctor	7 (20)	7 (20)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8.6)	4 (11.4)	9 (25.7)	10 (28.6)	16 (45.7)	14 (40)
FAQ (Chatbot)	7 (20)	9 (25.7)	0 (0)	0 (0)	2 (5.7)	2 (5.7)	6 (17.1)	7 (20)	12 (34.3)	13 (37.1)	8 (22.9)	4 (11.4)
Were you satisfied with the parts of the program?												
Voiding diary	7 (20)	9 (25.7)	0 (0)	0 (0)	0 (0)	0 (0)	6 (17.1)	8 (22.9)	12 (34.3)	10 (28.6)	10 (28.6)	8 (22.9)
Knowledge	6 (17.1)	7 (20)	1 (2.9)	0 (0)	2 (5.7)	2 (5.7)	6 (17.1)	7 (20)	13 (37.1)	14 (40)	7 (20)	5 (14.3)
Contact with doctor	7 (20)	7 (20)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8.6)	5 (14.3)	10 (28.6)	11 (31.4)	15 (42.9)	12 (34.3)
FAQ (Chatbot)	7 (20)	8 (22.9)	1 (2.9)	0 (0)	3 (8.6)	3 (8.6)	4 (11.4)	6 (17.1)	13 (37.1)	14 (40)	7 (20)	4 (11.4)

p value > 0.05, comparing number of each answer at the first month to that in the third month

TABLE 3. Result of usability questionnaire.

	None of the time		A little of the time		Some of the time		A good bit of the time		Most of the time		All of the time	
	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month	1st month	3rd month
Easy to use	4 (11.4)	5 (14.3)	3 (8.6)	2 (5.7)	4 (11.4)	5 (14.3)	6 (17.1)	7 (20)	7 (20)	8 (22.9)	11 (31.4)	8 (22.9)
Able to assess all around the part of program	4 (11.4)	4 (11.4)	2 (5.7)	0 (0)	3 (8.6)	6 (17.1)	7 (20)	5 (14.3)	9 (25.7)	9 (25.7)	10 (28.6)	11 (31.4)
Back to use program after leave for a while	4 (11.4)	4 (11.4)	2 (5.7)	1 (2.9)	1 (2.9)	4 (11.4)	6 (17.1)	6 (17.1)	12 (34.3)	9 (25.7)	10 (28.6)	11 (31.4)
Interesting and attractive to use	3 (8.6)	3 (8.6)	2 (5.7)	0 (0)	2 (5.7)	6 (17.1)	10 (28.6)	8 (22.9)	10 (28.6)	8 (22.9)	8 (22.9)	10 (28.6)
Can control bladder	13 (37.1)	13 (37.1)	5 (14.3)	3 (8.6)	2 (5.7)	4 (11.4)	8 (22.9)	7 (20)	3 (8.6)	3 (8.6)	4 (11.4)	5 (14.3)

p value > 0.05, comparing number of each answer at the first month to that in the third month

TABLE 4. Result of urinary complication.

	Baseline	1st month		3rd month	
Pain Mean (SD)	1.66 (1.8)	1.8 (2.1)	P = 0.74	2 (2.2)	P = 0.44
Leakage n (%)					
• Daily	9 (25.7)	10 (28.6)	P = 0.79	10 (28.6)	P = 0.79
• Non-daily	26 (74.3)	25 (71.4)		25 (71.4)	
UTI n (%)					
• UTI within last 3 month	12 (34.3)	11 (31.4)	P = 0.78	12 (34.3)	P = 1
• No UTI within last 3 month	23 (65.7)	24 (68.6)		23 (65.7)	

same time, half the participants used other methods for bladder management alongside IC; for example, some used indwelling catheterization while traveling outside their residence. Thus, these users had less chance to use and test the app. Consequently, they did not feel capable of expressing their opinion about the app when they had rarely used parts of the app. When some participants commented that they did not use a certain part of the app, this answer was not included in the satisfied status.

Keeping a voiding diary for persons with spinal cord injury is very useful. By analyzing the volume and frequency of each voiding, along with other parameters monitored in the diary, the physician can assess the diary to form an initial opinion about the patient's urodynamic profile.[9] The online voiding diary is more convenient to keep up with as it involves active interaction. The data are directly sent to administrative staff for providing early feedback to the patients. While a paper diary is still quite common with many patients, electronic diaries are becoming more common and can yield better compliance.[10] However, Thai doctors usually assign this choice of method to the patients. If we are able to provide evidence to support the effectiveness of an online voiding diary in the Thai, this might help popularize this method which may improve patient compliance of a voiding diary.

The usage rates for the knowledge guidebook, online voiding diary, and FAQ chatbot decreased at the third month, which may have been due to the familiarity with these aspects built up over time. As patients gain more experience of intermittent catheterization, they need less guidance and are able to solve most problems by themselves. Moreover, the compliance with program use might indicate the effectiveness of the app. Generally, patients are more likely to persist with an intervention if they feel it can help them avoid a more negative health condition.[11] Consequently, we tried to find some method to improve those compositions in the app.

Contact with a doctor was the part of the app that attracted the highest satisfaction level, in part because of it being an interactive activity. Patients could freely contact a doctor about their medical issues. Apart from gaining knowledge or asking queries, they could obtain specific information on primary practice and access to the doctor appointment system. In this study, contact with the doctor appointment system was performed via the private doctor's LINE® (Naver Corporation, Tokyo, Japan) account. We plan to add this element into our app in future updates. However, this incurred a much higher expense in addition to the official contact account. Therefore, we tried to adjust the usability of the app in other ways. The FAQs for communicating with the doctor will be increased in the FAQ chatbot during major changing among the two phases of this research. Besides, we tend to continuously update the program as we go along to save time.

Bladder control problems affect the way a person holds or releases urine.[12] Therefore, the key factor determining bladder control is urinary leakage. However, patients may be concerned that leakage is a problem when it accidentally occurs and they cannot manage control. Overall, 40% of participants thought that they could not control their bladder at any time; although only about 26% of participants complained about leakage every day. This result suggested that the question of bladder control in the usability questionnaire might not represent the problematic leakage issue correctly. The

effectiveness evaluation will need to be more specific for the questionnaire to be able to reveal the actual problem. Thus, clarification of this question could improve the accuracy of the results. In addition, the applicability of the app did not represent the real rate of app use, which would typically not be enough to help the daily bladder control of the participants.

Limitations

There were some limitations of this study to mention. Firstly, many older Thai SCI patients were unable to access the web-based app through their mobile phone. Thus, many elderly could not be included in this study. Along with the small sample size, which led to a low power to detect small effects, non-significant results on the secondary outcome when comparing baseline to post-intervention follow-up were observed. Secondly, some participants had tetraplegia and poor hand function. Their caregiver did the IC instead of the patients themselves, and both the patients and their caregivers used the app together. Most these patients used only the FAQ chatbot and educational knowledge guidebook, while the catheter users often used the online voiding diary as well. Thus, their opinion was summarized in just one survey. Thirdly, our study lacked a control group for comparison between the traditional educational method and this app. Finally, we could not strictly enforce them to spend more time with this program. Therefore, the time expenditure with the app was different among the participants, which likely influenced their satisfaction levels.

CONCLUSION

We successfully developed a web-based smartphone app based on the requirements of SCI patients using intermittent urinary catheterization. According to the study participants, the effectiveness of this app was considered satisfactory and every part of the program was usable. The study findings suggested, however, that the app might not actually help to improve their bladder control. We need to constantly modify the application over time in order to meet the needs of the patients. Educational videos, pop-up ratings, and urological check-up recording might be interesting functions to add to the app. Additional qualitative opinions and actual time use data for using the app should be collected in a future study.

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Success Rate of Radioactive Iodine Therapy in Graves' Disease Using Dose Corrected for Thyroid Gland Size

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ABSTRACT

Objective: Dose corrected for thyroid gland size is one of the methods used to determine I-131 activity for patients with Graves' disease. This study aimed to find the success rate of this method and the predictors for successful I-131 treatment.

Methods: This retrospective descriptive study conducted was in patients with Graves' disease who received the first dose of radioactive iodine (RAI) therapy. Patients received a fixed RAI dose of either 10, 15, 20, 25, or 30 mCi for corresponding thyroid gland size of ≤ 50, 51-100, 101-150, 151-200, and >200 grams, respectively. The treatment outcome assessed was between 6 to 9 months after the therapy based on serum free thyroxine and serum thyroid stimulating hormone. Successful treatment was defined as euthyroid and hypothyroid.

Results: A total number of 179 patients (126 females; mean age: 40.8 years) were enrolled. There was one patient exclusion from the outcome analysis due to undetermined laboratory results. The success rate of RAI therapy was 50% (95% CI: 42.4-57.6). Patients with gland size ≤ 50 gm had the highest success rate of 59.6%. Multivariable analysis showed no significant association between sex, thyroid gland size, prior antithyroid drug use and successful treatment.

Conclusion: First RAI therapy using dose corrected for thyroid gland size had a modest success rate of 50% in patients with Grave's disease. Sex, thyroid gland size, and prior antithyroid drug use were not significantly associated with the treatment outcomes.

Keywords: Radioactive iodine; Graves' disease; hyperthyroidism; success rate (Siriraj Med J 2021; 73: 108-113)

INTRODUCTION

Graves' disease is an organ-specific autoimmune disease and the most common cause of hyperthyroidism. The annual incidence is 20 to 30 cases per 100,000 individuals with approximately 3% and 0.5% lifetime risk in women and men, respectively.[1-3] Untreated or partially treated Graves' disease can lead to serious complications such as atrial fibrillation, neuropsychiatric symptoms, thyroid storm, or even death.[4,5] Thus, an appropriate treatment is the key to success for controlling hyperthyroidism symptoms and prevention of serious complications.

Radioactive iodine (RAI) therapy using the beta particle-emitting isotope, I-131, is the definitive treatment for Graves' disease by destroying thyroid follicular cells.[3,6]

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The goal of RAI therapy is to use sufficient activity of RAI to render the patient's hypothyroid.[4] There are two main methods to determine the RAI activity in clinical practice: estimation (the so called "fixed dose") and calculation of radioiodine uptake measurement and thyroid gland size.[7,8] The systematic reviews and meta-analyses showed equally successful treatment outcomes between the two methods.[9] However, the fixed dose regimen is simpler and more cost-effective.[10,11] Another approach to find an optimal I-131 activity in Graves' disease is dose corrected for thyroid gland size method by prescribing RAI activity according to the estimated thyroid gland size.[12] The advantages of this method are similar to the fixed dose in terms of cost and procedure. However, the treatment outcome of this method is not been well studied. Thus, we primarily aimed to find the success rate of first RAI therapy using dose corrected for thyroid gland size method in patients with Graves' disease. Moreover, we also evaluated predictive factors associated with the successful treatment.

MATERIALS AND METHODS

Patient selection

This retrospective descriptive study was approved by the Khon Kaen University Ethics Committee for Human Research (Reference number: HE601393) and the requirement for the informed consent was waived. From January 2012 to April 2017, patients enrolled for research had confirmed Graves' disease and had received first RAI therapy at Srinagarind Hospital. Patients were stratified into five groups according to thyroid gland size. Those with a history of thyroid surgery, received repeated doses of RAI therapy prior to first treatment outcome evaluation, or had undetermined laboratory results during the follow-up period because of recent thyroid hormone or antithyroid medication use were excluded.

Patient preparation and treatment

Patients treated at our center followed strict patient preparation as per our center's standard protocol. Antithyroid Drug (ATD) either methimazole (MMI) or propylthiouracil (PTU), was discontinued three to seven days prior to RAI therapy. Patients had an advice to take low-iodine diet for one week before the therapy. Pregnancy tests done potentially on all pregnant females on the day of treatment. The thyroid gland size estimation of each patient performed by one of four expert nuclear medicine physicians. The recorded thyroid gland size was used to determine RAI activity according to our center' standard protocol. Patients received a fixed RAI dose of either 10, 15, 20, 25, or 30 mCi orally for corresponding thyroid gland size of ≤ 50, 51-100, 101-150, 151-200, and >200 grams as assessed by palpation. Beta-blockers and/or restarting ATD allowed for controlling symptoms after RAI therapy. Then, clinical outcomes evaluated between 6 to 9 months after first I-131 administration. Thyroid function tests including serum free thyroxine (FT4) and serum thyroid stimulating hormone (TSH), clinical symptoms, and thyroid gland size assessed at the follow-up time point.

Outcome measurement

Successful RAI therapy was defined as patients with euthyroid (normal FT4 and TSH), subclinical hypothyroidism (normal FT4 and high TSH), or overt hypothyroidism (low FT4 and high TSH) 6 to 9 months after the treatment. The patients who had subclinical hyperthyroidism (normal FT4 and low TSH) or overt hyperthyroidism (high FT4 and low TSH) had classified as treatment failure. The normal reference range of serum FT4 is 0.78-2.11 ng/dL and serum TSH is 0.2-4.2 μIU/mL.

Statistical analysis

The success rate of RAI therapy presented as the number and percentage of patients with euthyroid, subclinical hypothyroid and overt hypothyroid divided by the numbers of all patients. The categorical data (sex, group of gland size, type of ATD use) presented the number and percentage. The continuous data (age, follow-up time, serum FT4, serum TSH) presented as mean ± standard deviation (SD) or median (with interquartile range). Univariable analysis and multivariable analysis by multiple logistic regression used to test association between sex, prior ATD use, thyroid gland size and successful treatment. All the statistics two-sided and p values of less than 0.05 considered statistically significant. Accompanying 95% confidence intervals (95% CI) were reported where appropriate. Statistical analysis carried out was using STATA 10.1 (StataCorp LP, College Station, TX, USA).

RESULTS

A total number of 179 patients enrolled with a mean age of 40.8±13.6 years. Most of the patients were female (n = 126, 70.4%). When patients were grouped by thyroid gland size, 52 (29.1%), 52 (29.1%), 39 (21.8%), 22 (12.2%), and 14 (7.8%) had gland size of ≤ 50, 51-100, 101-150, 151-200, and ≥ 200 grams, respectively. Regarding the ATD, most of the patients used MMI prior to RAI therapy (n = 131, 73.2%). Only five patients (2.8%)

did not receive ATD before I-131 administration. The median follow-up time after treatment was 6.6 (6.1-7.5) months. The patient's demographic and clinical data are as shown in Table 1.

After the 6- to 9-month follow-up, there was one patient with indeterminate laboratory results (low serum FT4 and TSH). Thus, the success rate of treatment in 178 patients analyzed. Eighty-nine patients (50%) achieved successful treatment, among which 30 (16.9%) were euthyroid, 30 (16.9%) were subclinical hypothyroid, and 29 (16.2%) were overtly hypothyroid. The remaining 89 patients (50%) had treatment failure, among which 51 (28.7%) were subclinical hyperthyroid and 38 (21.3%) were overtly hyperthyroid. The details of treatment outcomes are as shown in Table 2.

Regarding the treatment outcomes based on the thyroid gland size, patients with gland size equal or less than 50 grams had the highest success rate of 59.6% (95% CI: 45.1-73.0), while patients with larger gland size tended to have lower success rate. Patients with gland size of 151-200 grams had the lowest success rate, 22.7% (95% CI: 7.8-45.4). The success rate in each group of thyroid gland size is as shown in Table 3.

Multiple logistic regression demonstrated that females tended to have successful treatment than males but there was no statistical significance (adjusted OR = 1.28, 95% CI: 0.62-2.64, p value = 0.51). Regarding the thyroid gland size, patients with gland size 151-200 grams seemed to have lower successful treatment than those with gland size ≤ 50 gm but there was also no statistical significance (adjusted OR = 0.35, 95% CI: 0.08-1.59, p value = 0.17). Furthermore, use of MMI or PTU prior to the RAI therapy showed no significant association with the successful treatment as shown in Table 4. In addition, we also evaluated the impact of different ATD use prior to the therapy on successful treatment and found that there was no statistically significant difference between either MMI or PTU and the treatment outcomes (adjusted OR = 1.83, 95% CI: 0.86-3.92, p value = 0.12).

TABLE 1. Patient's demographic and clinical data.

Variables	Total 179 n (%)
Sex	
Male	53 (29.6)
Female	126 (70.4)
Age (year)	
Mean	40.8
SD	13.6
Estimated thyroid gland size (gram)	
≤ 50	52 (29.1)
51-100	52 (29.1)
101-150	39 (21.8)
151-200	22 (12.2)
> 200	14 (7.8)
Antithyroid drug	
Methimazole (MMI)	131 (73.2)
Propylthiouracil (PTU)	42 (23.5)
Both MMI and PTU	1 (0.5)
None	5 (2.8)
Follow-up time (month)	
Median	6.6
Interquartile range	6.1-7.5

TABLE 2. Outcomes of RAI therapy at the 6 to 9-month follow-up.

Outcome	Total 178[a] n (%)
Success	89 (50)
Euthyroid	30 (16.9)
Subclinical hypothyroid	30 (16.9)
Overt hypothyroid	29 (16.2)
Failure	89 (50)
Subclinical hyperthyroid	51 (28.7)
Overt hyperthyroid	38 (21.3)

[a]There was one patient with thyroid gland size > 200 grams whose thyroid function test cannot be determined. Thus, the treatment outcomes were analyzed in 178 patients.

TABLE 3. Outcomes of RAI therapy at the 6 to 9-month follow-up based on thyroid gland size.

Thyroid gland size (gram)	Median size (IQR)	Success	Failure	Percent success rate (95% CI)
≤ 50	35 (30-40)	31	21	59.6 (45.1-73.0)
51-100	70 (60-80)	28	24	53.9 (39.5-67.8)
101-150	120 (120-145)	19	20	48.7 (32.4-65.2)
151-200	200 (200)	5	17	22.7 (7.8-45.4)
> 200	250 (250-287.5)	6	7	46.2 (19.2-74.9)
Overall	80 (50-130)	89	89	50.0 (42.4-57.6)

Abbreviation: IQR, interquartile range

DISCUSSION

We studied the success rate of RAI therapy by dose corrected for thyroid gland size method in 178 patients with Graves' disease who received first-dose I-131 administration. The treatment outcomes evaluated at 6 to 9 months after the therapy. We decided to determine the treatment outcomes at this time point because there was variation in the follow-up period in each patient and hypothyroid could achieve up to 12 months after the therapy.[13] Eighty-nine patients achieved successful treatment accounts for only 50% success rate (95% CI: 42.4-57.6). This figure was lower than reported in the previous studies using the estimation method to determine I-131 activity with the success rate between 60-85%.[10,11,14-18] Several factors affected our therapeutic outcome. The first important factor that affected the outcome was thyroid gland size, well known to be an independent predictor of the response to I-131 therapy.[13] The median thyroid gland size of our patients was higher than those in other studies (80 grams vs 35-70 grams)[10,11,14,17] and 71.35% of our patients had thyroid gland size larger than 50 grams. Thus, this could lower the overall success rate. However, the patients with thyroid gland size ≤ 50 grams could achieve higher success rate approximately at 60%. Second, we used the palpation method for thyroid gland size estimation which could underestimate the size of larger goiter (greater than 40 mL).[19] The study by Canto et al. used thyroid ultrasound for gland size estimation and found that the overall success rate was 80% even though there were one-third of patients with gland size between

TABLE 4. Univariable and multivariable analyses of successful treatment.

Variable	Univariable analysis Crude OR (95% CI)	p value	Multivariable analysis Adjusted OR (95% CI)	p value
Sex				
Male	1		1	
Female	1.31 (0.69-2.49)	0.41	1.28 (0.62-2.64)	0.51
Thyroid gland size (gram)				
≤ 50	1		1	
51-100	1.36 (0.40-4.61)	0.62	1.15 (0.31-4.21)	0.84
101-150	1.11 (0.31-3.90)	0.87	0.97 (0.27-3.56)	0.97
151-200	0.34 (0.08-1.50)	0.16	0.35 (0.08-1.59)	0.17
> 200	1.72 (0.51-5.85)	0.38	1.63 (0.44-6.08)	0.47
Antithyroid medication				
None	1		1	
MMI	1.78 (0.29-10.98)	0.54	2.90 (0.43-19.38)	0.27
PTU	0.87 (0.13-5.78)	0.88	1.58 (0.22-11.37)	0.65

Abbreviations: Crude OR, crude odds ratio; Adjusted OR, adjusted odds ratio, MMI; methimazole, PTU; propylthiouracil

40-80 grams.[10] Third, we did not perform radioiodine uptake test (RAIU) that might identify patients with rapid I-131 turnover Graves' disease that maybe found in up to 15% of all Graves' disease patients and needed a higher I-131 activity or other therapeutic intervention such as lithium carbonate.[20] Fourth, although with a one-week low-iodine diet intake advised to the patients before RAI therapy, the actual amount of iodine intake is difficult to quantify. The study by Meller et al. found that there was 2-fold increased iodine excretion prior to the therapy corresponded to a decrease of the radioiodine uptake by 25%.[21] However, the prospective study by Santarosa et al. showed no difference in the rate of hypothyroidism 6 months after RAI therapy between patients with Graves' disease patients who consumed low-iodine diet and patients who took regular diet (86.7% vs 82.6%, p value = 0.74).[22] Lastly, since most of the patients had been referrals from other hospitals, some patients who had a higher chance to be cured with a single dose of I-131, such as patients with small gland size or mild hyperthyroidism, had been referred back to their primary hospitals for further follow-up. Thus, the assessment count of successful treatment numbers was difficult to achieve in our study results of this group of patients and this could lead to underestimation of treatment success.

Regarding the predictors for the therapeutic outcome, sex showed no significant association with successful treatment which was in line with most studies. There was no exact reason to explain the difference in the biological response to radioiodine between male and female.[13] For thyroid gland size, it was also no significant association with the treatment outcomes. This maybe explains the method to determine I-131 activity. We used dose correction for thyroid gland size; the larger gland size received the higher prescribed radioiodine activity. In addition, prior MMI or PTU use before RAI therapy, although known to have radioprotective effect[13], showed no significant association with successful treatment in our study. The result was consistent with a randomized clinical trial by Bonnema et al. which demonstrated no difference between failure rate of RAI therapy among Graves's disease patients who were and were not pretreated with PTU (40.0% vs 30.8%, p value = 0.81).[23] The prospective randomized study by Pirnat et al. also showed equally effective outcomes in Graves' disease patients who did not receive MMI and patients who had discontinued MMI seven days before RAI therapy (99.6% vs 99.0%).[24]

There were some limitations of our study. First, due to being a retrospective study, other potential predictive

factors such as pretreatment serum FT4 and TSH, duration of disease, duration of ATD use, and thyroid autoantibodies were difficult to evaluate. Second, the thyroid gland size was assessed by different nuclear medicine physicians could cause variation in estimating gland size. Thus, this could affect the prescribed I-131 activity in each patient. Third, the follow-up duration was varied among the patients ranging from 6 to 9 months which can affect the treatment outcomes.

An issue that needs clarification is the strategy to improve success rate of RAI therapy by using dose corrected for thyroid gland size method. Higher prescribed I-131 activity for each stratum of thyroid gland size needs consideration and further prospective study is required.

CONCLUSION

First RAI therapy using dose corrected for thyroid gland size had a modest success rate of 50% in patients with Grave's disease. Sex, thyroid gland size, and prior antithyroid drug use showed no significant association with the successful treatment.

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12-Month Single-Procedure Outcomes after Atrial Fibrillation Catheter Ablation in Phramongkutklao Hospital: A Single Center 10-Year Experience

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ABSTRACT

Objective: This study aimed to report the efficacy and safety of 1-year outcome for single-procedure radiofrequency catheter ablation (RFCA) at Phramongkutklao Hospital.

Methods: Review of medical records was carried out on consecutive patients with symptomatic atrial fibrillation (AF) who had undergone first-time RFCA in Phramongkutklao Hospital between January 2009 and December 2018. The efficacy and safety of outcomes after 1 year of RFCA were collected, analyzed, and validated using descriptive data.

Results: 61 patients underwent RFCA for the first time. 77.05% were male, with a mean age of 58.31 ± 10.83 years. Paroxysmal AF presented in 65.57%. 49.18% had hypertension, 9.84% had a history of ischemic stroke or transient ischemic attack, 6.56% had diabetes, 6.56% had coronary artery disease, and 4.92% had heart failure. 96.72% of RFCA procedures were performed under local anesthesia and conscious sedation. Pulmonary vein isolation was performed in all patients. Roofline, mitral isthmus line, and posterior wall isolation were created in 27.87%, 13.11%, and 3.28%, respectively. Additional complex fractionated atrial electrograms (CFAEs) were targeted in 19.67%. After 12 months, 45.45% remained in sinus rhythm, with only one patient experiencing a procedure-related complication with cardiac tamponade.

Conclusion: The 1-year results of single-procedure RFCA for treating AF at our center, while not highly successful in our first decade, were comparable to other series. Notably, there was a relatively low rate of complications.

Keywords: Atrial fibrillation; radiofrequency ablation (Siriraj Med J 2021; 73: 114-120)

INTRODUCTION

Atrial fibrillation (AF) is a significant health problem and the most common form of arrhythmia. The prevalence tends to fluctuate between 1-4% in European countries, but 0.49-1.9% in Asian countries.[1] In Thailand, the prevalence is 1.88% in the elderly population.[2] This prevalence tends to be higher in patients with comorbidity, such as 3.46% in patients with hypertension and 22.55% in patients with ischemic stroke.[3,4] Moreover, AF is one of the severe independent risk factors of mortality. It is associated with an increased risk of death, at 2.15 times in female patients and 1.72 in male patients.[5] It is also associated with an increased risk of stroke, at 3.2 times in females and 3.4 times in males. Furthermore, it causes increased risk of heart failure at 3.4 times in both females and males.[6] In addition to the treatment of specific comorbidity and anticoagulant therapy for stroke prevention in patients with AF, rhythm control is an advertent practice. This approach can help relieve patient's symptoms and improve quality of life, which demonstrates its higher effectiveness

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and safety compared to antiarrhythmic drug therapy.[7] Besides symptoms improvement, it can also enhance the left ventricular ejection fraction (LVEF) by up to 9%.[8] There are numerous trends showing the additional benefits of catheter ablation in patients with AF, though data is sparse concerning aspects such as reduced stroke rate, mortality rate, and the risk of dementia.[9,10]

Treating AF patients with catheter ablation was developed and has increased in popularity over the last decades. In 2019, data from the Asia-Pacific region showed this procedure was performed in 446.1 patients per 1 million in the Japanese population, but in only 1.9 patients per 1 million in the Thai population.[11] Even though this treatment method has been used for many years, the success rate is a point of concern. Although the success rate of catheter ablation is higher than antiarrhythmic therapy, the success rate for these treatments is only 64% and 58%, respectively.[12]

The strategy used in catheter ablation, learning curve, and experience of the operator are all critical success factors. Phramongkutklao Hospital, the largest hospital serving the Royal Thai Army, has played a significant role in caring for soldiers and civilians with AF for decades. Information for patients with AF and treatment outcomes after catheter ablation would be beneficial for the development of patient care. The aim of this single-center, retrospective, observational study was to analyze the safety and efficacy of single-procedure catheter ablation for AF.

MATERIALS AND METHODS

Population and data collection

Consecutive patients with symptomatic AF who had undergone first-time radiofrequency catheter ablation (RFCA) at Phramongkutklao Hospital between January 2009 and December 2018 were enrolled in this research. The study protocol was approved by the institutional review board of the Royal Thai Army Medical Department (Issued No. S069h/2019_Exp). AF diagnosis was confirmed by documentation of 12-leads electrocardiography (ECG) or ambulatory ECG monitoring. AF was classified into two groups as paroxysmal and persistent type according to all standard international guidelines. We collected the essential baseline characteristics of the patients, which included age, gender, weight, height, comorbid diseases, antiarrhythmic drug use, and history of electrical cardioversion. Echocardiographic data before the procedure, which could affect the outcomes, were also recorded.

Pre-procedural care

Pre-procedural care was performed in the usual manner, with adequate anticoagulant administered for at least three weeks or until there was no thrombus in the left atrium detected by transesophageal echocardiography, before performing the procedure.

Ablation strategies

The RFCA was performed in the fasting state under conscious sedation with local anesthesia or general anesthesia according to the patient's and operator's preference. The ablation technique and strategy were designed by the operator, but pulmonary vein isolation (PVI) was targeted in all patients with point-by-point RF ablation widely encircling the antrum of the pulmonary veins. PVI strategy alone were performed in patients with paroxysmal AF. Additional ablation such as the roofline, mitral isthmus line, posterior wall isolation, cavotricuspid isthmus, and complex fractionated atrial electrograms (CFAEs) ablation were performed according to the operator's consideration in patients with persistent AF. Ablation catheters with contact force sensing were used in all patients. The radiofrequency energy was delivered with the power of 30-35 watts at anterior wall and 25-30 watts at posterior wall. The endpoint of the procedure was PVI, which confirmed by entrance block into pulmonary vein. Anticoagulant management with activated clotting time was performed under standard guidelines. The fluoroscopic time was also collected. If any complications occurred, the details were prescribed.

Post-procedural care

All patients were monitored for 24 hours as inpatient before discharge. Unless there were complications, the anticoagulant was routinely restarted in the evening on a procedural day. We also monitored all the possible complications throughout the period of admission.

Follow-up and outcome measures

All patients received initial follow-up at Phramongkutklao Hospital in an outpatient clinic not more than two weeks post-procedure, followed by every one to three months according to the doctor and patient's preference. To provide adequate time concerning the evaluation of the efficacy and safety of the procedure, patients' data with at least twelve months of follow-up period were included in the analysis of outcomes. At follow-up, each patient's heart rhythm was clinically evaluated and subjected to 12-lead electrocardiogram (ECG). Selected patients had 24 or 48 hours of ambulatory ECG monitoring if the doctor requested, depending on each patient's symptoms. After three months of the blanking period, each patient's rhythm was recorded at

every outpatient visit for 12 months after the procedure. The antiarrhythmic drugs utilized after the procedure were also recorded.

The recurrence of arrhythmia was defined as any episode of atrial tachyarrhythmia, including atrial fibrillation, atrial flutter, or atrial tachycardia, lasting more than 30 seconds recorded beyond the first three months after the procedure.

Clinically-relevant complications associated with the procedure were monitored throughout the follow-up period.

Statistical analysis

The data are presented using descriptive statistics. Continuous variables are expressed as mean ± standard deviations and categorical variables as percentages. To determine the success rate of the procedure, we assessed arrhythmia-free survival using the Kaplan-Meier method.

RESULTS

Patient characteristics

From January 2009 to December 2018, a total of 72 RFCA procedures were performed. Sixty-one patients underwent RFCA for the first time, while 11 had a previous AF ablation. The baseline characteristics of the patients who underwent RFCA for the first time are shown in Table 1. Overall, 77.05% of patients were male, with a mean age of 58.31 ± 10.83 years. Mean body mass index (BMI) was 26.11 ± 6.53 kg/m^2. Paroxysmal AF presented in 65.57% of the patients, while 34.43% had persistent AF. According to the comorbidity of the patients, 49.18% had hypertension, 9.84% had a history of ischemic stroke or transient ischemic attack, 6.56% had diabetes, 6.56% had coronary artery disease, and 4.92% had heart failure. The mean CHA_2DS_2VASc was 1.46. The mean time between initial diagnosis and the procedure was 2.33 ± 2.95 years.

In terms of pre-procedural management, 11.48% underwent electrical cardioversion prior to RFCA. Antiarrhythmic drugs were prescribed in 60.66% of patients. Amiodarone, propafenone, and flecainide were prescribed in 34.43%, 24.59%, and 1.64% of patients, respectively.

Echocardiographic findings

The mean LVEF was 64.10 ± 11.12 %. The mean LA size was 42.15 ± 5.31 mm in diameter and 63.23 ± 27.01 ml in volume. The mean tissue Doppler E/E' ratio was 9.18 ± 4.09.

Procedural details

In 61 patients who underwent RFCA for the first time, 96.72% of procedures were performed under local anesthesia and conscious sedation. Pulmonary vein isolation was performed in all patients. Roofline, mitral isthmus line, and posterior wall isolation were created in 27.87%, 13.11%, and 3.28% of patients, respectively. Additional CFAEs were targeted in 19.67%. The mean fluoroscopic time was 109.03 ± 32.12 minutes. Table 2 provides the details of the procedure.

Procedural outcome

After 12 months of follow-up, there was complete data in 44 patients. Twenty patients (45.45%) remained in sinus rhythm after a single RFCA. Among the patients for whom sinus rhythm could not be maintained, eighteen patients (40.91%) had atrial fibrillation, and six patients (13.64%) had atrial flutter recurrence within one year. Table 3 shows the overall outcomes. Arrhythmia-free survival curve after a single RFCA attempt is shown in Fig 1.

Complications

From a total of 61 patients, only one patient (1.64%) had cardiac tamponade, while one patient (1.64%) had non-clinically significant pericardial effusion. In the latter case, the operator detected minimal pericardial effusion during RFCA and decided to stop the procedure. There was no esophageal injury, phrenic nerve injury, vascular complication at the puncture site, deep vein thrombosis, or stroke/transient ischemic attack found.

DISCUSSION

AF is the most common type of arrhythmia and is increasing in terms of its prevalence. Hence, there are numerous patients who require treatment. Apart from treating patients' comorbidity, lifestyle modification, and anticoagulant therapy to prevent stroke, rhythm control by RFCA is one of the procedures gaining interest due to its promising outcomes. Due to the complexity of this procedure, which may result in some complications, however infrequently, it can be life-threatening. The single-procedure success rates demonstrated in several studies vary depending on not only the patients' characteristics such as type of AF and comorbidity, but also the center's experience. According to a recent meta-analysis, the pooled overall single-procedure success rate, defined as the percentage of patients free of atrial arrhythmia or not requiring a second procedure at 12 months, was

TABLE 1. Baseline characteristics of the patients.

Characteristics	Patients (*n*=61)
Age (years) mean ± SD	58.3 ± 10.8
Male n (%)	47 (77)
BMI (kg/m^2) mean ± SD	26.4 ± 7.6
Type of atrial fibrillation n (%)	
Paroxysmal	40 (65.6)
Persistent	21 (34.4)
Comorbidity n (%)	
CAD	4 (6.6)
Previous stroke/TIA	6 (9.8)
Heart failure	3 (4.9)
Hypertension	30 (49.2)
Diabetes	4 (6.6)
CHA_2DS_2VASc score mean ± SD	1.5 ± 1.4
Previous cardioversion n (%)	7 (11.5)
Time between initial diagnosis and procedure (years) mean ± SD	2.3 ± 2.9
AAD before procedure n (%)	
Amiodarone	21 (34.4)
Flecainide	1 (1.6)
Propafenone	15 (24.6)
AAD after procedure n (%)	
Amiodarone	26 (42.6)
Flecainide	0 (0)
Propafenone	14 (23)
Echocardiographic features mean ± SD	
LVEF (%)	64.1 ± 11.1
LA diameter (mm)	42.2 ± 5.3
LA volume (ml)	63.2 ± 27
E/e'	9.2 ± 4.1

Abbreviations: AAD, antiarrhythmic drug; BMI, body mass index; CAD, coronary artery disease; LA, left atrium; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

TABLE 2. Details of the procedure.

Characteristics	Patients (*n*=61)
RFCA strategy n (%)	
PVI	61 (100)
Roofline	17 (27.9)
MI line	8 (13.1)
CFAEs	12 (19.7)
PWI	2 (3.3)
CTI	11 (18)
Fluoroscopic time (minutes) mean ± SD	109 ± 32.1

Abbreviations: CFAEs, complex fractionated atrial electrograms; CTI, cavotricuspid isthmus; MI, mitral isthmus; PVI, pulmonary vein isolation; PWI, posterior wall isolation; RFCA, radiofrequency catheter ablation

TABLE 3. Efficacy and safety outcome after 12 months of follow-up.

Outcome	Patients (*n*=44)
Overall free from atrial arrhythmia n (%)	20 (45.4)
Complication n (%)	
Pericardial effusion	1 (1.6)
Cardiac tamponade	1 (1.6)
Esophageal injury	-
Phrenic nerve injury	-
DVT	-
Vascular complication at puncture site	-
Stroke/TIA	-
Death	-

Abbreviations: DVT, deep vein thrombosis; TIA, transient ischemic attack

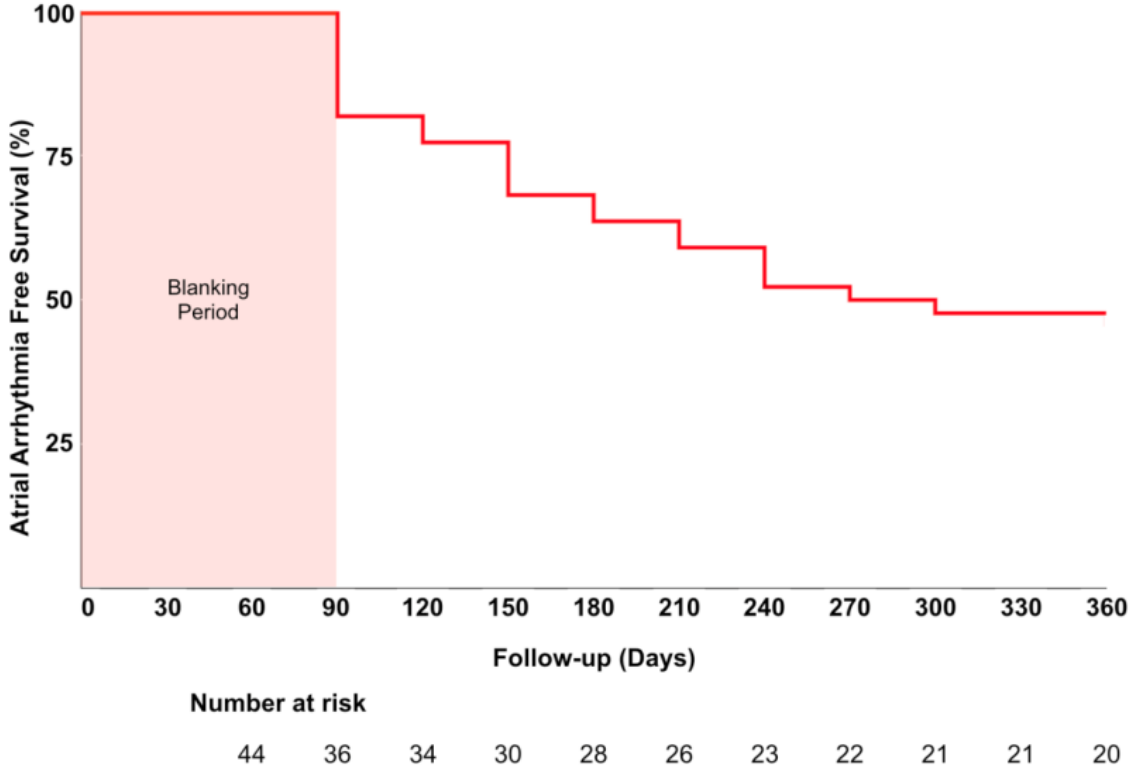

Fig 1. Atrial arrhythmia free survival after 12 months of follow-up.

64.2%.[13] Although a pioneering group demonstrated a very high success rate of 86% in treating paroxysmal AF with RFCA[14], the rate decreased to less than 70% in more recent studies. A study comparing the success rate based on the results of 7-day Holter monitoring at six months follow-up in two different RFCA strategies showed 42% after circumferential, and 66% after segmental pulmonary vein ablation in sinus rhythm.[15] Another study revealed the arrhythmia-free survival rate after single RFCA was 40% at one year.[16] These differences in outcomes can be attributed to the learning curve and supplementing technological development. In our studies, the overall success rate after a single RFCA was 45.45%, which is somewhat lower than some published data. The higher recurrence may have been due to the operator's experience; it should be presumed there are many things to deal with in the learning curve for this new procedure. Moreover, certain sophisticated technologies which could improve the success rate were not available at our center in the early part of the past decade. An individual patient's characteristics also might influence the outcome after RFCA. In our series, there were a number of non-paroxysmal AF patients and also a long duration between the time of first diagnosis and RFCA, which could have caused higher recurrence rates. The latter factor is one of the variables in a simple score model for predicting AF recurrence after RFCA.[17] Even with the lack of operator's learning curves and advanced technologies, the complication rate related to RFCA in our series was relatively low. Only one patient had a significant procedure-related complication, cardiac tamponade, which was promptly treated and resulted in a good outcome. Cardiac tamponade remains the most common potentially life-threatening complication associated with RFCA. The overall incidence of pericardial complication is 1.5%, which corresponds to our series. Importantly, the infrequency of complications at our center can ensure patients' safety with our safety protocols.

The data from this study demonstrate the safety and efficacy of RFCA for AF patients in our center. However, there were some limitations, which are commonly seen in retrospective studies. First, there was missing follow-up data in a number of patients. Second, symptom improvement and quality of life were the main treatment targets, but data was not systematically recorded. Hence, data collection was not possible for analysis. Finally, an important limitation was the lack of several lifestyles and risk factor modification data, which evidently may reduce the AF burden.[18] While we applied this treatment strategy to all AF patients, there were many missing

records. If individual risk factors are not be modified, it could cause the recurrence of atrial arrhythmia, even after successful RFCA.

CONCLUSION

The 1-year results of single-procedure RFCA for treating AF at Phramongkutklao Hospital, while not highly successful in our first decade, were comparable to other series. Notably, there was a relatively low rate of procedure-related complications. Other factors, which were not measured in this study, such as the operator's experience and ongoing advanced technologies as well as the enthusiastic treatment of associated risk factors, may contribute to improved outcomes in AF patients.

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Multimodal Imaging of Unaffected Fellow Eyes in Patients with Polypoidal Choroidal Vasculopathy and Neovascular Age-Related Macular Degeneration

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ABSTRACT

Objective: To identify retinal abnormalities in the unaffected fellow eyes of patients with unilateral polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (n-AMD).

Methods: In this cross-sectional, retrospective case series, the medical records of patients with PCV and n-AMD were reviewed and the baseline patient characteristics recorded. Abnormal findings on spectral-domain optical coherence tomography (SD-OCT) (steep/notched pigment epithelial detachment [PED], double-layer sign, hyporeflective lumen within the PED), fundus autofluorescence (FAF) (ring/patch patterns), and indocyanine green angiography (ICGA) (punctate hyperfluorescence spot [PHS]) were studied.

Results: Seventy-one fellow eyes of patients with PCV and 64 fellow eyes of patients with n-AMD were included. FAF showed abnormalities in 26 (36.6%) and 33 (51.6%) fellow eyes of those with PCV and n-AMD, respectively (p=0.081). SD-OCT detected abnormalities in 25 (35.2%) and 36 (56.3%) fellow eyes of those with PCV and n-AMD, respectively (p=0.014). ICGA detected PHS in 47 (66.2%) and 34 (53.1%) fellow eyes of PCV and n-AMD, respectively (p=0.122).

Conclusion: Multimodal imaging showed abnormalities in most asymptomatic fellow eyes of patients with PCV and n-AMD. Regular and long-term self-monitoring and fundus evaluation are important for these patients. The current findings support the differences in the pathogeneses of PCV and n-AMD.

Keywords: Multimodal imaging; fellow eye; Age-related macular degeneration; Polypoidal choroidal vasculopathy (Siriraj Med J 2021; 73: 121-127)

INTRODUCTION

Age-related macular degeneration (AMD) is a bilateral disease characterized by either bilateral drusen or retinal pigment epithelium (RPE) abnormalities. The deposition of lipid-rich material in the basal lamina of the RPE and the inner collagenous layer of Bruch's membrane has been reported in histologic studies of eyes with AMD and associated positively with choroidal neovascularization.[1,2] An estimated 20% of patients with AMD have neovascular AMD (n-AMD) and most have unilateral disease at presentation.[3] The fellow eyes of patients with n-AMD almost always have clinical abnormalities; however, the vision is unaffected.

Polypoidal choroidal vasculopathy (PCV) with a presentation of serosanguinous maculopathy is difficult to distinguish from n-AMD clinically, and many clinicians

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believe that PCV is a subtype of n-AMD. However, recent multimodal imaging studies have suggested different pathogeneses of PCV and AMD. PCV is a clinical manifestation within pachychoroid disease, which is a disease spectrum characterized by attenuation of the choriocapillaris overlaying dilated choroidal vessels and associated with pigmentation changes in RPE cells, RPE dysfunction, and new vessel formation.[4] Unlike AMD, the fundi of the fellow eyes of patients with PCV are usually unremarkable.

The fellow eyes of patients with unilateral n-AMD or PCV are the eyes that are at risk. Results from the Age Related Eye Disease Study showed that the highest risk level for progression to an advanced stage in the fellow eyes of patients with unilateral advanced AMD was 50% by 5 years and 71% by 10 years.[5,6] Imaging studies in those eyes may provide preclinical information about AMD and PCV and the difference in the disease pathogeneses. We used multimodal retinal imaging to identify the fundus abnormalities.

MATERIALS AND METHODS

The Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 057/2015) approved the study protocol. This study complied with the tenets of the Declaration of Helsinki (1964) and all of its subsequent provisions. This retrospective chart review was conducted in patients with PCV and n-AMD in the outpatient unit, Department of Ophthalmology, Siriraj Hospital, Mahidol University, between October 2012 and January 2016. All patients had been diagnosed with PCV or n-AMD based on fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus fluorescein angiography (FFA), and indocyanine green angiography (ICGA). We used the Everest study criteria to diagnose PCV based on clinical and ICGA findings[7]; to diagnose n-AMD, we adhered to the eligibility criteria given in the Macular Photocoagulation Study using FFA.[8]

The current study included only patients for whom data from SD-OCT, fundus autofluorescence (FAF), and ICGA from the fellow eyes were available. We excluded patients who underwent a previous macular laser treatment, photodynamic therapy, or intravitreous injections; patient with other macular diseases, such as macular scars, geographic atrophy, myopic maculopathy, and macular holes; and those with poor-quality images.

The data collection included the best-corrected visual acuity (BCVA), intraocular pressure, and any underlying systemic diseases. The fundus investigations included SD-OCT, FAF, and ICGA (Heidelberg Retina Angiography 2, Heidelberg Engineering, Inc., Heidelberg, Germany).

One co-author (S.P.) reviewed all the images included in the study. We set up a prototype image of each characteristic in each investigation as shown in Fig 1. The FAF findings were defined as abnormal hypo- or hyperautofluorescence, i.e., a ring pattern (round hypoautofluorescence surrounded by hyperautofluorescence ring), and a patch pattern (hypo/hyperautofluorescence patch without identification of round-shaped hypoautofluorescence)

The SD-OCT findings were categorized into four patterns[9,10]: 1) a steep pigment epithelium detachment (PED), defined as a steep, sharp, peak-like, perpendicular RPE elevation with underlying moderate reflectivity in the peak; 2) a notched PED, a PED with a V-shaped depression between two PEDs; 3) a double-layer sign; two highly reflective separated layers, defined as an undulating RPE line and the hyperreflective straight line of Bruch's membrane, and moderate hyperreflectivity between these two lines; and 4) a hyporeflective lumen within the PED, a delineated round/oval hyporeflective cavity in the PED.

The ICGA findings were punctate hyperfluorescence spots (PHS) in mid-phase (5 minutes) was the characteristic in ICGA.

Abnormal findings in all investigations were graded as present or absent. Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Categorical data are presented as the number or number and percentage, and continuous data are presented as the mean ± standard deviation. The demographic data were summarized using descriptive statistics. The chi-square test was used to evaluate qualitative variables. $P< 0.05$ was considered statistically significant.

RESULTS

Two hundred and thirty-five eyes were enrolled in this study. We excluded 34 eyes with uncertain diagnoses, 35 with poor-quality retinal images, 30 with old fibrotic scars, and one previously treated eye. Ultimately, 71 unaffected fellow eyes of those with PCV (36.6% were right eyes) and 64 fellow eyes of those with n-AMD (46.9% were right eyes, p=0.23) were enrolled. The average patient ages were 64.8 years and 73.3 years for those with PCV and n-AMD, respectively (p<0.01). Thirty-eight patients (53.5%) in the PCV group and 25 (30%) of n-AMD group were women.

The mean logarithm of the minimum angle of resolution VA of the fellow eyes of those with PCV and n-AMD were, respectively, 0.23 and 0.36 (p=0.09). No significant differences among the groups were seen

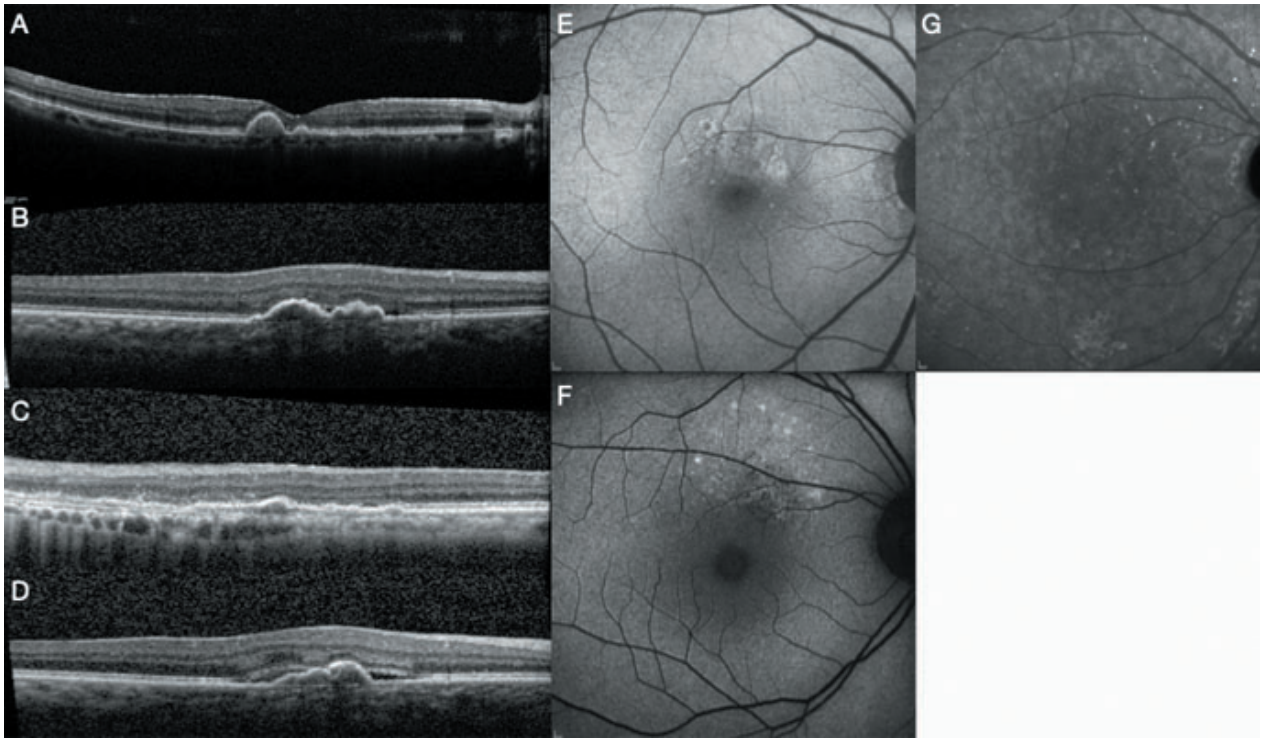

Fig 1. Representative images of abnormal imaging findings. Abnormal findings on spectral-domain optical coherence tomography (SD-OCT) images are classified as: **(A)** a steep pigment epithelial detachment (PED) characterized by steep/sharp peak-like and perpendicular elevation of the retinal pigment epithelium (RPE) with underlying moderate reflectivity in the peak; **(B)** a notched PED, a PED with a V-shaped depression between two PEDs; **(C)** a double-layer sign characterized by two highly reflective separated layers, which represent an undulating RPE line and a hyperreflective straight line of Bruch's membrane, and moderate hyperreflectivity between these two lines; and **(D)** a hyporeflective lumen in PED, which is a delineated round/oval sub-RPE cavity. Abnormal fundus autofluorescence is classified into two patterns: **(E)** a ring pattern, round hypoautofluorescence surrounded by a hyperautofluorescence ring and **(F)** a patch pattern, a hypo/hyperautofluorescence patch without identification of round-shaped hypoautofluorescence. **(G)** An abnormal finding in the indocyanine green angiography images is punctate hyperfluorescence spots characterized by multiple hyperfluorescent dots at the 5-minute time point.

in gender, laterality, or BCVA. However, patients with n-AMD were significantly older than those with PCV (Table 1).

Abnormalities of retinal imaging were found in 65 (91.5%) patients with PCV and 57 (89.1%) patients with AMD. Fundus autofluorescence showed abnormalities in 26 (36.6%) of those with PCV and in 33 (51.6%) of the fellow eyes of those with n-AMD (p=0.081). In the fellow eyes of those with PCV, a ring pattern was observed in eight eyes (11.3%) and a patch pattern in 18 eyes (25.4%). In the fellow eyes of those with n-AMD, ring and patch patterns were identified in 12 eyes (18.8%) and 21 eyes (32.8%), respectively.

SD-OCT detected abnormalities in 25 fellow eyes (35.2%) of those with PCV compared to 36 fellow eyes (56.3%) of those with n-AMD (p=0.014). In the PCV group, steep or notched PEDs were seen in 23.9%; whereas 1.4% and 11.3%, respectively, had a hyporeflective lumen or double-layer sign. In the n-AMD group, steep or notched PEDs and double-layer sign were found 46.9% and 10.9% respectively.

ICGA identified PHS in 47 (66.2%) fellow eyes of those with PCV and 34 (53.1%) fellow eyes of those with n-AMD (p=0.12) (Table 2). ICGA showed the highest rates of abnormalities compared to FAF and OCT in PCV (40.8%, 14.1% and 2.8%, respectively) and n-AMD (25%, 4.7%, and 7.8%, respectively).

Abnormalities in multimodality imaging were shown in Table 3. Only abnormal findings in both OCT and FAF were found significantly higher in n-AMD patients comparing with PCV patients, 23.4% and 8.5% respectively (p<0.01).

DISCUSSION

To the best of our knowledge, this is the first study to use multimodal imaging to evaluate the unaffected fellow eyes of patients with PCV and n-AMD. Based on previous reports, the rates of fellow eye involvement have

TABLE 1. Demographic data of the patients categorized by disease of affected eye.

	PCV	n-AMD	P-value
Number of eyes	71	64	
Gender n (%)			0.12
Male	33 (46.48)	39 (60.94)	
Female	38 (53.52)	25 (30.06)	
Age; min-max (mean)	2-82 (64.78)	56-90 (73.28)	<0.01
Laterality n (%)			0.23
Right	26 (36.62)	30 (46.88)	
Left	45 (63.38)	34 (53.12)	
BCVA; mean logMAR	0.23	0.36	0.09

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; BCVA, best corrected visual acuity; logMAR, logarithm of the Minimum Angle of Resolution.

TABLE 2. Abnormal findings in multimodal imaging.

	PCV n (%) Total 71 eyes	n-AMD n (%) Total 64 eyes	P-value
Abnormal findings in FAF	26 (36.6)	33 (51.6)	0.081
Ring pattern	8 (11.3)	12 (18.8)	
Patch pattern	18 (25.4)	21 (32.8)	
Abnormal findings in SD-OCT	25 (35.2)	36 (56.3)	0.014
Steep and/or notched PED	17 (23.9)	30 (46.9)	
Hyporeflective lumen within PED	1 (1.4)	0	
Double-layer sign	8 (11.3)	7 (10.9)	
Abnormal findings in ICGA			
Punctate hyperfluorescence spots	47 (66.2)	34 (53.1)	0.122

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography; PED, pigment epithelium detachment; ICGA, indocyanine green angiography.

TABLE 3. Abnormal findings in combined modalities.

	PCV n (%) Total 71 eyes	n-AMD n (%) Total 64 eyes	P-value
SD-OCT and FAF	6 (8.5)	15 (23.4)	0.008
SD-OCT and ICGA	8 (11.3)	3 (4.7)	0.149
FAF and ICGA	1 (1.4)	2 (3.1)	0.501
SD-OCT, FAF and ICGA	9 (12.7)	13 (20.3)	0.232

Abbreviations: PCV, polypoidal choroidal vasculopathy; n-AMD, neovascular age related macular degeneration; FAF, fundus autofluorescence; SD-OCT, optical coherence tomography; ICGA, indocyanine green angiography.

ranged from about 6% to 11% in n-AMD and 12% in PCV.[11-15] This indicated that the unaffected fellow eyes of patients are the eyes at risk. Multimodal investigations are useful for early detection of diseases in asymptomatic fellow eyes and understanding disease pathogeneses.

Photoreceptor phagocytosis is a major function of RPE cells. When the RPE phagocytoses the photoreceptor outer segments, lipofuscin accumulates as an oxidative byproduct within the RPE cells. Lipofuscin contains the pigment A2E, which causes autofluorescence. Abnormalities of the RPE cells are accompanied by loss of A2E and lead to hypoautofluorescence.[16] In conditions in which the RPE has an incomplete phagocytosis process, excessive build-up of lipofuscin material and hyperautofluorescence in FAF can result.[10] Dysfunction of the RPE can present with either hypo or hyperautofluorescence depending on the disease stage. Therefore, FAF can indirectly represent the physiology of the RPE.

The pathogenesis of AMD begins with dysfunction in the RPE cells and leads to accumulation of both intracellular and extracellular material. Structural changes in the basement membrane of the RPE and lipid deposition in the inner aspect of Bruch's membrane have been reported in histologic studies of AMD.[1,2] Impaired permeability of nutrients and water in Bruch's membrane causes metabolic stress in the RPE cells and leads to consequent cellular atrophy or neovascular formation.[17] While the pathogenesis of PCV originates from the deep choroidal vessels, dilatation of the choroidal vessels in Haller's layer results in focal or diffuse attenuation of the inner choroidal vessel and choriocapillaris, which ultimately can affect the overlying RPE.[18-20] Therefore, in early-stage PCV, patients can present with unremarkable fundi if the RPE is not yet involved.

The current study showed FAF abnormalities in fewer fellow eyes of those with PCV than in the fellow eyes of those with n-AMD (36% vs. 51%, respectively). Moreover, the abnormalities seen on the SD-OCT images of the fellow eyes of those with PCV also were seen less often than in PVC (35% vs. 56%, respectively). Our explanation is that the pathogenesis of PCV originates in the choroid and FAF and SD-OCT can detect abnormalities only when the RPE is involved, not in the very early stage of PCV in which the RPE is still intact. While the pathogenesis of AMD begins in the RPE cells in which FAF can detect physiologic dysfunction and SD-OCT can visualize structural changes even in early stage, the current findings confirmed that the pathogeneses of AMD and PCV are distinct in origin. Furthermore, both FAF and SD-OCT can detect early abnormalities even in asymptomatic eyes.

SD-OCT can detect the structural changes in the RPE in many patterns and some of them are specific to PCV such as a steep PED, notched PED, double-layer sign, and hyporeflective lumen inside PEDs.[10] However, in the current study, all of the aforementioned patterns, except for the hyporeflective lumen inside the PEDs, also were detected in the fellow eyes of those with n-AMD. Therefore, a steep PED, notched PED, and double-layer sign may not be specific OCT findings of PCV.

In our study, fellow eyes with abnormalities in both OCT and FAF were found significantly higher in n-AMD which confirmed the pathogenesis of AMD originates from RPE dysfunction as mentioned earlier. While other combinations of imaging did not show significant correlation with PCV or n-AMD. Yamagishi and colleagues[23] described abnormal FAF in PCV as confluent hypoautofluorescence represented by well-

demarcated hypoautofluorescence surrounded by hyperautofluorescence, which we refer to as the ring pattern in the current study. This finding was associated with the polypoidal lesions seen on ICGA images. This characteristic was observed in most eyes with PCV and not in typical n-AMD. Those authors proposed that the anterior protrusion of polyp lesions may induce RPE damage.[21] However, in the current study, a ring pattern also was seen in 18% of the fellow eyes of those with n-AMD. Therefore, this finding in FAF may not be specific to PCV. Any pathology that involves the RPE and causes RPE damage can demonstrate a ring pattern as well, while a patch pattern, represented by hypo/hyperautofluorescence, is a nonspecific FAF finding that may represent changes in RPE function in early-stage diseases of the RPE cells and adjacent structures.

ICGA is an invasive investigation. Because of its longer operating wavelength, ICG can fluorescence through the RPE better than fluorescein dye. ICGA is useful for detecting abnormal choroidal vasculature. The specific characteristics of ICGA in PCV were reported and used as diagnostic criteria.[7] However, a non-specific finding in ICGA, such as PHS, has been described previously in choroidal vasculopathy disorders. Those punctate spots were believed to be in the inner choroid and possibly the RPE layer and were found to be associated with the hyperpermeability of the choroidal vessels causing dye leakage in the late phase.[22,23] Park and colleagues[26] reported a higher incidence of PHS in PCV than n-AMD in affected and contralateral eyes. Those authors suggested that PCV may arise from choroidopathy and be distinct from typical n-AMD.[24] In the current study, PHS was detected in the fellow eyes of those with PCV and n-AMD and the difference did not reach significance (66% in PCV vs. 53% in n-AMD). Because the punctate spots can be present in either the inner choroid or RPE, this nonspecific finding may be associated with both PCV and AMD. Therefore, PHS may not be a finding specific to PCV, in that it can be detected in AMD as well.

In the current study, compared to FAF and SD-OCT, ICGA detected the most abnormalities in the fellow eyes of those with PCV. About two-thirds of the fellow eyes of those with PCV had abnormalities on ICGA images compared with only one-third of patients with abnormalities on FAF or SD-OCT images. This result may suggest that patients who have normal findings on FAF or SD-OCT still have a risk of developing PCV in their fellow eyes and those eyes should be monitored regularly. Although ICGA seems to be the best investigation for detecting choroidal pathologies, especially in early or even preclinical disease stages, ICGA is not likely to be performed during routine screenings because it is invasive and complex. FAF and SD-OCT are noninvasive and reproducible investigations, so they are more likely to be used for screening PCV in asymptomatic eyes, even though their abilities to detect abnormalities are lower than that of ICGA.

The current study had several limitations. The retrospective cross-sectional design may cause a systematic bias toward population selection. The small sample size and lack of follow-up also were drawbacks. Finally, the evaluation of all images was lacking in quantitative analysis results in subjective information.

In conclusion, most asymptomatic fellow eyes of those with PCV and n-AMD, which are the better eyes of patients, showed abnormalities in all current investigations and may represent the eyes at risk. Patients and physicians should be more concerned about the status of these eyes. The correlation between abnormal findings in each imaging modality may contribute to important information that can predict possible disease progression. Additional longitudinal long-term studies may facilitate a better understanding of the pathogeneses and course of these diseases.

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The Preparation for Interprofessional Practice (IPP) in Nursing Students at Mahidol University, Thailand: The Situation Analysis

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ABSTRACT

Objective: This study involved a situation analysis of nursing students' preparation and demand for interprofessional practice (IPP) with an aim to make improvements to the interprofessional education (IPE) curriculum.
Methods: This was a situation analysis involving 58 responses (75.32%) from the Faculty of Nursing, Mahidol University, Thailand, performed between August and December 2019. Personal information, closed-ended questionnaires, and descriptive questionnaires were utilized to assess the participants' perspectives regarding their approach to their preparation and demand for IPP. Reflection and interpretation methods were used to categorize the participants' descriptive answers. Additionally, data are reported as the mean, frequency, percentage, and p-value as appropriate.
Results: Overall, 45 (77.6%) participants had never taken the IPE course before. Of those who had taken the IPE course, 22.4% stated that having good communication skills was the main ability needed for multidisciplinary nursing practice in an open-ended question, participants indicated that their self-identity had the key effect on their confidence in multidisciplinary nursing practice (Non-IPE attendants, n = 19 (32.76%), IPE attendants, n = 6 (10.34%)). Furthermore, 77.78% of respondents said they prefer to perform nursing practice to prepare themselves to work with other healthcare professionals collaboratively.
Conclusion: IPE not only benefits healthcare students by preparing them to be able to work in their field but also prepares them to be able to collaboratively operate with different healthcare personnel. In particular, communication skills, self-confidence, and nursing practice skills are important attributes that need to be prepared.

Keywords: Interprofessional education; interprofessional practice; the nursing profession; healthcare personnel; situation analysis (Siriraj Med J 2021; 73: 128-140)

INTRODUCTION

Interprofessional education (IPE) is a key strategy for developing healthcare professional learners to prepare them to be able to give patient care in a collaborative team environment. The basic tenet of IPE is that when healthcare professionals work together, patient care is

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improved.[1-4] Previous research has shown that IPE can enhance the quality of healthcare services, empower health systems, and lead to better health outcomes.[5-9] Furthermore, IPE can bring students together with instructors from two or more health professions during their training practice. This situation allows all participants to learn from each other and to exchange ideas with each other. Consequently, this leads to the creation of shared knowledge and greater synergy among the various healthcare professions.[9-10]

In several countries, the perception of IPE has been improving and it is seen as a fundamental determinant for enhancing the effectiveness of health services.[11-12] Besides, numerous institutions, such as the World Health Organization, National Academies Practice, and the American Public Health Association, have indicated their support for IPE.[4,9,13] The previous literature reports how IPE, reviews of conferences, and regional IPE networks are becoming more common in many countries. A systematic review and meta-analysis of interprofessional education in healthcare revealed a statistically significant outcome of intervention by the IPE program in healthcare (the effect summary value of 1.37 with a confidence interval of 0.92 - 1.82). Nevertheless, the author recommended that additional investigation of clinical trials may help distinguish the effect of the IPE program on the students' clinical competence.[14]

Particularly in modern times, due to the complexity of health conditions and the ever-increasing number of patients, healthcare personnel need to be well trained and highly versatile to provide a high quality of care. Increasingly, working collaboratively with other healthcare professionals is needed. For nursing teaching staff, it is clear that they not only need to prepare students to be nurses but also need to prepare them to be competent interprofessional team members.[15]

In the Faculty of Nursing, Mahidol University, Thailand, after two years of delivering teaching courses for IPE in the classroom as a selective course, as known as NSID 332 Enhancing patient safety through inter - professional collaborative practice, which concerns about the science of safety, how it relates to problems with patient safety in health care system, role of individuals and inter-professional health care team in problem-solving, team work, and team communication, we are now looking to develop IPE education in the clinical field for interprofessional practice (IPP) in cooperation with two other faculties, namely the Faculty of Medicine and Faculty of Pharmacy. However, to develop a comprehensive IPE curriculum, we need to observe and understand how students prepare themselves for IPP. Previous research has suggested that the interpretation of IPE could actually be a barrier to the implementation of IPE.[4] Moreover, the result of a primer for implementing IPE within the pharmacy and health sciences curricula showed that it could provide tools, guidance, and lessons for educators to better know the process of improving practical IPE activities, performing successful IPE programs, and evaluating students' educational results. Furthermore, collaborative IPE programs can install a standard commission across professional programs, develop effective health care teams, form an assessment plan of students' competencies, and enhance patient care.[16]

Accordingly, we adapted our questionnaire from a survey that we generally survey students before they attend their first practicum section in the medical unit therefore so our questionnaire related to IPE in terms of nursing profession and multidisciplinary nursing practice that cloud improve outcomes for the students with regard to the students' needs. Our objective in the present study was to conduct a situation analysis regarding nursing students' preparation and demand toward IPP in order to gain insights to guide the development of the IPE curriculum at Mahidol University.

MATERIALS AND METHODS

Study setting

Mahidol University has grown since its official foundation in 1943 into one of the most prestigious universities in Thailand, and is now globally recognized for its high-quality research and teaching and its many exceptional accomplishments in teaching, research, international academic collaboration, and professional co-operation. In the university's Faculty of Nursing, the study strategies in the practicum nursing course are clear, whereby students are closely supervised by professional mentors, which provides students with opportunities to learn from other healthcare professionals while learning and practicing their skills.

Also, practicing in a medical unit in the Faculty of Nursing facilitates the students gaining a clearer understanding of the various roles in interprofessional teams, aided by the curriculum design, and of the complexity of diseases. Conventionally, nursing students are split into four groups to ensure an optimal group size for team-based learning, especially third-year students. Practical sections, including in medical, surgical, pediatrics, and maternity units, are fundamental units that are mandatory for all nursing students to take. Third-year nursing students also gain collaboration experience by working with fourth-year nursing students, sixth-year medical students, and pharmacists while practicing in

medical units. These settings allow the learners to be a part of a healthcare team under the supervision of their mentors.

This provides a good setting to collect data and consequently, in this study, data were collected and analyzed at the Faculty of Nursing, Mahidol University, Thailand.

Study design

This study involved a situation analysis of interprofessional education (IPE) using a quantitative method that included a questionnaire with closed-ended and descriptive questions. The study was conducted before developing the IPE curriculum. It will guide us to identify the preference for the IPE curriculum; establishes a clear, detailed, practical view of the possibilities, resources, difficulties, and limitations concerning students' perspectives and the quality of the situation analysis may affect the success of the entire effort to develop further strategies.[17]

Population and sample

As the annual assessment of readiness and perception of students prior to starting the practical class performed by the Medical Nursing Department, this situation analysis of IPE was launched on August 9, 2019. The target population consisted of 77 third year undergraduate nursing students who had completed the fundamental nursing courses and will study their first practicum section in the medical unit. Sampling was not decided, since we wanted to reach all of the target population. The questionnaire was distributed online, and 58 questionnaires were returned (a response rate of 75.32%).

Study instruments

The participants were asked to fill out an online questionnaire which comprised three parts as follows.

Part 1: Personal Information Inquiries

This part gathered information on the participants' demographics, including age and gender (as "Men" or "Women"), and their background in IPE (i.e., whether participants had "ever studied an IPE course before" or "never studied an IPE course before").

Part 2

This part involved a single descriptive question to back up part 1: How does the inspiration from IPE study help students to apply their skills in multidisciplinary nursing practice? If the respondents had IPE class experience (i.e., they had answered "Yes" to the question "Have you ever studied an IPE course before?" in question 3 of part 1), then they needed to type the answer to this part. These qualitative answers would be interpreted by manual qualitative analysis using Microsoft words.

Part 3

This section consisted of 5 questions that essentially inquired about the participant's attitude toward IPE.

The first question asked about their personal confidence in applying IPE skills in nursing practice. This was answered on a visual analog scale: a score of 0 meant no confidence, whereas, 10 was the most confident. As shown in the study that self-confidence is the one of the factors that influence the success in IPP.[18]

This question asked about the circumstances that convinced them about the importance of multidisciplinary nursing practice (e.g. the activities that nursing students feel most confident performing). This was answered on an ordinal scale: participants needed to arrange 8 examples of situations from the highest confidence rating to the lowest.

The third descriptive question asked about the reasons why students might lose confidence in multidisciplinary nursing practice. This is a qualitative question, and allows the students to provide detail about what causes them to lose confidence.

The fourth question required the students to provide a score for their comfort level with other professions in multidisciplinary nursing practice (scale from 0 to 10, with 0 the lowest score and 10 the highest score).

Finally, we asked the nursing students how they prepare themselves for practicing and learning with other healthcare professionals. This question is an open-ended question.

Data collection

After the information was provided, participants who had answered the questions online voluntarily (through Google forms) were invited to take part in the full study and then to submit to a questionnaire that would take approximately 15 to 20 minutes.

Data analysis

For the descriptive answers, we first reflected on the answers in order to interpret the student's thoughts and then categorized them in groups. For the quantitative data, the data were inputted into Excel software for the measurements and analysis. Data are reported here as the means, frequency, percentages, and p-value as appropriate.

RESULTS

Part 1: Personal Information Inquiries

Between August and December 2019, 58 out of the

77 participants (75.32%) had completed and returned the questionnaires, of whom 98.3% were female, 96.5% were in the age range 19-21 years old, and 22.4% had participated in the IPE elective course previously (Table 1).

Part 2

This part comprised the descriptive question related to part 1: How does the inspiration from IPE study help students to apply their skills in multidisciplinary nursing practice? If the respondents had prior IPE class experience, they must answer this part of the questionnaire. The result showed that 22.4% of the participants had taken the IPE course previously. Of these, 40.00%, 26.67%, 20.00%, and 13.33% of them thought that the IPE course would help them to apply communication skills, nursing practice skills, collaboration skills, and patient safety skills more effectively in working with other healthcare personnel, respectively (Table 2).

Part 3

This section consisted of 5 questions that essentially inquired about a participant's attitude toward IPE.

The first question asked about their confidence in IPE in preparing them for nursing practice. This was scored on a visual analog scale, where a score of 0 meant no confidence, while 10 was the most confident. The results revealed that their confidence scores in multidisciplinary nursing practice averaged 5.64 out of 10, with 37.9% of participants scoring their confidence as 7 or more out of 10. The confidence scores in multidisciplinary nursing practice for students who had participated in the IPE course averaged 7.07 out of 10 (n = 13), while students who had not taken that subject before scored this question 5.12 on average (n = 45) (p-value [P] = 0.000, 95% confidence interval [CI]: -2.969 to -0.918) (Fig 1).

This second question asked about the circumstances that students were confident about using their skills in multidisciplinary nursing practice. This was scored on an ordinal scale; whereby participants needed to arrange 8 examples of situations, ranking them from the highest confidence to the lowest. The result showed that 34.48% (n = 20) of respondents had the most confidence in taking a patient's vital signs, while 25.86% (n = 15) were confident doing fall prevention practice, and 24.14% (n = 11) felt they could confidently perform wound dressing for patients (Fig 2).

The third descriptive question asked about the reasons why students might lose confidence in multidisciplinary nursing practice. The results showed that almost half the respondents (43.10%: 32.76% of non-IPE attendants, 10.34% of IPE attendants) stated that their self-identity had the most impact on their confidence in multidisciplinary nursing practice, while 18.97% (17.24 % of non-IPE attendants, 1,72% of IPE attendants) revealed that this impact was caused by relationship with healthcare workers, and 12.07% (5.17% of non-IPE attendants, 6.90% of IPE attendants) said that their communication and the patients were factors that contributed to their reduced confidence, respectively (Table 3).

The fourth question required the respondents to rank their comfort score with other professionals in multidisciplinary nursing practice (scale from 0, as the lowest score, to 10, as the highest score). The result showed that students felt the most comfortable performing multidisciplinary nursing practice with classmates, with the highest average score of 8.35 out of 10, followed by teachers and nurse preceptors, with average scores of 8.18 and 8, respectively (Fig 3).

Finally, we asked the nursing students how they prepare themselves for practicing and learning with other healthcare professionals. The results showed that almost 79.37% of the students preferred to prepare their nursing practice skills to work with other healthcare personnel. Moreover, 7.94%, 6.35%, 3.1%, and 3.17% stated that collaboration skills, communication skills, patient safety skills, and other skills need to be prepared, respectively (Table 4).

TABLE 1. Characteristics of the study participants.

Responses	Total n = 58	%
Sex, no (%)		
Men	1	1.7
Women	57	98.3
Age, years		
19	2	3.4
20	43	74.1
21	11	19
24	1	1.7
27	1	1.7
Experience of IPE course		
Studied IPE course before	13	22.4
Never studied IPE course before	45	77.6

TABLE 2. Application of the IPE course skills with multidisciplinary nursing practice.

Code	Description	Responses	Frequency (n=15)
Communication skills	The students who studied the IPE course before responded that the IPE course improves their communication skills among the multidisciplinary team by learning how to communicate more efficiency	*"I have learned the differences and responsibilities of each professional field, and expect that this will be useful for our communication"*	6 (40.00%)
		"Obtain new knowledge that can be utilized to enhance patient safety, such as how to communicate with other professions more efficiently"	
		"This course helps us clarify the multidisciplinary team's responsibilities, which improve team communication, and collaboration in the future"	
		" To determine the experience of impermanence that has happened, being more careful and communicating well with other relevant professions"	
		"There are guidelines for organizing for efficient communication with multidisciplinary groups"	
		"Work more comfortably, communicate better"	
Nursing practice skills	The IPE course emphasizes the nursing practice as a crucial skill for the practice in IPP to the students.	*"Have knowledge of operational skills needed in the ward"*	4 (26.67%)
		"Increase knowledge for applying in nursing practice"	
		"It would benefit to be more prepared for the practicum nursing course"	
		"I would like to develop innovation and implement it with patients"	
Collaboration skills	The students apply for the IPE course in collaborating work by enhancing collaboration skills such as clarifying the roles of team members, and identifying and solving problems as a team.	*"I have learned the differences and responsibilities of each professional field, and expect that this will be useful for our communication"*	3 (20.00%)
		"I have learned that the mistakes that occurred may come from numerous individuals. So, working collaboratively would make us achieve the goal"	
		"This course helps us clarify the multidisciplinary team's responsibilities, which improve team communication, and collaboration in the future"	
Patient safety skills	The IPE course accentuates the importance of patient safety to the students.	*"Being conscious of the risks that encompass us would allow everyone to live in safety and reduce harm to themselves and patients"*	2 (13.33%)
		"Helping to be knowledgeable about patient safety"	

TABLE 3. Causes of students losing confidence in multidisciplinary nursing practice.

Code	Description	Responses	Frequency (n=58)	
Self-identity	The aspect of one's self-perception which generate from the individual memories, belief, motivation, emotion, and self-attribution	**From The students who studied IPE course before**	6 (10.34%)	25 (43.10%)
		"Lack of knowledge"		
		"Fear"		
		"Little knowledge or excitement"		
		"Knowledge is not well-rounded"		
		"Being blamed without being told what the mistake was"		
		"Lack of the courage to speak up for oneself"		
		From The students who never studied IPE course before	19 (32.76%)	
		"Wrong nursing practice"		
		"Not having enough knowledge and concerns"		
		"Not having enough knowledge to provide nursing services to patients and incorrect operations that may cause harm to patients"		
		"Knowledge and experience are not enough to conduct multidisciplinary practice"		
		"Mistakes that occur due to insufficient knowledge"		
		"The knowledge I have is not accurate"		
		"Not having enough knowledge and confidence in nursing practice"		
		"Not having enough knowledge, so may not understand the treatment order of other professions"		
		"We are unprepared to perform"		
		"Insecurity in nursing for patients and inexperience"		
		"Concerns about lack of knowledge and fear"		
		"Being rushed and receiving everyone's suggestion, which makes it hard to know whom I have to listen to"		
		"Not confident in knowledge or fluent in procedures"		
		"Not as fast as I should be"		
		"Being unfamiliar, inaccurate, and afraid to make mistakes"		
		"Not yet proficient"		
		"When someone tells you to do what you do; it might cause uncertainty"		
		"Too excited to do"		
		"Excited and worried about not doing well"		

TABLE 3. Causes of students losing confidence in multidisciplinary nursing practice. (Continue)

Code	Description	Responses	Frequency (n=58)	
Relationship with healthcare workers	The way in which two or more people between nursing students and healthcare workers including nursing teacher and nurse preceptor feel and behave towards each other	**From The students who studied IPE course before** *"Working with people with more experience"* **From The students who never studied IPE course before** *"Being accused of being wrong and not listening. For example, if I did a mistake and the teacher would give suggestions for improving, such as telling me how to perform in better ways, I would be ready to understand, but if there are sentences such as "Why can't I just do this?, Don't you have any intellect to do this? etc., it would cause me to lose my confidence and I do not want to do that"* *"Being scolded by a teacher with harsh words and psychological abuse leads to a loss of confidence and feelings of discouragement, and a lack of energy in nursing"* *"Fear of being scolded by the teacher despite sometimes being prepared to learn, but the form of each person's teaching is different"* *"Teachers and senior nurses put too much pressure on while practicing"* *"Preceptors"* *"Being rigorously blamed by seniors or others until I'm afraid to do anything"* *"The interdisciplinary members can do better nursing than nurses"* *"Mentors"* *"Being scolded"* *"Being stared at"*	1 (1.72%) 10 (17.24%)	11 (18.97%)
Communication	Verbal speech or other methods of expressing information	**From The students who studied IPE course before** *"Worried about communication because of misunderstanding medical terminologies"* *"Unclear communication such as doctor's handwriting"* *"Being with a large group of people"* *"Teacher speech"* **From The students who never studied IPE course before** *"Communication"* *"The excitement that may cause communication errors"* *"Do not understand when talking with colleagues"*	4 (6.90%) 3 (5.17%)	7 (12.07%)

TABLE 3. Causes of students losing confidence in multidisciplinary nursing practice. (Continue)

Code	Description	Responses	Frequency (n=58)	
Patients	To worry or feeling nervous from patients' condition or about practicing nursing procedure that could affect patient	**From The students who studied IPE course before** *"Unsuccessful or successful procedures that affect the patient's body"* *"Patients feel pain while receiving care"* **From The students who never studied IPE course before** *"Patients have abnormal symptoms from what we do"* *"Dangerous to patients"* *"Fear of hurting patients"* *"Insecurity in nursing for patients and inexperience"*	2 (3.45%) 3 (5.17%)	5 (8.62%)
Others		**From The students who never studied IPE course before** *"The pressure from the environment"* *"Errors"* *"When making a mistake"* *"Nursing operations are unsuccessful or errors occur"* *"Making a mistake and getting cursed at"* *"Pressure"* *"Loud noise"* *"Activities that must be sterile"* *"Environment"* *"Contaminated, errors that may occur while operating"*	10 (17.24%)	10 (17.24%)

TABLE 4. The preparation of students toward a multidisciplinary nursing practice.

Code	Description	Examples	Frequency (n=63)
Prepare knowledge and practice skills	The students think that preparing nursing preparing nursing knowledge by reading a book, watching the related video, and practicing skills before the class is the crucial method for practicing with a multidisciplinary team	*"Prepare accurate knowledge to be ready to face various problems"* *"Summarize the lessons learning about nursing practice skills"* *"Regularly review the knowledge learned from practice, remember the name of the drug, and the mechanism of action of the drug"* *"Watch video clips of nursing activities and read the pathology of diseases that are likely to be found in most patients, such as diabetes, in advance and prepare for what may be encountered"* *"Study the necessary knowledge for practicing. However, would also like the teacher to help"* *"Apply the knowledge gained from the IPE subject"*	50 (79.37%)
Collaboration	The students think that preparing themselves by learning the roles and responsibilities of the healthcare team will help them work together effectively	*"Learn the duties and work that need to be done together"* *"Study and understand the work of each profession"* *"Try to understand as much as possible other professions and find enough knowledge to understand instructions for the treatments given to patients"*	5 (7.94%)
Communication	The students think that practicing clear and concise communication will be useful	*"Practice clear and concise communication and plan for what can occur with patients together to come up with a solution to the problem in our responsible role"*	4 (6.35%)
Patient Safety	The students think that patient safety will be helpful	*"Learn and practice to prevent mistakes"* *"Seek additional knowledge to gain accuracy in work"*	2 (3.17%)
Others		*"Be mindful and concentrate, relax a lot, seek more knowledge and diligently practice as a person who notices the diversity of ourselves and others"* *"Review the content learned and get enough sleep"*	2 (3.17%)

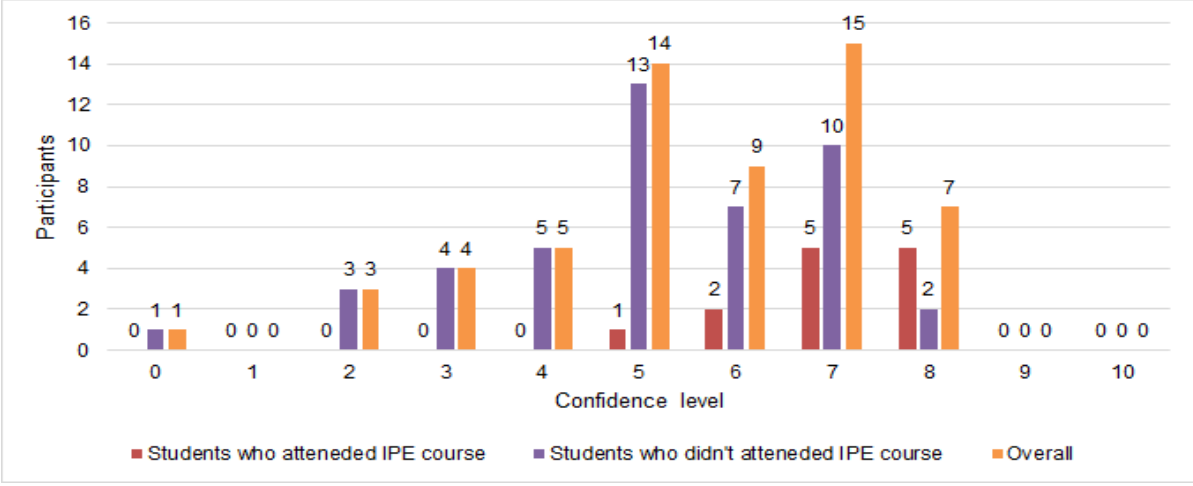

Fig 1. Confidence level of the students in multidisciplinary nursing practice.

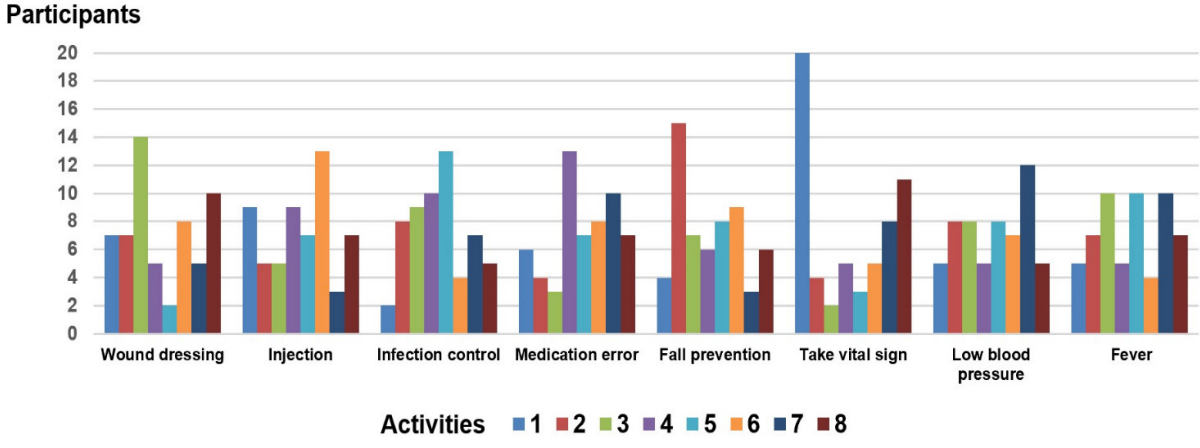

Fig 2. The circumstances that students are confident about using their skills in multidisciplinary nursing practice. This was scored on an ordinal scale; whereby participants needed to arrange 8 examples of situations, ranking them from the highest confidence (1) to the lowest (8).

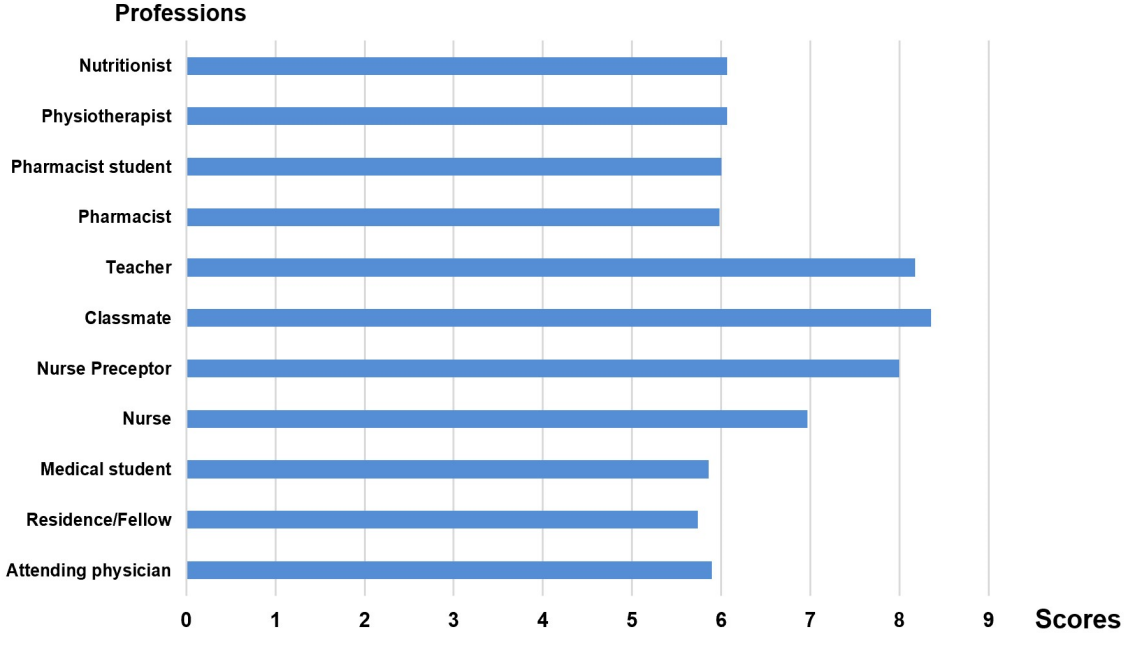

Fig 3. The average scores of how comfortable students are working with other professionals in multidisciplinary nursing practice.

DISCUSSION

IPE has been attracting lots of interest internationally.[19] Some institutions offer an IPE course as an elective course or even solely for undergraduate students, such as the universities in Germany.[20] In Thailand, numerous universities are currently seeking to make changes to their courses from the traditional method of students or faculty members doing an activity, taking courses, or performing clinical practice individually to a model of doing such things collaboratively.[15] Previous research has shown that working collaboratively can result in more effective outcomes, and, moreover, have suggested that working collaboratively should even be defined as a core competency.[20] In this study, we found that having good communication skills is an important factor to facilitating students to be able to work effectively with other healthcare professionals.

According to the results from Table 2, IPE helps students to be able to work in multidisciplinary teams through developing their communication, nursing practice, collaboration, and patient safety skills. The majority of students in the present study who had completed the IPE course previously mentioned that IPE improved their communication skills, which they felt were necessary for working in multidisciplinary teams. Correspondingly, previous studies have reported similar results, namely that IPE facilitates teaching students how to communicate, collaborate, and learn from other healthcare professionals.[21] In particular, skills in interprofessional communication are a precondition to improving IPP and can be facilitators or barriers to IPP.[22-23] Therefore, IPE, which strengthens and promotes cooperation within multidisciplinary teams, can play a pivotal role in preparing students for IPP through helping the students to develop several key skills they will need in clinical practice, especially communication skills.

Fig 1 shows that the students in the present study who had previously participated in the IPE course tended to have a higher self-perceived confidence level due to their better understanding of the complexities of care and the purposes of interprofessional teamwork. Longitudinal studies of the impact of IPE learning have also found that the participants show continuous improvements in confidence related to their improving communication skills and positive attitudes toward interprofessional relationships.[24] Both findings demonstrate that encouraging students who have participated in IPE courses to become leaders in practical sections would be useful.

We also gathered data regarding some situations where students would be confident in utilizing their skills in multidisciplinary nursing practice, as shown in Fig 2. The results demonstrated that the majority of respondents selected taking vital signs, which is a fundamental and important activity for nursing practice as it can aid the early detection of many consequences. Even though this part of the questionnaire is a survey that we generally survey students before they practice in clinical settings, this part of data allows us to know what students' interest is, which leads to designing the course or scenario based on student centered learning. Also, simulation would help students practice working collaboratively as suggested in a previous research, which stated that nursing students should be able to obtain ample opportunities to engage in teamwork learning experiences with other healthcare professionals to practice collaborative working.[25] Thereby, simulating fundamental practices, like taking vital signs, would engage students to practice teamwork, communication skills, and clinical decision-making more effectively.

Furthermore, according to Fig 3, their classmates are the people that most of the students felt the most comfortable working with. This is in line with previous research that reported that the strategy of enlisting students as interprofessional leaders or facilitators could be considered a successful strategy that has been applied in the past few years.[26] Given this, utilizing students who have experience in IPE as an educational resource in our setting needs to be explored in the future.

The students who had previously participated in the IPE course reported higher self-confidence levels. However, all the participants, including the IPE students, perceived that having low self-confidence, which is the main part of self-identity can also be a barrier to working in multidisciplinary teams, as shown in Table 3. In other words, someone who has weak self-identity, which is an individual's belief in his/her ability that he/she cannot complete the task, will result in poor readiness, and discourage cooperation with team members.[27] They realized that preparing themselves by practicing procedures and reviewing nursing information would be an essential method to increase their confidence. As we mentioned, we designed the questionnaire from our general survey, which normally surveys students before they practice in clinical settings. This information also benefits designing IPE curriculum, although building nursing-specific clinical knowledge and skills should be taught in profession-specific settings. For IPE courses, we would focus on integrating and strengthening nursing knowledge and skills, and in the meantime, interprofessional skills would be developed. Thereby, IPE would be a catalyst for facilitating students to integrate and strengthen nursing skills in practice. Recent research revealed that IPE is key

to effective interprofessional teaching and learning, with deep implications for preparing students for practice.[28] Additionally, with the complexity of modern healthcare environments, students are increasingly required to obtain some learning in IPE, which would provide the foundation for them to develop systems thinking and critical thinking in complex healthcare systems.[29]

CONCLUSION

To reach the most desirable outcomes for patients, the students recognized that preparing themselves by improving their skills is imperative, and low self-confidence is their weakness. In this regard IPE has many benefits in that it not only could help them to prepare themselves but would also increase their self-confidence by improving their communication and collaboration skills. Additionally, IPE would be a bridge between healthcare professions, which would facilitate multidisciplinary teams to be able to work and learn together effectively. This situation analysis would help us to improve IPE curriculum focused on preparing nursing students for IPP by based on the student centered learning. Nevertheless, for our future studies, we need to further study the impact of IPE in terms of its application to improve the IPE course and to ensure it fits our students' needs.

Author contributions

Wimolrat Puwarawuttipanit designed and conceived the whole study. Chitchanok Benjasirisan, Lalipat Phianhasin, and Suebsarn Ruksakulpiwat performed the survey, data analysis, drafting, and revising the article, these authors equally contributed to this work. Others help to prepare students for interprofessional education classes and suggest the design of the curriculum. All authors gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Annual Report's SMJ-2020

Editor-in-Chief: Prof. Thawatchai Akaraviputh

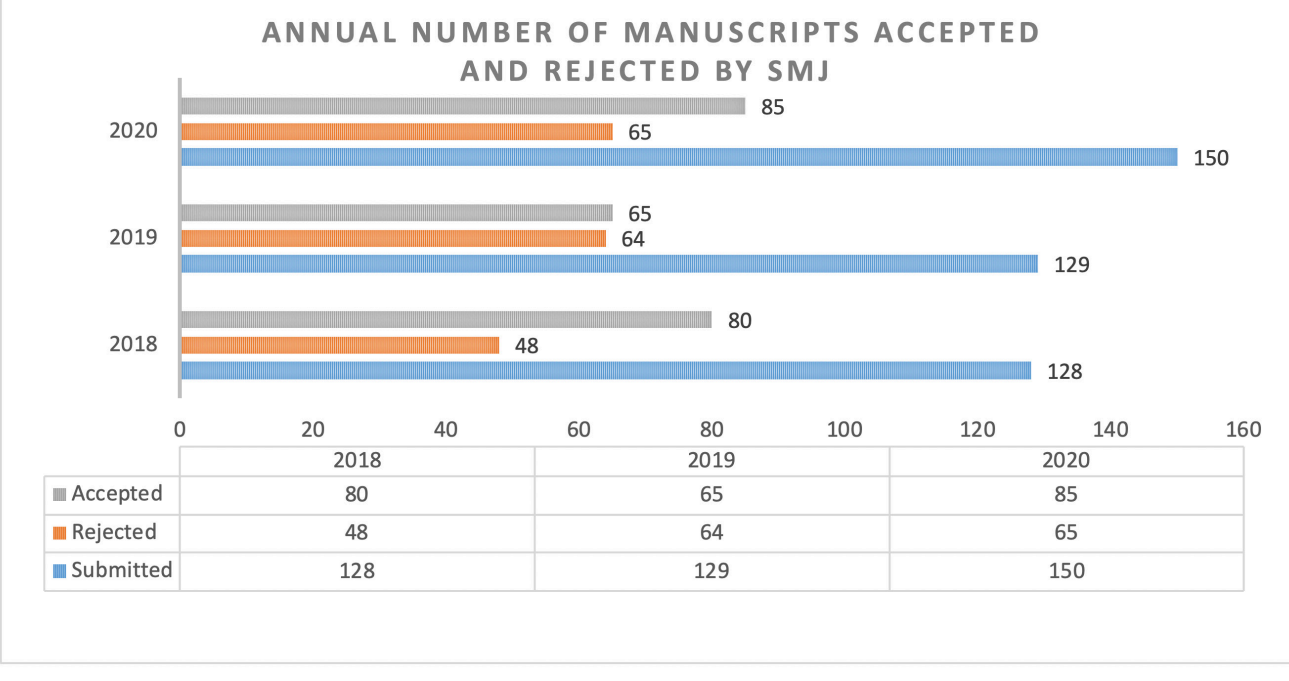
Since 1948 the journal has been introduced to the academia under the name of "Siriraj Hospital Gazette". In 2007 the journal was converted into English version and the journal name was changed to "Siriraj Medical Journal". The Siriraj Medical Journal is named after Prince Siriraj Kakudhabhand, the 18-month-old son of King Rama V, who passed away from dysentery a year before the opening of the Siriraj Hospital. The medical school was established two years later in 1890. The Siriraj Medical Journal (SMJ) has published more than 70 issues continuously for the past 70 years.

SMJ is now an open access, peer-reviewed journal governed by the Faculty of Medicine Siriraj Hospital, Mahidol University and also the official journal of Thai Association of Gastrointestinal Endoscopy (TAGE) and International Association of Surgeons Gastroenterologists and Oncologists (IASGO) Thai Chapter.

In 2020, 150 articles were completely submitted to the SMJ. This number is constantly growing over the last few years. The acceptance rate is now about 50-60%. Most authors whose articles did not reach to scientific quality or priority for publication would be notified within 4 weeks after complete submission.

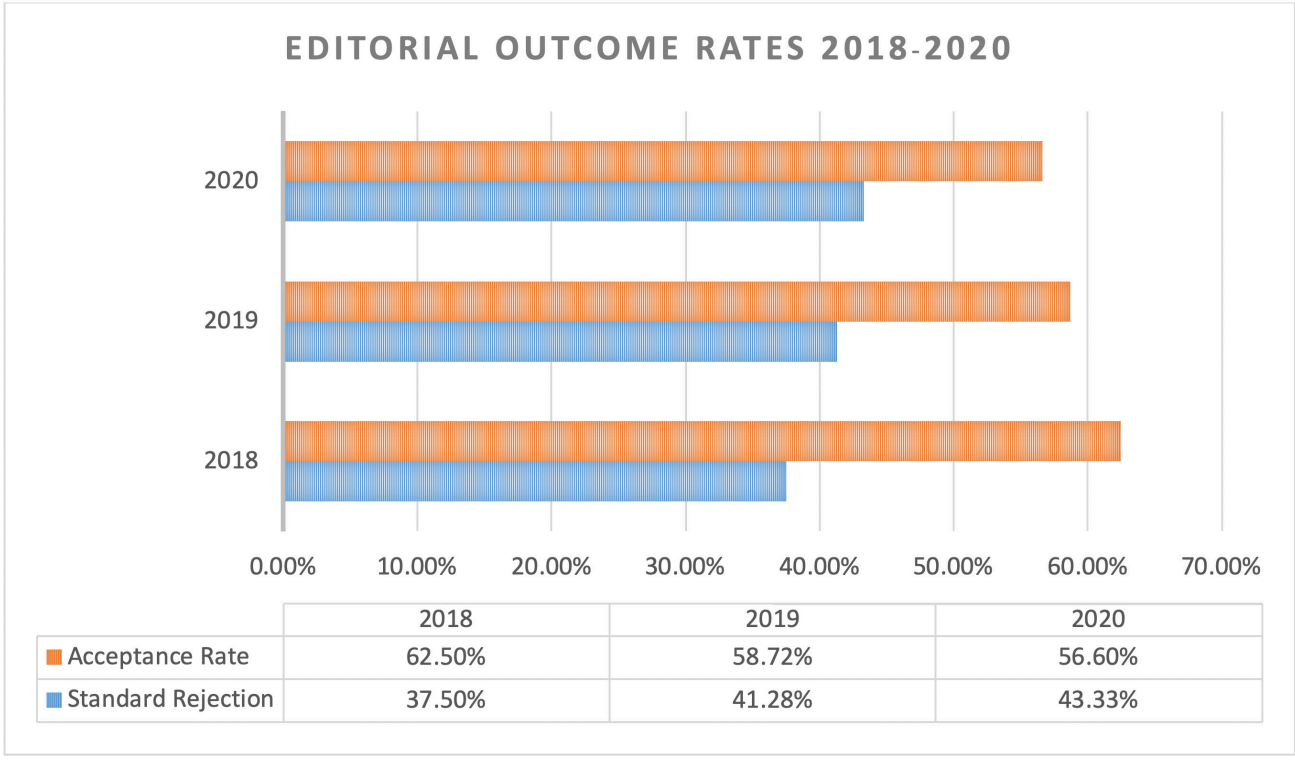
In 2021, the journal aim to publish an issue in a monthly basis which could increase the number of publication up to 120 articles per annum. International, multi-national or multi-institute articles are most welcome to be published in this journal with both international and national peer reviewers.

TABLE 1. Annual number of manuscripts accepted and rejected by SMJ



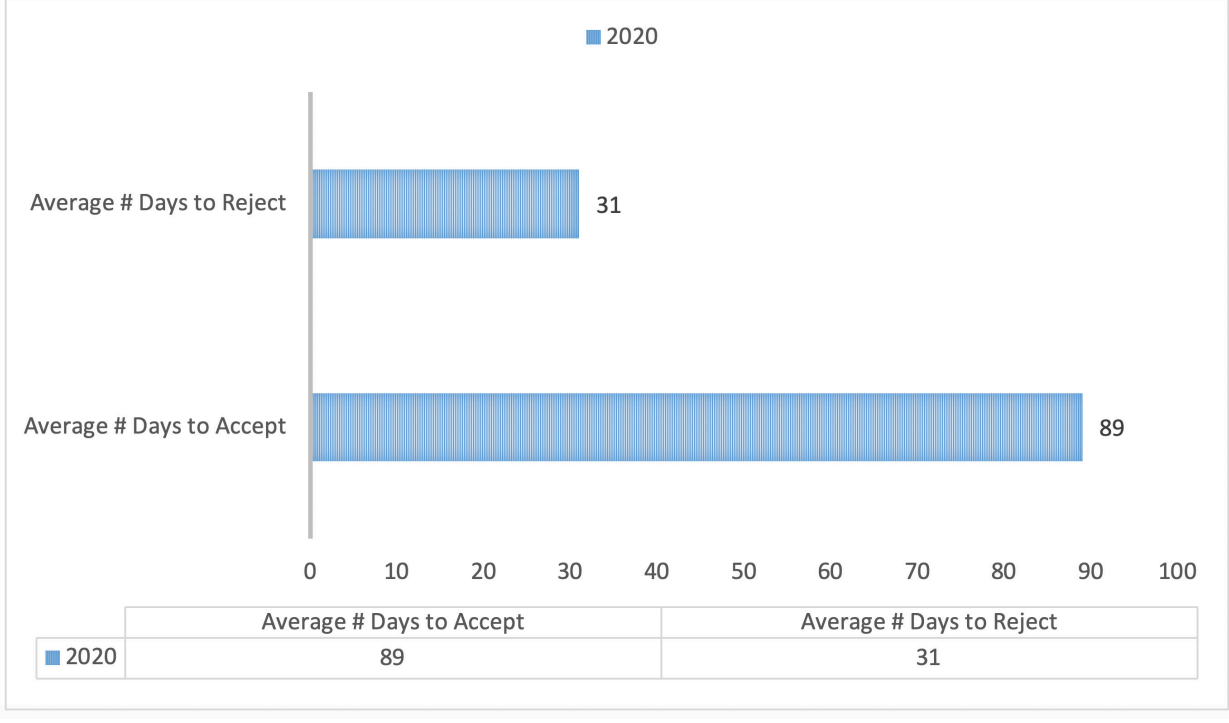
	2018	2019	2020
Accepted	80	65	85
Rejected	48	64	65
Submitted	128	129	150

TABLE 2. Editorial Outcome rates 2018-2020



	2018	2019	2020
Acceptance Rate	62.50%	58.72%	56.60%
Standard Rejection	37.50%	41.28%	43.33%

TABLE 3. Average speed for accepting or rejecting manuscripts by SMJ.



	Average # Days to Accept	Average # Days to Reject
2020	89	31

- Submissions in 2018-2020 came from over 20 different countries; Thailand represented 80% of total submissions to SMJ and 70% of accepted articles.

TABLE 4. The top countries of authors from which articles were accepted to be published in SMJ.

Country	Number of manuscripts (total = 222)		
	2020 (63)	**2019** (74)	**2018** (85)
Thailand	58	74	84
United States	5	1	8
Malaysia	2	2	4
India	2		
Japan	1		6
Singapore	1	2	2
Myanmar	1		2
Germany		1	1
Denmark		2	
Nepal			3
Taiwan			3
France			2
Australia			2

- Journal metrics
  In 2019, the ranking of the SMJ was in the 4th quartile of Scopus database. The CiteScore was 0.1, SJR 0.114 and SNIP 0.065 which is the first outcome of the journal.

- Top 5 cited articles of the SMJ (according to Scopus) published since 2016

TABLE 5. The most cited SMJ publications (to January 8, 2021)

Manuscripts	Citations	2018	2019	2020	2021	Total
	Yr./Total	*1*	*10*	*24*	*1*	*36*
1. An association of Cryptococcus neoformans/ C. gattii genotype and HIV status in Asia: A systematic review	**2019**			**2**		**2**
2. Robotic surgery in Thailand: Current status and future development	**2018**			**2**		**2**
3. The normal reference values of carrying angle from birth to adolescence	**2018**			**2**		**2**
4. The association between mammographic and ultrasound features and histologic grade in invasive ductal carcinoma of the breast	**2018**		**2**			**2**
5. Significance of microscopic residual tumor in adenocarcinoma of stomach and esophagogastric junction after gastrectomy with D2 lymphadenectomy	**2018**		**1**	**1**		**2**

- Top 10 articles viewed & downloaded from the official website (https://he02.tci-thaijo.org/index.php/sirirajmedj) until end of 2020.

Article Details 19 of 944 articles

Title	Search by title, author and ID	Abstract Views	File Views	PDF	HTML	Other	Total
Kongkam et al. The Practice of Endoscopy during the COVID-19 Pandemic:Recommendations from the Thai Association for Gastrointestinal Endoscopy (TAGE) In collaboration with the Endoscopy Nurse Society (Thailand)		343	398	398	0	0	741
Norphun et al. Stress and Coping Strategies among Thai Medical Students in a Southern Medical School		250	321	321	0	0	571
Srikong et al. Immersive Technology for Medical Education: Technology Enhance Immersive Learning Experiences		256	168	168	0	0	424
Suntirukpong et al. Postmortem Scavenging of Human Remains by Domestic Cats		351	52	52	0	0	403
Khunthason et al. Factors Influencing the Occurrence of Hand Foot and Mouth Disease Among Children in Day Care Centers in Northern Thailand		354	45	45	0	0	399
Tongyoo et al. Albumin Versus Gelatin Solution for the Treatment of Refractory Septic Shock: A Patient Baseline-Matched-Cohort Study		304	61	61	0	0	365
Ninlerd et al. Effect of home-based rehabilitation exercise program for elderly patients with femoral neck fracture after bipolar hemiarthroplasty		198	155	155	0	0	353
Ngamjarus n4Studies: Sample Size Calculation for an Epidemiological Study on a Smart Device		233	96	96	0	0	329
Shimizu et al. International Telemedicine Activities in Thailand		38	282	282	0	0	320
Wasuwanich et al. Coronavirus Disease 2019 (COVID-19) and Its Gastrointestinal and Hepatic Manifestations		164	142	142	0	0	306

- Special Issue published.

In 2019, SMJ published a special issue with the title "Surgery" in volume 73, No.6, November-December. There are 12 original articles. We plan to publish a special issue of "Pediatric" in next year.

- Looking ahead.

In 2021 we will focus on attracting more high-quality submissions from around the world, improving our editorial process by using editorial manager system, publishing more papers and increasing our citescore. We will monitor the progress in these aspects closely. We also aim to expand the visibility of the journal through partnerships and more prominent social media presence.

For all that SMJ has achieved this year, I am deeply indebted to the editorial board both national and international, and also to Managing Editor, Associated Editor and Assistant Editor. I would like to convey my gratitude to the many scholars who peer reviewed SMJ manuscripts during the past year. We thank all of our partners for the publishing and enthusiasm by which they sustain our operations.

Prof. Thawatchai Akaraviputh
M.D., Dr. med. (Hamburg)
Editor-in-Chief