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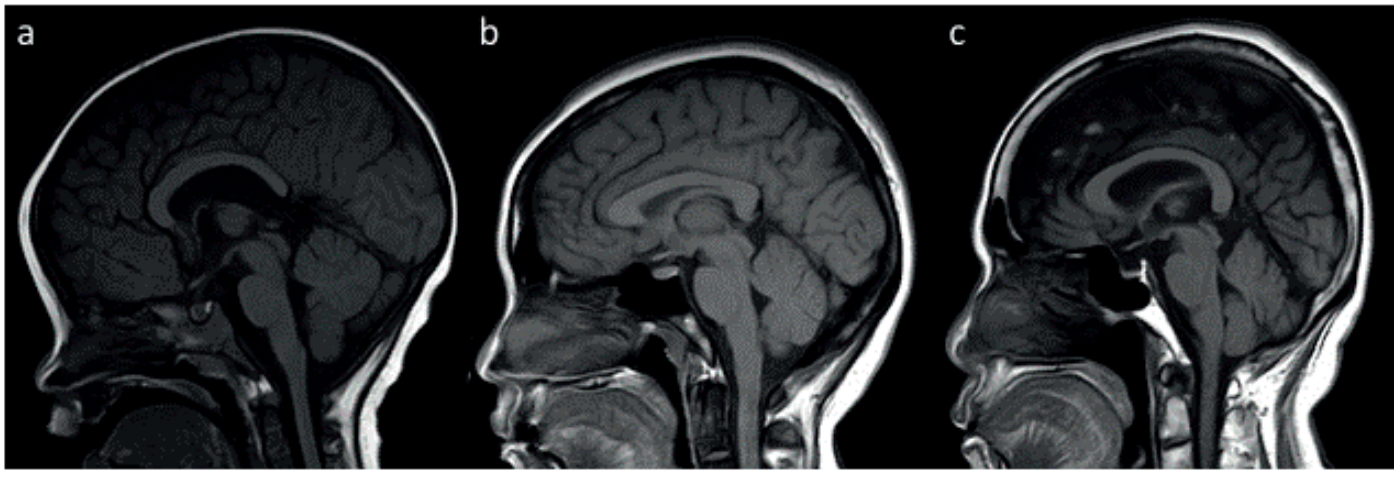

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Assessment of Psychological Distress and Coping Strategies among Dental Undergraduate Students in a Malaysian University during COVID-19 Pandemic

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ABSTRACT

Objective: Drastic changes took place in Malaysia due to COVID-19 pandemic including education where the students had to undergo remote teaching and learning at their respective hometown to prevent the spread of COVID-19. This change in the mode of learning is a stressful event faced by the students. This study aimed to assess the psychological distress and the coping strategies of undergraduate dental students during COVID-19 pandemic.

Materials and Methods: A cross sectional study was conducted on a sample of 224 undergraduate students of Faculty (Kulliyyah) of Dentistry in the academic session of 2020/2021. The psychological distress level was assessed using the Kessler psychological distress scale (K10) and the coping mechanisms of the students were determined using the Brief-cope questionnaire.

Results: The rate of severe psychological distress was found to be 40.18%, while 22.32% and 18.75% had mild and moderate distress respectively. Students that are less than 21 years old showed a significantly lower mean of psychological distress compared to students above 21 years old. There was no statistically significant difference in psychological distress in terms of gender. More students showed approach coping strategy than avoidant coping. Approach coping showed a negative correlation with psychological distress while avoidant coping showed a statistically significant positive correlation with psychological distress.

Conclusion: Psychological distress during COVID-19 pandemic is occurring at a high rate among dental students. Psychological distress level is increased in students with avoidant coping strategies.

Keywords: Coping strategy; COVID-19; dental student; Malaysia; psychological distress (Siriraj Med J 2022; 74: 350-356)

INTRODUCTION

Psychological distress in characterized by as a state of emotional suffering that may manifest two major form of symptoms such as depression (e.g. hopelessness, sadness, lack of interest) and anxiety (e.g. palpitations, lightheadedness, restlessness). Each of these forms consists of two types of symptoms which are mood and malaise. Mood refers to feelings such as sadness or angst while malaise refers to somatic manifestations such as restlessness and stomach upset.[1] Psychological distress is widely used as an indicator of public mental health or as an outcome for intervention studies and

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clinical trials. University students are generally at risk of developing symptoms of depression and anxiety as the prevalence of psychological distress is high among university students compared to the general population data.[2] Students can be impacted in a variety of ways, their ability to learn and their ability to interact and function, mental health well-being, and general health. All of these are due to the presence of stressors during their education in the university.[3] In addition to the academic stressors, in terms of technology, schooling, culture and society, almost everything is fast-paced today. This causes high societal expectations on students to perform various roles which may be ambiguous, contradictory and unachievable in the present and even in the future, which then causes heavy stress on students.[4]

Being in the transition from adolescence to adulthood is a crucial stage of development for university students and they are more likely to experience mental illnesses as a result of this transition.[5] A survey conducted in Malaysia also have demonstrated that people in the age of 16–24 year age group had the highest prevalence of acute and chronic suicidal ideation compared to the other age group.[6] In addition to that, sudden drastic changes to the learning environment of the students due to the COVID-19 situation has caused psychosocial changes to the students during home quarantine.[7] Together with this pandemic situation, the effect of COVID-19 may amplify these stresses. A study done in Malaysia among medical students using The Depression, Anxiety, and Stress Scale (DASS-21) concluded that COVID-19 led to significant mental health issues among students whereby 15.8% of the students had mild stress, 4.2% moderately stressed, and 2% severely stressed.[8] While another study in Malaysia also using DASS-21 among 1,005 students found a total percentage of 22.0% of students suffering from stress.[9] Also a study done among undergraduate students of the three faculties (Medicine, Dentistry and Health Sciences) using the General Health Questionnaire-12 showed the level of psychological disorder among university students has been high during the pandemic where 36% of the students had distress.[10]

Since the studies assessing psychological distress among dental students in Malaysia during COVID-19 pandemic are limited. Hence, the aim of this study is to determine the level of psychological distress and assess the coping strategies and their relation with psychological distress among dental students during COVID-19 pandemic.

MATERIALS AND METHODS

This is a cross sectional study using online google form was conducted on a sample of 224 dental students, faculty (Kulliyyah) of dentistry (KOD) International Islamic University Malaysia during academic session of 2020/2021. The sample size was calculated by using an online sample size calculator by the Australian bureau of statistics. The minimum sample size required was 144. However, to increase the power and precision of the study, sample size was increased to a minimum of 200 undergraduate students from KOD, International Islamic University Malaysia, Kuantan campus comprising year 1 until year 5. Prior to conducting this study, the ethical approval has been approved from the International Islamic University Malaysia Research Ethical Committee.

The study was conducted during movement control order due to COVID-19 pandemic where the students underwent remote online teaching and learning (RTL). The study was also performed during the semester and far away from exams to reduce stressful factors. The inclusion criteria were students who voluntarily accept to participate in the study, and who are currently undergraduate dental students of KOD, IIUM. Students who did not agree to participate and did not provide consent were excluded. The structure of KOD program is a 5 year course which is divided into two phases; the preclinical phase is the first two years of the course and the clinical phase are the remaining 3 years. The sociodemographic of every participant was obtained including information about their age, marital status, gender, year of study, and household income.

The study was conducted online by distribution of the following self-rated questionnaires via emails using google forms. The questionnaires used were the following:

1. Kessler psychological distress scale (K10)[11]
2. Brief-COPE questionnaire.[12]
3. Sociodemographic questionnaire.

The K10 questionnaire is a 10-item questionnaire and each item pertains to an emotional state and has a five-level scale response: 'None of the time', 'A little of the time', 'Some of the time', 'Most of the time' and 'All the time'. Each item is scored from one 'none of the time' to five 'all of the time'. Scores of the 10 items are added up giving a minimum sum of 10 and maximum of 50. Low scores give an indication of low level of psychological distress and vise versa. A set of cut-off scores has been used as a guide for categorizing for psychological distress as adopted by The 2001 Victorian Population Health Survey[13]; 10 - 19 Likely to be well, 20 - 24 Likely to have a mild disorder, 25 - 29 Likely to have a moderate disorder, 30 - 50 Likely to have a severe disorder. K10 has good psychometric properties as it has strong scale reliability with Cronbach's α greater than 0.88.[14,15]

The Brief-COPE questionnaire, consists of a multidimensional assessment of different strategies used for coping in the face of stressors. There are two main subscales to assess coping; each is made up of 14 items. The two subscales measure approach coping and avoidant coping behaviors. The following coping strategies are assessed: 1) self-distraction, (2) active coping, (3) denial, (4) substance use, (5) use of emotional support, (6) use of instrumental support, (7) behavioral disengagement, (8) venting, (9) positive reframing, (10) planning, (11) humor, (12) acceptance, (13) religion, and (14) self-blame. The scores for each subscale are presented for the two overarching coping styles which were avoidant coping which were associated with poorer physical health among those with medical conditions and approach coping which was associated with more helpful responses to adversity, including adaptive practical adjustment, better physical health outcomes and more stable emotional responding.[16]

Regarding the psychometric properties of Brief-COPE, the reliability and validity of the scale indicated a high Cronbach's alpha values for some domains such as Religion (α=0.82) and Substance use (α=0.90). Other domains indicated acceptable values of Cronbach's alpha. They are Active coping (α=0.68), Planning (α=0.73), Positive Reframing (α=0.64), Acceptance (α=0.57), Humor (α=0.73), Using Emotional Support (α=0.71), Using Instrumental Support (α=0.64), Self-distraction (α=0.71), Denial (α=0.54), Venting (α=0.50), Behavioral disengagement (α=0.65) and Self-blame (α=0.69).[12]

Statistical analysis

SPSS 25.0 was used for analyzing the data. The analysis of the variables such as age group, gender, nationality, monthly household income, marital status, year of study, and type of accommodation were presented in numbers and percentages. Mann Whitney U test and Kruskal-Wallis test were used to determine the effects of the socio-demographic characteristics on the psychological distress among undergraduate students. Spearman's correlation test was used to observe the correlation between approach coping and avoidant coping with psychological distress level, A p-value of less than 0.05 was considered statistically significant.

RESULTS

The overall response rate in this study was 77.77% (224 out of 288 KOD students). The respondents were 56 year 1 students, 61 year 2 students, 25 year 3 students, 50 year 4 students and 32 year 5 students. The overall prevalence of psychological distress among KOD students was 81.75% which was 182 out of 224 students who had some degree of psychological distress. The rate of severe psychological distress was found to be 40.18%, while 22.32% and 18.75% had mild and moderate distress respectively (Table 1). When assessing factors determining significant psychological distress level, only age ($p = 0.033$) was statistically significant, whereby students that are less than 21 years old showed a significantly lower mean of psychological distress compared to students above 21 years old. (Table 2). There were no significant differences in comparing mean scores of other factors such as gender, marital status, phase of study and household income.

Regarding coping strategies, KOD students practiced approach coping mechanisms more than avoidant coping (Table 3). The most practiced coping mechanisms (in descending order) according to the subscale of Brief-Cope were positive reframing, self-distraction, planning, active coping and use of informational support. (Table 4). Spearman's correlation was performed in this study to correlate psychological distress with different coping strategies; approach coping and avoidant coping. The statistically significant results ($p < 0.05$) was a positive correlation between psychological distress and avoidant coping. Approach also showed a negative correlation however it was not statistically significant (Table 5).

DISCUSSION

There is no doubt about the disastrous effects of COVID-19 pandemic on the whole world. The education sector has been affected significantly by the sudden drastic change in the mode of delivery of education which was changed to remote teaching and learning which was very new to most students. The most affected students are those undertaking courses that need practical skills and actual face to face interaction. A very good example

TABLE 1. Prevalence of psychological distress among KOD students according to K10 scoring.

Psychological Distress Level	N (%)
Not distressed	42 (18.75)
Mild	50 (22.32)
Moderate	42 (18.75)
Severe	90 (40.18)

TABLE 2. Factors determining significant psychological distress level.

Variables	N (%)	Mean psychological distress score (SD)	P-value
Gender			0.908
Male	59 (26.3)	26.98 (6.969)	
Female	165 (73.7)	27.39 (8.690)	
Age			0.033
≤ 21	106 (47.3)	26.14 (8.467)	
> 21	118 (52.7)	28.56 (7.867)	
Household income per month			0.306
<RM4369 (B40)	56 (25)	28.46 (8.041)	
RM4369 - RM9196 (M40)	94 (42)	27.17 (8.299)	
>RM9196 (T20)	74 (33)	26.54 (8.382)	
Marital status			0.059
Married	2 (0.9)	39 (5.657)	
Single	222 (99.1)	27.18 (8.212)	

TABLE 3. Mean and SD for 2 coping mechanisms according to Brief-Cope.

Coping mechanism	Mean (SD)
Approach Coping	33.1429 (6.1489)
Avoidant Coping	25.95 (5.5255)

of such students are dental students who need to get clinical training on patients and who have a list of clinical procedures that they must fulfill correctly to pass to the next academic year and to graduate. Dental students were affected by the pandemic in more than one aspect; first the change to online learning meant that all their clinical training was withheld till an uncertain time. Second; even in case of being able to do limited clinical training the students faced the fear of contracting the virus through close contact with the patients. These factors and other general factors contributed significantly to development of stress in dental students and from this overview we can expect to find a high level of psychological distress among dental students.

TABLE 4. Mean (SD) of subscale components for coping mechanisms.

Coping mechanism	Mean (SD)
Positive reframing	5.9196 (1.6438)
Self-Distraction	5.8929 (1.6477)
Planning	5,6696 (1.7405)
Active Coping	5.5659 (1.3505)
Use of Informational Support	5.5357 (1.35215)
Self-Blame	5.3304 (2.0482)
Emotional Support	5.3170 (1.5740)
Acceptance	5.1480 (1.3085)
Venting	4.7589 (2.1397)
Behavioural Disengagement	4.0759 (1.6454)
Denial	3.5491 (1.5697)
Substance Use	2.1295 (0.5409)

TABLE 5. Correlation of Psychological distress with social support, approach coping and avoidant coping.

Variable	Correlation coefficient	Sig. Level
Approach Coping	-0.092	0.168
Avoidant coping	0.435	0.00

The prevalence of psychological distress in this study was found to be 81.25% of which 40.18% are having severe distress. These results are comparable with the findings from another study using the same tool done among dental students in Bangladesh during COVID-19 pandemic in which the overall rate was 84.1% of which 34.6% are having severe distress.[17] However it is higher than another study which was done among year 5 dental students at University Malaya during COVID-19 lockdown using K10 scale which reported a prevalence of 52.2%[18] this difference can be due to smaller sample size and year of study. A study conducted during the COVID-19 pandemic in Pakistan, showed that COVID-19 has created psychosocial changes and has increased among students during home quarantine.[6] Together with that, a study conducted in China among healthcare students has also demonstrated the increased prevalence of psychological distress compared to their baseline data which were before the COVID-19 pandemic.[19]

Other studies that were conducted on university students before COVID-19 pandemic had varied results with most of them having lower prevalence of psychological distress which was in the range of 30% to 50% compared to our study which was 81.25%.[20-24] Apart from the effect of COVID-19 pandemic, the variations in rates could be due to differences in sample size, study design, and methods of assessing distress, including the type of questionnaire utilized and the cutoff score used.

Pertaining to the factors determining significant psychological distress level, age is a determining factor as students aged 21 years and below had significantly lower psychological distress level compared to students older than 21 years. This may be due to the fact that older students are more affected by online teaching and learning because of reduction of clinical exposure and worries about fulfilling their assignments with a higher academic workload. This can be supported by the findings from similar previous studies conducted before COVID-19 pandemic showed no significant difference between age groups.[20-22] Gender wise, both males and females were equally affected by psychological distress which is similar with findings of previous studies.[17,23]

A coping mechanism is a psychological strategy or adaptation that a person uses to deal with stress. Sometimes, coping mechanisms are intentional choices, while other times a person may be unaware that they're using them. Coping strategies can be categorized into two broad types which are approach coping and avoidant coping, under these two main types fall different behaviors of coping that allows a person to manage their life and deal with various situations.

It is also to be noted that coping mechanisms also play a role in 'buffering' or intensifying psychological distress levels. Approach coping has been found to be associated with more cognitive appraisals and less negative effects of stressors.[25,26] On the contrary, avoidant coping behavior has been linked to negative outcomes in terms of stress management.[27,28] This can be explained justified because approach coping allows the person to analyze their stressor and take action to deal with the stressful and reduce its effect on the person, while avoidant coping leads to backing out on the problem and avoiding to deal with it which can lead to augmentation of the stressor and increase in psychological distress.

In this study more students practiced approach than avoidant coping mechanisms, this indicates that the students at KOD have the ability to cope with stressful factors however the reason for having high psychological distress in this study maybe due to the overwhelming nature of the current situation of going through a pandemic which they have never been exposed to before. In accordance with other studies, our study found that avoidant coping has positive correlation with psychological distress and this correlation is statistically significant.[29] While approach coping was found to have a negative correlation with psychological distress although it was not statistically significant. The result of this correlation was also parallel with a study that observed the relationship between coping strategies and stress.[30] Previous study has also proven adolescents that practiced approach-oriented coping mechanisms manifest less signs and symptoms of depression compared to adolescents that practiced avoidance-oriented coping mechanisms that exhibit more severe signs and symptoms of depression.[31,32] Implication of this result may be used in counseling sessions in universities to introduce types of coping together with their advantages and disadvantages.

CONCLUSION

Dental students are affected by a high rate of psychological distress during COVID-19 pandemic. Students using approach coping mechanisms less psychological distress level compared to students that practice avoidant coping mechanisms.

Limitations and suggestions:

The limitations of this study is that it was only conducted on Faculty of Dentistry students, we suggest to expand the study to include other faculties and to compare between dental students from different universities in Malaysia.

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Effect of the COVID-19 Pandemic on Compliance with Contact- and Droplet-precaution Measures in Siriraj Hospital's Internal Medicine and Pediatrics Ward Nurses

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ABSTRACT

Objective: To determine the effect of the COVID-19 pandemic on personal medical discipline toward infection preventive measures.

Materials and Methods: An online questionnaire on personal preventive measure was developed. The content of the questionnaire was reviewed by content experts and tested for internal consistency reliability. Nurses in the Internal Medicine and Pediatrics wards were invited to answer the questionnaire.

Results: In total, 188 individuals were included. Sixty-five percent of the protective measure statements showed a statistical improvement in compliance during the pandemic. Most of the protective measures, including hand washing, wearing a mask, and wearing glasses or a face shield, were statistically more complied with during the pandemic. However, some important protective measures, such as wearing a mask when performing aerosol-generating procedures or when in close contact with droplet-precaution patients, did not show a statistically significant increase in compliance during the pandemic. There was no significant correlation between the demographic data and compliance level. The main reasons for non-compliance were time constraints, thought that the measures are not important, and equipment inadequacy.

Conclusion: During the COVID-19 pandemic, there was some improvement in compliance with contact- and droplet-precaution measures in Siriraj Hospital's Medicine and Pediatrics wards, but compliance with measures against some high-risk procedures that can spread the infection, such as aerosol generation or contacting with droplets, were not followed properly. The importance of precaution measures should be emphasized and the adequacy of protective equipment should be addressed to reduce the risk of spreading infection to healthcare workers and other patients.

Keywords: COVID-19; pandemic; contact precaution; droplet precaution; compliance (Siriraj Med J 2022; 74: 357-363)

INTRODUCTION

Nosocomial infection can have negative impacts on patients and healthcare systems, such as leading to an increased length of stay and increased cost of treatment.[1] The elimination of drug-resistance nosocomial infection can reduce the cost of treatment and increase the quality-adjusted life years of patients.[2] A previous study at Siriraj Hospital, which is a tertiary care university hospital in the capital of Thailand, demonstrated that between 2009 to 2013, 8.01% of pediatrics inpatients contacted nosocomial infection.[3]

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Various precaution methods can be used to prevent nosocomial infection, such as contact precaution, droplet precaution, and airborne precaution. A previous study in another tertiary care university hospital in Bangkok revealed that their medical staff were aware of these precaution measures but did not or could not fully comply with them.[4]

Coronavirus disease 2019 (COVID-19) is an emerging disease caused by SARS-CoV2 virus. The disease is spread rapidly and becomes pandemic in March 2020. COVID-19 patients may suffer not only from respiratory symptoms such as cough, dyspnea but also from non-respiratory symptoms such as diarrhea, nausea and vomiting, increase transaminase levels[5], and sudden sensorineural hearing loss.[6] Moreover, some patients may experience persistent symptoms after recovery or Long COVID which can cause fatigue, dyspnea, cardiovascular abnormality, cognitive impairment, and others.[7] These symptoms have negative impact on physical function, cognitive function, and quality of life.[8]

Since the start of the SARS-CoV2 outbreak up to July 22, 2021, there have been more than 190M COVID-19 cases and more than 4M deaths globally resulting from the ongoing pandemic.[9] Due to the inadequacy of proper personal protective equipment in low to middle income countries, these countries have suffered high rates of nosocomial COVID-19 infections.[10] Preventing healthcare workers from COVID-19 infection is crucial to maintain the resilience of the healthcare system during the pandemic.[11] In this regard contact- and droplet-precaution measures are critical as the virus can be transmitted via respiratory droplets and via contact fomites.[12]

A previous study in Hong Kong after the outbreak of severe acute respiratory syndrome (SARS) in 2004 showed there was a significant improvement in compliance with hand hygiene practice after the outbreak, with the rate of handwashing after contact with a patient increasing from 72.5% to 100%.[13] However, a study in Qatar during the COVID-19 outbreak demonstrated that compliance with utilizing full personal protective equipment was still not perfect. The report showed that among COVID-19-infected healthcare workers, 82% and 68% of the personnel from COVID-19 facilities and from non-COVID-19 facilities used full personal protective equipment properly.[11] During the current COVID-19 pandemic, a study in Iran demonstrated a reduction in the nosocomial infection rate.[14] A study in Wuhan, China, demonstrated that overall hand hygiene compliance among healthcare workers improved after the outbreak of COVID-19 from 88.69% to 96.37%, and overall droplet-isolation compliance improved from 76.93% to 87.94%.[15] However, the effect of the pandemic on the compliance with infectious diseases prevention in Thailand has not yet been reported.

Consequently, this study focused on the effect of the COVID-19 pandemic on compliance with contact- and droplet-precaution measures in Siriraj Hospital's Internal Medicine and Pediatrics wards. The objective of this study was to gain an insight into the interaction between a pandemic and medical personal discipline with regards to precaution measures. The result of this study can be used for further study to explore the behavioral factors affecting compliance with infectious control precaution measures.

MATERIALS AND METHODS

This study was a questionnaire-based cross-sectional study approved by Siriraj Institutional Review Board (Si 606/2020), conducted between July 2020 and February 2021. Eligible participants were registered nurses and practical nurses who had been working in Siriraj Hospital's Internal Medicine and Pediatrics wards at least since September 2019. Recruitment of the participants was conducted via electronic messages. A Thai-language self-administered online questionnaire was provided with the recruitment messages and informed consent was obtained at the first page of the questionnaire survey. In total, 188 participants consented and answered the questionnaire.

The questionnaire consisted of three parts. The first part focused on the characteristics of the participant, including gender, age, department, professional category, number of years worked, and whether the participant had enrolled in a training course on nosocomial infection prevention. The second part involved a 5-point Likert rating scale composed of 20 statement questions designed to evaluate the compliance of the medical staff with contact- and droplet-precaution measures prior to and during the COVID-19 pandemic, concerning both patient safety and staff safety. The questions in this part could be classified into two groups: the first group consisted of 12 questions about compliance with the contact-precaution measures and the second group consisted of 8 questions about compliance with the droplet-precaution measures. These 20 questions were reviewed by 2 content experts and analyzed for internal consistency reliability using Cronbach's alpha. The third part of the questionnaire involved an open-ended question, asking for the reason for non-compliance, if there was any instance of non-compliance. Participants were permitted to leave the answer to the third part blank or to provide more than one reason.

Good compliance with the precaution measures was defined as a rating of 4 or 5 on the Likert scale, while poor compliance was defined as a rating lower than 4. Data analysis was performed using PASW Statistics for Windows version 18 (SPSS Inc., Chicago, Ill, USA) and STATA 16.0. The Fisher exact test was used to compare compliance before and during the pandemic. A p-value of less than 0.05 was considered statistically significant.

The sample size calculation was based on data from Yang et al[15] which showed overall hand hygiene compliance among health care workers improved after outbreak of COVID-19 from 88.69% to 96.37%, and overall droplet isolation compliance improved from 76.93% to 87.94%. Thus, the sample size needed for this study was calculated as followed.

$$\text{Sample size} = \frac{(Z_{1-\alpha/2})+Z_{\beta})^2\,[P_1\,(1-P_1)+P_2\,(1-P_2)]}{d^2}$$

Where $Z_{1-\alpha/2} = 1.96$ for significant level of 0.05, $Z_{\beta} = 0.84$ for 80% power. Then the sample size needed for determining the change in overall hand hygiene compliance is 180 and for determining the change in overall droplet isolation compliance is 184.

RESULTS

The characteristics of the participants are as shown in Table 1. Most of the participants were female and most of them were registered nurses.

The Cronbach's alpha coefficients for internal consistency reliability of groups of items in the questionnaire are as shown in Table 2.

The results of the second part of the questionnaire, converted into the level of compliance, are shown in Table 3. Out of 20 statements about compliance with the contact- and droplet-precaution measures, 14 statements were found to indicate a statistically significant improvement in compliance during the pandemic.

Table 4 demonstrated logistic regression which was performed to determine whether age, department, professional category, number of years worked, or had enrolled on a nosocomial prevention course had any correlation with increasing compliance with the protective measures. Data from participants who reported good compliance in all items was not included in this analysis. Thus, the number of participants included in this analysis was 123. No significant correlation was demonstrated.

The third part of the questionnaire was answered by 47 participants. The answers were classified as shown in Table 5. The most common reason for non-compliance with the protective measures was time constraints. The second most common reason was the inadequacy of the protective equipment.

TABLE 1. Characteristics of the participants.

Characteristics	N (%)
Gender	
Male	6 (3.2)
Female	180 (95.7)
Other	2 (1.1)
Department	
Medicine	79 (42)
Pediatrics	109 (58)
Professional category	
Registered nurse	129 (68.6)
Practical nurse	59 (31.4)
Had enrolled in a training course on nosocomial infection prevention	
Yes	140 (74.5)
No	48 (25.5)
	Mean (SD)
Age	35.78 (10.98)
Number of years worked	14.09 (11.16)

TABLE 2. Characteristics of the participants.

Groups of Items	Cronbach's alpha Coefficient
Questions about compliance with the contact-precaution measures prior to the pandemic	0.93
Questions about compliance with the droplet-precaution measures prior to the pandemic	0.89
Overall preventive measure prior to the pandemic	0.95
Questions about compliance with the droplet-precaution measures during the pandemic	0.96
Questions about compliance with the contact-precaution measures during the pandemic	0.91
Overall preventive measure during the pandemic	0.96

TABLE 3. Level of compliance with contact- and droplet-precaution measures prior to and during the pandemic.

Statement	Prior to the pandemic		During the pandemic		P-value
	Good compliance	Poor compliance	Good compliance	Poor compliance	
Wash your hands before contact with every patient.	154	34	176	12	0.001
Wash your hands before performing every clean or sterile procedure.	169	19	184	4	0.002
Wash your hands after contact with a patient's secretion, wound, or abnormal skin, whether you are wearing gloves or not.	182	6	186	2	0.284
Wash your hands instantly after taking off your gloves.	167	21	179	9	0.035
Wash your hands when changing from a contaminated site to a sterile site while performing a procedure on the same patient.	138	50	179	9	<0.001
Wash your hands after contact with a patient's environment.	148	40	180	8	<0.001
Wash your hands after contact with every patient.	167	21	182	6	0.004
Wear gloves every time before contact with contact-precaution patients.	172	16	184	4	0.010
Wear gloves every time before contact with droplet-precaution patients.	160	28	178	10	0.003
Wear gloves before contact with a patient's secretion, mucosa, or abnormal skin.	179	9	184	4	0.258
Change your gloves during procedures when your gloves contact an object that seems to be contaminated.	175	13	183	5	0.088
Change your gloves when you move on to perform a procedure on another patient.	181	7	184	4	0.543
Clean equipment which is shared between patients after use.	175	13	182	6	0.156
Wear a gown every time when performing aerosol-generating procedures on every patient.	143	45	171	17	<0.001
Wear a gown every time when examining or performing procedures on contact-precaution patients.	156	32	174	14	0.007
Wear a gown every time when examining or performing procedures on droplet-precaution patients.	145	43	172	16	<0.001
Wear a mask every time when performing aerosol-generating procedures on every patient.	175	13	181	7	0.250
Wear a mask every time when you are in close contact with droplet-precaution patients.	178	10	184	4	0.171
Wear glasses or a face shield every time when performing aerosol-generating procedures on every patient.	95	93	153	35	<0.001
Wear glasses or a face shield every time when you are in close contact with droplet-precaution patients.	96	92	155	33	<0.001

TABLE 4. Logistic regression analysis result.

Demographic data	Odds ratio	P-value	95% Confidence interval
Age	0.88	0.389	0.67 – 1.17
Department	1.08	0.907	0.31 – 3.70
Professional category	2.50	0.220	0.58 – 10.79
Numbers of years worked	1.12	0.449	0.84 – 1.48
Had enrolled on a nosocomial prevention course	3.12	0.064	0.94 – 10.38

TABLE 5. Reasons for non-compliance with the protective measures.

Reasons	Number of participants who agreed with the answer (N = 47)
Time constraints, such as emergency situations and heavy workloads.	26 (55.32%)
Thought that the measures are not important.	12 (25.53%)
Inadequacy of protective equipment.	11 (23.40 %)
The equipment was considered an obstacle to work, regardless of the time constraints, such as blurred vision from wearing a face shield and feeling hot from wearing a gown.	7 (14.89%)
Protective equipment was not readily available at the site.	3 (6.38%)
Forgot the protective measures.	2 (4.26%)

DISCUSSION

According to the study results, 65% of the protective measure statements showed a statistical improvement in compliance with the protective measures during the pandemic. However, even though the statistics indicated that compliance was better during the pandemic, it was still not perfect. For example, 18.62% of participants still had poor compliance with wearing glasses or a face shield every time when performing aerosol-generating procedures on every patient, which might not be enough to prevent the spread of the pandemic or to protect from any pathogens in general. A systematic review and meta-analysis has revealed that protection of the eyes was correlated with a lower infection rate,[16] hence the improvement of eye protection compliance should be emphasized to reduce the workplace infection risk. The other 35% of protective measure statements might not statistically show more compliance during the pandemic because some of them already having nearly perfect compliance in the first place. Other factors including age of participants, department where participants work, professional category (technical or registered nurse), duration of work in years, and had training in nosocomial prevention course do not have significant association with improvement in preventive measure. However, training in nosocomial prevention may still be necessary for medical personnel to ensure compliance with protective measures for both patients' and personnel's safety.

The third part of the survey, which was an open-ended question, revealed some of the reasons for the non-compliance, with the main reason being time constraints. In fact, there were quite a few true emergency situations

in the Medicine and Pediatrics wards where rapid action is critical. To improve compliance with the precaution measures, there is a need to emphasize the importance of maintaining the safety of the practitioners, which also reflects on the safety of the patients, in every situation. Other reasons for non-compliance were concerns about the inadequacy or inconvenience of the protective equipment; hence there is a need to make sure that the protective equipment is adequate, easy to use, and readily available. It is also important to acknowledge that staff avoiding these infection-control measures risk increasing the rate of nosocomial infection in both patients and staff, which can lead to increasing the length of hospital stay for the patient, the staff workload, and the cost of hospitalization.

A study by Brewe et al[17] demonstrated some protective behavior regression after vaccination. Further study might investigate whether compliance with current COVID-19 protective measures declines after immunization.

In April 2020, Royal college of Surgeons of Thailand had published an announcement on guidance for surgery in COVID-19 patients[18], which provided meticulous details on management of patients, staffs, and operating room in COVID-19 cases from patient transportation to post-operative management. Thai Association for Gastrointestinal Endoscopy and Endoscopy Nurse Society (Thailand) had also provided recommendations for the practice of endoscopy during the COVID-19 pandemic.[19] Further study might investigate the compliance of the staff with these recommendations.

There are some limitations to note with this study, including the fact the study involved a self-administered questionnaire and the selection of participants was not done by randomization, so there might have been a reporting bias and volunteer bias. In addition, this study might not be a good representation of the true practices in wards, which consist of multidisciplinary teams of other professionals rather than nurses alone. Also, a recall bias might have occurred because the questionnaire asked about compliance in the past. The questions used in this questionnaire for this study were validated only by experts in infectious diseases and prevention.

CONCLUSION

During the COVID-19 pandemic, while there was some improvement in compliance with contact- and droplet-precaution measures by nurses in Siriraj Hospital's Medicine and Pediatrics wards, precaution measures for some high-risk procedures that can spread the infection, such as aerosol generation or contacting with droplets, were not always followed properly. The importance of precaution measures should be emphasized because if healthcare workers are infected, healthcare workforce would be immediately affected and long COVID might affect healthcare workforce in the long term. Also, the adequacy of the protective equipment should be assured to decrease the risk of spreading infection to healthcare workers and other patients.

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Effect of Gestational Weight Gain on Overweight and Obese Pregnant Women

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ABSTRACT

Objective: To examine the adherence of gestational weight gain (GWG) recommendations and pregnancy outcomes among overweight and obese pregnant women.

Materials and Methods: The medical records of 405 overweight or obese pregnant women who delivered at Siriraj Hospital between September 2018 and June 2019 were reviewed. The adherence to GWG recommendations according to pre-pregnancy body mass index (BMI) was examined. The characteristics and pregnancy outcomes of the overweight and obese pregnancies as well as between the adherence and non-adherence to the GWG recommendations groups were studied and compared between the groups.

Results: Adherence to the GWG recommendations between the overweight and obese pregnancy groups were significantly different at 60.2% and 44% respectively (p-value = 0.002), although the average GWG was significantly lower in the obese than overweight pregnancies (p-value = 0.003). Pre-pregnancy BMI was significantly higher in the non-adherence group compared with the adherence group (p-value = 0.025). Pregnancy outcomes as well as the prevalence of gestational diabetes mellitus between these two groups were comparable. Also, adverse pregnancy outcomes were not statistically significantly different among the adherence and non-adherence groups.

Conclusion: The adherence to gestational weight gain recommendations in obese and overweight pregnancies is still a challenge. Obese pregnant women are less likely to control weight gain during pregnancy. Pre-pregnancy BMI is an important factor for overweight and obese pregnant women to achieve the GWG goal. Ensuring a proper GWG alone might not improve most adverse pregnancy outcomes in overweight and obese pregnancies.

Keywords: Obese pregnancy; overweight pregnancy; gestational weight gain; pregnancy outcomes (Siriraj Med J 2022; 74: 364-370)

INTRODUCTION

Obesity is a medical condition with public health concern. In pregnancy, the pre-pregnancy body mass index (BMI) can significantly affect the pregnancy outcome. Nowadays, many women are getting pregnancy with an high BMI; which leading to the higher the risk of maternal and fetal complications.[1-4] Gestational weight gain (GWG) is a modifiable risk factor for adverse pregnancy outcomes. GWG outside the recommended level has been found to be related with a higher risk of many adverse pregnancy outcomes.[5-8] Pregnant women in all BMI categories are more likely to gain excessive weight during pregnancy. However, a higher pre-pregnancy BMI and higher GWG are associated with a higher risk of pregnancy complications.[9-13]

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In overweight or obese women, the GWG is particularly problematic due to the narrow range of optimal weight gain, and as the chances of a difficult delivery is dramatically increased with excessive GWG, along with other adverse pregnancy outcomes, such as postpartum hemorrhage, cesarean section, and genital tract injury. Risk of pregnancy- induced hypertension, and gestational diabetes mellitus also increased among obese pregnancy due to changes of many peptides.[14,15] Such pregnancies with excessive GWG are also more common to have postpartum weight retention, which is an important risk factor for metabolic disease development in the future. In addition, infants born to overweight or obese mothers with excessive GWG have a higher risk of large for gestational age (LGA), macrosomia, birth hypoxia, and birth injury, and a higher probability of childhood obesity and impaired glucose tolerance. Unfortunately, many pregnant women, especially those in the overweight/obese categories, lack knowledge about personal BMI, GWG targets, and appropriate weight management during pregnancy.[16,17]

Pre-conception weight loss is ideal to prevent adverse pregnancy outcomes; however, this is unlikely to be practiced. Counseling for diet, exercise, lifestyle behavioral changes, and motivation to maintain appropriate GWG throughout pregnancy is crucial.[18] Proper weight gain through different dietary interventions during pregnancy is one of the keystones to optimizing maternal and neonatal outcomes, especially in overweight/obese pregnancy.[19]

Our previous study showed the relation between gestational weight gain, using institutional criteria (Siriraj GWG recommendation), and pregnancy outcomes.[20] In comparing the adherence to GWG for all pre-pregnancy BMI categories between the Siriraj and the 2009 Institute of Medicine (IOM) guidelines[21], the pregnancy outcomes yielded similar results; however, 60% of Thai pregnant women were able to adhere to the Siriraj guideline, compared to only 40.5% who adhered to the 2009 IOM guideline.[20]

This study was confined to overweight and obese pre-pregnancy BMI categories only. Siriraj optimal GWG recommendations were made and monitored throughout the pregnancy period. The primary objective of this study was to examine the adherence to GWG recommendations among these two groups of obese and overweight pregnant women. The association between pre-gestational BMI (overweight and obese) and the effect of adherence to GWG recommendations (based on the Siriraj guideline) on the rates of adverse pregnancy outcomes were also evaluated.

MATERIALS AND METHODS

This study was a retrospective study that involved a review of the medical records of 405 overweight or obese pregnancies delivered at Siriraj Hospital between September 2018 and June 2019. Ethical approval for this study was obtained from the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University (Si 717/2020).

In Siriraj Hospital, the height of each pregnant woman is measured. The self-reported pre-pregnancy weight is recorded at the first antenatal visit. Pre-gestational BMI is calculated as weight (kg)/height^2 (m^2). In this study, overweight (25.0–29.9 kg/m^2) and obese (30.0 kg/m^2 or higher) pregnant women were the target participants.

Gestational weight gain (GWG) was obtained from the difference between a woman's weight at delivery and her pre-gestational weight. The inclusion criteria for this study were singleton pregnant women with a first antenatal visit before 20 weeks' gestation, and a maternal pre-pregnancy BMI of 25 kg^2/m or more with available pre-pregnancy weight data. The exclusion criteria included multiple pregnancies and fetal anomalies. Pregnant women were categorized into two groups based on their GWG relative to Siriraj recommendations (adherence and non-adherence). The Siriraj GWG recommendations for overweight and obese pregnant women are 6–14 kg and 4–8 kg, respectively. All the pregnant women were offered dietary counseling and advice on physical activity during antenatal care.[20]

We examined the following maternal and neonatal outcomes: gestational age at delivery, route of delivery, gestational diabetes mellitus (GDM), preeclampsia, postpartum hemorrhage (≥ 500 ml for vaginal delivery and ≥1,000 ml for cesarean delivery), birthweight <2,500 g (low birth weight) and ≥ 4,000 g (macrosomia), Apgar scores <7 at 1 minute and 5 minutes, neonatal intensive care unit (NICU) admission, neonatal hypoglycemia, brachial plexus injury, fracture clavicle, and neonatal death.

Statistical analysis

Descriptive statistics were used for analyzing the data, including the mean, standard deviation (SD), median, interquartile range (IQR), number, and percentages as appropriate. The chi-square test was used to compare characteristics between two groups. Logistic regression analysis was used to determine the independent associated factors for gestational diabetes outcome, adjusted for potential confounders. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the study period, a total of 405 women fitted the inclusion criteria and were enrolled in the study. Two-thirds (65.2%) of them were overweight (pre-pregnancy BMI = 25–29.9 kg/m^2), while the others were obese pregnancies (pre-pregnancy BMI ≥ 30.0 kg/m^2). The maternal characteristic of these two groups are shown in Table 1. Both groups were comparable in terms of age, parity, and gestational age at first antenatal care (ANC) visit. The overweight group significantly adhered to the GWG recommendations more than the obese group, 60.2% vs. 44.0% respectively; although the mean GWG in the overweight pregnancy was significantly higher than in the obese pregnancy. Table 2 shows a comparison of the maternal characteristic according to the adherence to the GWG recommendations. Only BMI was significantly lower among the adherence group compared to the non-adherence group. The pregnancy outcomes were also compared among the groups, and the details are listed in Tables 3 & 4. None of the pregnancy outcomes were statistically significantly different between the adherence and non-adherence groups as well as the overweight and obese pregnancies. For the most common pregnancy complication, namely GDM, this condition was still seen in about one-third of the women, even those who adhered to the GWG protocol (53/159 and 21/62 in the overweight and obese groups, respectively). (Table 4)

DISCUSSION

This study showed that the overall adherence to GWG recommendations in the overweight and obese pregnancies was only a half (54.6%). Adverse pregnancy complications and pregnancy outcomes were not found to be statistically significantly different between the adherence and non-adherence groups. Pre-pregnancy BMI is a highly important factor for overweight and obese pregnancy to achieve the GWG goal.

Adherence to the Siriraj GWG recommendations was higher, with statistical significance, in the overweight group (60.2%) compared to in the obese group (44.0%). This might be explained by the wider range of GWG (6–14 kg) in the overweight pregnancy, compared with the narrower range (4–8 kg) in the obese pregnancy.[20] Most Asian studies to date have used the IOM 2009 GWG recommendation as a reference data with Asian populations due to the lack of well-established GWG recommendations and as no consensus has yet been reached for Asian populations. Siriraj Hospital proposed our own GWG recommendations in 2014 for all pre-pregnancy BMI categories according to the appropriate fetal birth weight.[20]

Similar to previous studies, this study showed that the rates of pregnancy complications in the overweight and obese pregnancies were higher than those in overall pregnancy especially for GDM (31.4% and 27.7%, respectively).[22,23]

TABLE 1. Comparison of the maternal and clinical characteristics between overweight and obese pre-pregnancy BMI categories (n = 405).

Characteristics	BMI 25–29.9 N = n (%) 264 (65.2)	BMI ≥ 30 N = n (%) 141 (34.8)	P-value
Maternal age (years) median (IQR)	32 (28, 36)	32 (27, 36)	0.398
Parity			0.969
Nullipara	81 (30.7)	43 (30.5)	
Multipara	183 (69.3)	98 (69.5)	
GA at 1st ANC (weeks) median (IQR)	9 (7, 13)	9 (7, 12)	0.374
GWG during pregnancy (kilograms) mean (SD)	11.3(5.1)	9.7 (5.3)	0.003
Adherence	159 (60.2)	62 (44.0)	0.002

Abbreviations: ANC; antenatal care, BMI; body mass index, GA; gestational age, GWG; gestational weight gain.

TABLE 2. Comparison of the maternal and clinical characteristics between adherence and non-adherence to the Siriraj gestational weight gain recommendation groups (n = 405).

Characteristics	Adherence N = n (%) 221 (54.6)	Non-adherence N = n (%) 184 (45.40)	P-value
Maternal age (years), median (IQR)	32 (27, 36)	32 (27, 36)	0.956
Parity			0.719
Nullipara	66 (29.9)	58 (31.5)	
Multipara	155 (70.1)	126 (68.5)	
Body mass index (kg/m^2), median (IQR)	27.8(26.2, 30.9)	29.2 (26.6, 31.6)	0.025
25–29.9	159 (71.9)	105 (57.1)	0.002
≥ 30	62 (28.1)	79 (42.9)	
GA at 1st ANC (weeks), median (IQR)	9 (7,13)	9 (7, 12.2)	0.714

Abbreviations: ANC; antenatal care, GA; gestational age, kg/m^2; kilogram per square meter.

TABLE 3. Comparison of the pregnancy outcomes between overweight and obese pre-pregnancy BMI categories (n = 405).

Outcomes	BMI 25–29.9 N = n (%) 264 (65.2)	BMI ≥ 30 N = n (%) 141 (34.8)	P-value
Gestational age at delivery (weeks)	38 (38, 39)	38 (37, 39)	0.241
24–33	5 (1.9)	6 (4.3)	0.205
34–36	25 (9.5)	18 (12.8)	
≥ 37	234 (88.6)	117 (83.0)	
Route of delivery			0.063
Normal labor	112 (42.4)	64 (45.4)	
Operative vaginal delivery	10 (3.8)	0 (0)	
Cesarean delivery	142 (53.8)	77 (54.6)	
Pregnancy complications			
Gestational diabetes	83 (31.4)	39 (27.7)	0.499
Preeclampsia	24 (9.1)	18 (12.8)	0.325
Post-partum hemorrhage	17 (6.4)	13 (9.2)	0.413
Birth weight (grams), median (IQR)	3160 (2900, 3455)	3150 (2870, 3430)	0.48
<2,500	23 (8.7)	16 (11.3)	0.642
2,500–3,999	228 (86.4)	117 (83)	
≥ 4,000	13 (4.9)	8 (5.7)	
Apgar score at 1st minute <7	22 (8.3)	20 (14.2)	0.095
Apgar score at 5th minute <7	3 (1.1)	2 (1.4)	1
Neonatal hypoglycemia	16 (6.1)	15 (10.6)	0.146
NICU admission	5 (1.9)	4 (2.8)	0.725
Brachial plexus injury	0	2 (1.4)	0.121

Abbreviations: DFIU; dead fetus in utero, NICU; neonatal intensive care unit.

TABLE 4. Comparison of the pregnancy outcomes between adherence and non-adherence to the Siriraj gestational weight gain recommendation groups (n = 405).

Outcomes	Adherence N = n (%) 221 (54.6)	Non-adherence N = n (%) 184 (45.40)	P-value
Gestational age at delivery (weeks)			0.532
median (IQR)	38 (38, 39)	38 (37, 39)	
24–33	6 (2.7)	5 (2.7)	0.893
34–36	22 (10.0)	21 (11.4)	
≥ 37	193 (87.3)	158 (85.9)	
Route of delivery			0.608
Normal labor	95 (43.0)	81 (44.0)	
Operative vaginal delivery	4 (1.8)	6 (3.3)	
Cesarean delivery	122 (55.2)	97 (52.7)	
Pregnancy complications			
Gestational diabetes	74 (33.5)	48 (26.1)	0.132
Preeclampsia	23 (10.4)	19 (10.3)	1
Post-partum hemorrhage	17 (7.7)	13 (7.1)	0.961
Birth weight (grams), median (IQR)	3130 (2850, 3360)	3215 (2900, 3492)	0.083
<2,500	23 (10.4)	16 (8.7)	0.699
2,500–3999	188 (85.1)	157 (85.3)	
≥ 4,000	10 (4.5)	11 (6.0)	
Apgar score at 1st minute <7	20 (9.0)	22 (12.0)	0.429
Apgar score at 5th minute <7	1 (0.5)	4 (2.2)	0.181
Neonatal hypoglycemia	3 (1.4)	6 (3.3)	1
NICU admission	17 (7.7)	14 (7.6)	0.311
Brachial plexus injury	0	2 (1.1)	0.206

Abbreviations: DFIU; dead fetus in utero, NICU; neonatal intensive care unit.

These can be explained by the existence of a pre-existing degree of glucose intolerance and insulin insensitivity in the overweight and obese pregnant women from them having a high BMI, placing them at increased risk of developing GDM. A systematic review and meta-analysis revealed that physical activity and diet interventions designed for controlling GWG are still beneficial and effective for reducing the incidence of GDM.[24] However, the prevalence of GDM in this study was not statistically significantly different among the adherence and non-adherence to the GWG recommendations groups. The stronger association of weight gain in the first trimester with the development of GDM might affect this finding[25], although our data for first trimester weight gain was limited.

Systematic reviews have shown that excessive GWG is associated with multiple adverse maternal and fetal outcomes. There is the evidence that lifestyle interventions during pregnancy could be decrease excessive weight gain, however benefit for most adverse pregnancy outcomes have not been shown.[26,27] Similar to this study, the immediate fetal and maternal outcomes (e.g., preterm birth, macrosomia, low Apgar score) and pregnancy complications (e.g., preeclampsia, gestational diabetes,

postpartum hemorrhage) between the overweight and obese groups as well as between the adherence and non-adherence groups were not statistically significantly different. On the contrary, meta-analysis and a review of the systematic reviews revealed that the risks of macrosomia, pregnancy-induced hypertension, and neonatal respiratory distress syndrome in pregnancies with overweight or obese could be effectively reduced by multi-component diet and physical activity interventions. In addition, diet-only interventions could reduce the risks of pregnancy-induced hypertension and GDM in this people.[28] The different results of these studies might be explained by the evidence that pre-pregnancy BMI is more strongly associated with adverse pregnancy outcomes than the amount of gestational weight gain alone.[29] Therefore, in overweight and obese pregnancies, more research on innovative interventions, including pre-conception counseling, should be considered to achieve proper pregnancy outcomes.

There are some limitations in this study. First, this is a retrospective observational study with some confounding factors that might have affected the pregnancy outcomes. Second, information on the long-term maternal and neonatal outcomes was limited. Last, the ability to identify statistical significance in the analysis of pregnancy outcomes related to gestational weight gain adherence and pre-pregnancy BMI might be limited by the relatively small sample size.

CONCLUSION

Obese pregnancies were less likely to control weight gain during pregnancy, although pregnancy complications were not significantly different to those in overweight pregnancies. More innovative interventions are still needed to overcome this public challenge.

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Effectiveness of Mindfulness-Based Parenting Programs in Reducing Parenting Stress in Parents of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder: Systematic Review and Meta-Analysis

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ABSTRACT

Objective: To systematically evaluate the effectiveness of mindfulness-based parenting programs in reducing parenting stress in parents of children and adolescents with ADHD.

Materials and Methods: Studies published in English or Thai before February 2020 were identified through the PubMed, Embase, and Thai-Journal Citation Index databases. Studies were included if they used mindfulness-based parenting interventions for parents of children and adolescents with ADHD, and parenting stress was measured. The risk of bias was evaluated with the Cochrane risk-of-bias assessment tool for randomized trials, and with the ROBIN-I tool for non-randomized studies.

Results: Six studies were included. The 2 randomized controlled trials reported significant reductions in parenting stress in the intervention groups compared with the control groups at post-test, and this effect was maintained at the 8-week follow-up of one of the studies. However, the 4 pre-experimental studies reported conflicting results. Two reported significant reductions in parenting stress from pre- to post-intervention, with one of those studies reporting a further reduction in parental stress at the 6-week follow-up. In contrast, another study reported a significant reduction in parental stress from pre- to post-intervention for fathers but not mothers; this effect was maintained at the 8-week follow-up. The fourth study reported no significant changes in parental stress from pre- to post-intervention. A meta-analysis of 3 studies demonstrated no significant changes in parenting stress from pre- to post-intervention.

Conclusion: The effectiveness of mindfulness-based parenting programs in reducing parenting stress in parents of children and adolescents with ADHD is still inconclusive, although promising. Further studies are needed.

Keywords: Attention-deficit/hyperactivity disorder; mindfulness-based parenting program; parenting stress (Siriraj Med J 2022; 74: 371-380)

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric condition in children and adolescents, with a prevalence of 5% to 12% worldwide.[1] ADHD is often comorbid with many psychiatric disorders, including oppositional defiant disorder[2]; conduct disorder[3]; mood disorders[4,5]; anxiety disorders[6-8]; learning disorders[9]; Tourette's disorder[10]; and substance use disorder.[11] ADHD negatively affects not only the patients but also their families. High levels of distress in the families-particularly inmothers[12]-of children with ADHD have been reported, and this can lead to difficulties in the caring for, and parenting of, the children. Effective parent management is a key component of behavioral management for children with ADHD. Previous studies found that parents under stress failed to demonstrate parenting skills despite their participation in a parent-training program, and they were likely to feel frustrated.[13] This may be due to the parents lacking awareness of their own emotions when they are under stress.

Mindfulness is the awareness that arises through purposely and nonjudgmentally focusing on the present moment. There is strong evidence that mindfulness-based therapy is an effective treatment for a variety of psychological problems, and it is especially effective for reducing anxiety, depression, and stress.[14] Mindful parenting is one of the modern approaches to child rearing which reduces parents' reactivity to children's behaviors.[15] It also affects family functions through reducing parenting stress and focusing on the psychological pathology of parent-child.[16,17] It exerts its effect via the following 5 processes: attentive listening, nonjudgmental acceptance of oneself and one's children, awareness of emotions and self-regulation in childrearing relationships, and compassion toward oneself and one's children.[18] However, the results of studies on the effectiveness of mindfulness-based approaches to reducing parenting stress have been controversial.

The present review therefore aimed to systematically evaluate the effectiveness of mindfulness-based parenting programs in reducing parenting stress in the parents of children and adolescents with ADHD.

MATERIALS AND METHODS

Search strategy

A literature search was conducted via the PubMed, Embase, and Thai-Journal Citation Index databases from inception to February 9, 2020. The keywords used for the search were (mindfulness OR meditation) AND (parent OR parenting) for PubMed; and (mindfulness OR mindfulness-based stress reduction OR mindfulness-based therapy OR meditation) AND (parent OR parenting) for Embase. As to the Thai-Journal Citation Index database, the keywords were (mindful AND parent AND ADHD). In addition, the reference lists of eligible articles were scanned, and a Google search was used for relevant articles. The process of article selection is illustrated in Fig 1.

Eligibility criteria and study selection

To be eligible for inclusion in the meta-analysis, a study needed to meet all of the following criteria.

The study investigated the efficacies of mindfulness-based, parent-training interventions for the parents of children and adolescents with ADHD. The interventions included mindfulness-based stress reduction, mindfulness training for parents, and mindfulness-based cognitive therapy. The interventions had to be delivered by qualified leaders for at least 1 hour per week over a minimum of six weeks.

The study participants were the parents of children up to 18 years of age with ADHD. The ADHD diagnoses were based on either the Diagnostic and Statistical Manual of Mental Disorders criteria for Attention Deficit Hyperactivity Disorder, or the Strengths and Weakness of Attention Deficit Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN).[19-22]

The study was designed as a randomized controlled trial, a case-control study, or an uncontrolled trial.

Parenting stress was measured and compared using at least one of the following instruments: the Parenting Stress Index–Short Form (PSI-SF)[23]; PSI-25[24]; and the Stress Index for Parents of Adolescents (SIPA).[25] The assessments were made at pre-intervention, post-intervention, and follow-up, with or without a control group.

The study had been published in English or Thai.

Data extraction and quality assessment

One of the authors identified the included studies, and 2 authors independently extracted data from each paper. The data were the participants' characteristics, youth age and gender, study design, intervention characteristics, the instrument used to measure parenting stress, and the points-of-time of parenting-stress assessments (Table 1).

The qualities of the included studies were independently assessed by 2 authors. For the randomized controlled studies, the Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used.[26] In the case of non-randomized controlled studies, the authors utilized ROBINS-I.[27] Disagreements about the qualities of the studies were resolved by consultation with the third author.

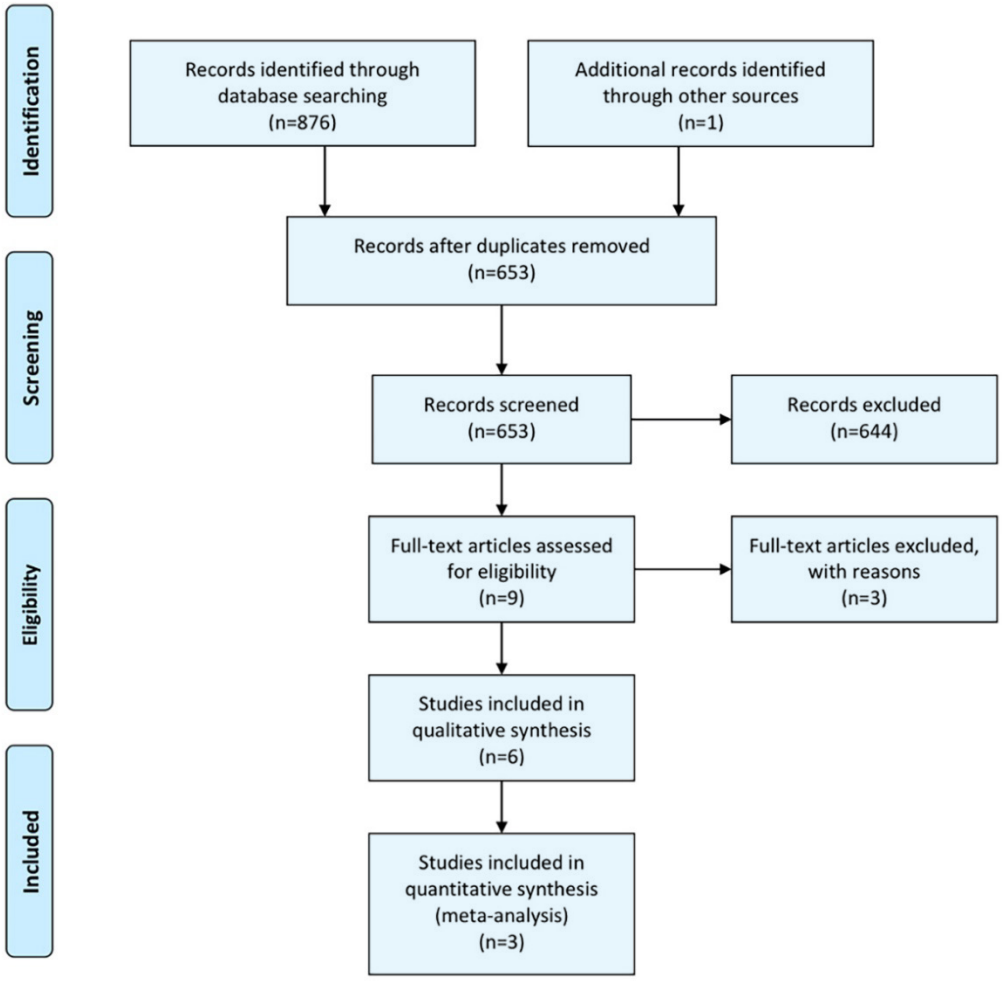

Fig 1. PRISMA (2009) flow diagram.

Statistical analysis

Cohen's d effect size was used to estimate the effect of the mindfulness-based, parent-training intervention between the pre- and post-intervention time-points for each study. Three studies were subsequently included in a meta-analysis, using Cohen's d effect size to estimate the overall effect of the mindfulness-based, parent-training intervention between pre- and post-intervention.

RESULTS

Study selection

As shown in Fig 1, the database search identified 876 articles. One study was added from another resource. After duplicates were removed, 653 remained. Through the title and abstract screening process, 644 studies were considered non-eligible for inclusion in the systematic review. The full text of 9 studies was examined. Three studies did not meet the selection criteria for at least one of the following reasons: (a) the outcome measures reported stressful life events rather than parenting stress; (b) the intervention was not a parenting program but psychoeducation; or (c) the outcome measurement was in the form of a descriptive report. The 6 studies that met the selection criteria were included in the systematic review.

Study characteristics

Table 1 details the main characteristics of the 6 included studies. Four studies used a single-group design (pre-post intervention), whereas the remaining two were randomized controlled trials. The majority of the participants in each study were mothers and male children. Four studies reported no changes in medication during the study period. As to the other two, all the children in both groups received either risperidone or Ritalin in one study, while the other did not mention any medications.

In addition, two studies reported comorbid disorders in the children: learning disability, depressive disorder, anxiety disorder, speech disorder, developmental delay, genetic disorder, and Tourette's syndrome. The interventions for the parents were mindfulness-based cognitive therapy and mindfulness-based stress reduction. Five studies had an intervention for children and adolescents. All studies were published in English.

TABLE 1. Details of included studies.

Author	Country	Study design	Sample size (parent's gender)	Youth age years (mean) (child's gender)	Intervention characteristics		Sessions	Instrument used to measure parental stress	Points-of-time for assessment
					Intervention program	Intervention groups			
Herman H.M.Lo et. al.[28]	Hong Kong	2-armed RCT: 1.MP 2.wait list control	n = 100 (96% mothers)	5–7 (6.25) (83% boys)	1.MP adapted from Bögels and Restifo., 2014 and Coatsworth et al., 2010 2.control: nil (offered MP after waitlist)	MP: Parent group and separate child mindfulness group Control: Nil	MP: 6 weeks x 1.5 h; total 9 h (for parent group) 8 weeks x 1 h (for child group)	PSI-SF (36 items)	T1 – baseline T2 – after intervention
Dexing Zhang et.al.[29]	Hong Kong	Uncontrolled trial: 1.MP	n = 10 (64% mothers)	8–12 (9.5) (73% boys)	MP adapted from mindfulness-based intervention (MYmind) of van de Weijer-Bergsma et al., 2012 and van de Oord et al., 2012	Parent group and separate child mindfulness group	MP: 8 weeks x 1.5 h; total 12 h (for both parent and child groups)	PSI-SF (36 items)	T1 – baseline T2 – after intervention
Mahdiyeh Behbahani et.al.[30]	Iran	2-armed RCT: 1.MP 2.wait list control	n = 56 (100% mothers)	7–12 (66% boys)	1.MP (Bögels and Restifo, 2014) 2.control: nil	MP: Parent group Control: Parent group	MP: 8 weeks x 1.5 h; total 12 h for parent group	PSI-SF (36 items)	T1 – baseline T2 – after intervention T3 – 8 weeks follow up
Van de Oord et.al.[31]	The Nether-lands	Uncontrolled trial: 1.MP	n = 22 (95% mothers)	8–12 (9.55) (73% boys)	MP adapted for parents of children with ADHD from Bögels et al., 2008 and Bögels et al., 2010	Parent group and separate child mindfulness group	MP: 8 weeks x 1.5 h; total 12 h (for both parent and child groups)	PSI-SF (25 items)	T1 – waitlist T2 – pretest T3 – posttest T4 – 8 weeks follow up

TABLE 1. Details of included studies. (Continue)

Author	Country	Study design	Sample size (parent's gender)	Youth age years (mean) (child's gender)	Intervention characteristics			Instrument used to measure parental stress	Points-of-time for assessment
					Intervention program	Intervention groups	Sessions		
Haydicky et.al.[32]	Canada	Uncontrolled trial: 1.MP	n = 17 (94% mothers)	13–18 (15.5) (72% boys)	MP adapted from Bögels et al., 2008	Parent group and separate child mindfulness group	MP: 8 weeks x 1.5 h ; total 12 h (for both parent and child groups)	SIPA	T1 – waitlist (4 weeks pre-intervention) T2 – pretest T3 – posttest T4 – 6 weeks follow up
Van de Weijer-Bergsma et.al.[33]	The Nether-lands	Uncontrolled trial: 1.MP	n = 11 (55% mothers)	11–15 (13.4) (50% boys)	MP (Bögels et al., 2008 and Bögels et al., 2010)	Parent group and separate child mindfulness group	MP: 8 weeks x 1.5 h; total 12 h (for both parent andchild groups) + 1xjointparent and adolescent booster at 8 weeks post-completion	PSI-SF (25 items)	T1 – baseline T2 – after intervention T3 – 8 weeks follow up T4 – 16 weeks follow up

Abbreviations: MP; mindfulness-based parenting program, PSI-SF; Parenting Stress Index–Short Form, SIPA; Stress Index for Parents of Adolescents

Synthesis of the results

The results of the 6 studies (summarized in Table 2) indicated that the mindfulness-based parenting programs tended to reduce parenting stress. The 2 randomized controlled trials reported significant reductions in parenting stress, with nearly a small effect size (d = 0.19; $p = 0.009$) in the intervention group compared with the control group at post-test. This effect was maintained until the 8-week follow-up of one of those 2 studies. The 4 pre-experimental studies reported conflicting results. Van de Oord et al. and Haydicky et al. reported significant reductions in parenting stress from baseline to the 8-week follow up with a medium effect size (d = 0.57), and from post-intervention to the 6-week follow up with a large effect size (d = 0.81), respectively. By contrast, Van de Weijer-Bergsma and colleagues reported a significant reduction in parenting stress from pre- to post-intervention for the fathers, but not for the mothers; this effect was maintained at the 8-week follow-up. On the other hand, Dexing Zhang et al. reported no significant changes in parenting stress between the pre- and post-intervention time-points.

Three studies with the same outcome measures were included in the meta-analysis. In all, there were 166 participants. The meta-analysis did not reveal any significant changes in parental stress between pre- and post-intervention (Fig 2).

Risk of bias in individual studies

Fig 3 illustrates the risk-of-bias assessments of the 2 randomized controlled studies. Both studies were judged to have a high risk of bias for blinding of outcome assessment. Table 3 shows the risk of bias assessment for the 4 non-randomized studies using the ROBIN-I quality assessment tool; their overall risk of bias was moderate.

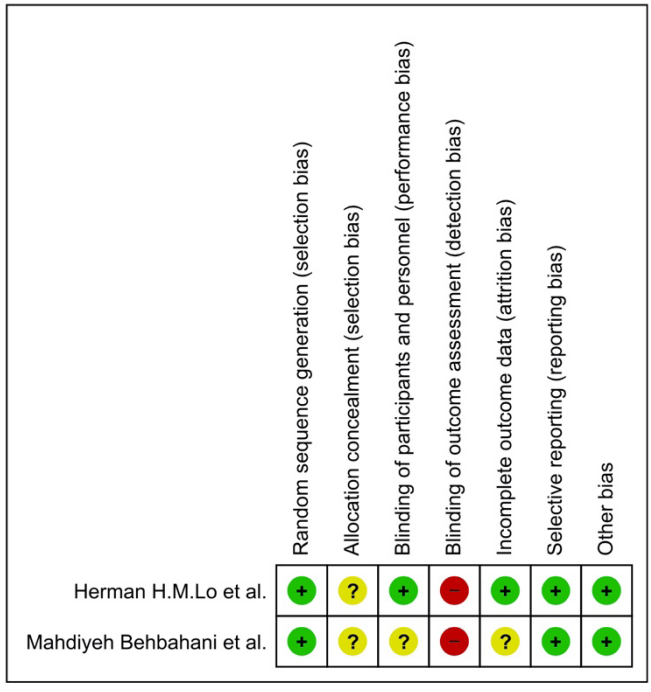

Fig 3. Risk-of-bias assessment for the included randomized controlled studies.

DISCUSSION

The main results of this study were that the 2 randomized controlled trials reported significant reductions in parenting stress in the intervention groups compared with the control group at post-test, while the 4 pre-experimental studies reported conflicting results. A meta-analysis of 3 studies demonstrated no significant changes in parental stress from pre- to post-intervention.

To our knowledge, this is the first systematic review on this topic, which means that there are no previous studies to compare with. However, there are some factors that may influence the differences in the main outcome-parenting stress-of each study. Only 2 studies mentioned comorbid disorders (speech disorders, developmental delay, genetic disease, Tourette's syndrome, learning disability, depressive disorder, and anxiety disorder), and only one study mentioned the severity of ADHD. It is reasonable to assume that both comorbidity and severity can affect the effectiveness of mindfulness-based parenting programs aimed at relieving parenting stress. For example, parents of children with more comorbid disorders or the more severe symptoms of ADHD are likely to experience more stress and more challenges in

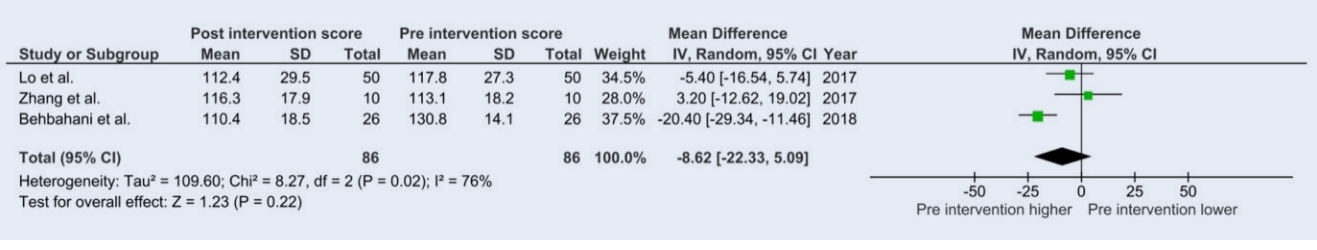

Fig 2. Meta-analysis of 3 studies

TABLE 2. Results of mindfulness-based parenting programs for parenting stress.

Study	Instrument used to measure parental stress	Intervention group			Control group			P-value			Cohen's d		
		Pre-test (T1) Mean (S.D.)	Post-test (T2) Mean (S.D.)	Follow-up (T3) Mean (S.D.)	Pre-test (T1) Mean (S.D.)	Post-test (T2) Mean (S.D.)	Follow-up (T3) Mean (S.D.)	T1-T2	T2-T3	T1-T3	T1-T2	T2-T3	T1-T3
Herman H.M.Lo et al., 2017	PSI-SF (36 items)	117.82 (27.29)	112.36 (29.51)	–	110.02 (24.95)	111.28 (25.17)	–	0.009	–	–	0.19	–	–
Dexing Zhang et al., 2017	PSI-SF (36 items)	113.1 (18.2)	116.3 (17.9)	–	–	–	–	0.01	–	–	-0.18	–	–
Behbahani et.al., 2018	PSI-SF (36 items)	130.8 (14.1)	110.4 (18.5)	109.4 (18.9)	132.4 (11.6)	128.0 (17.6)	130.3 (18.0)						
van de Oord et al., 2012	PSI-SF (25 items)	70.68	65.41 (-1.73)	58.18 (-3.64)	–	–	–	>0.05	–	<0.01 (8 weeks)	–	–	0.57 (8 weeks)
Haydicky et al., 2015	SIPA	58.82 (9.50)	55.78 (8.50)	51.36 (6.40)	–	–	–	–	0.010 (6 weeks)	–	–	0.81 (6 weeks)	–
van de Weijer-Bergsma et al., 2012	PSI-SF (25 items)	64.1 (17.4) Mother	73.1 (20.6) Mother	67.4 (19.4) Mother	–	–	–	>0.05	–	>0.05 (8 week)	0.5	–	0.2 (8 weeks)
		73.8 (27.8) Father	54.1 (28.7) Father	46.1 (24.0) Father	–	–	–	<0.01	–	<0.01 (8 weeks)	0.7	–	1.1 (8 weeks)

Abbreviations: PSI-SF; Parenting Stress Index–Short Form, SIPA; Stress Index for Parents of Adolescents

TABLE 3. Risk-of-bias assessments of included non-randomized studies, using ROBIN-I quality assessment tool.

Studies	Confounding	Selection of participants	Classification of interventions	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall quality
Dexing Zhang et al., 2017	–	–	–	–	/	/	–	Moderate
van de Oord et al., 2012	–	–	–	–	–	/	–	Moderate
Haydicky et al., 2015	–	–	–	–	–	/	–	Moderate
van de Weijer-Bergsma et al., 2012	–	–	–	–	–	/	–	Moderate

+ critical; x serious; / moderate; –low; ? no information

practicing mindfulness in parenting. Moreover, parents' continuous practicing of mindfulness and the parenting skills they learned from a program are other factors that can affect the outcomes. Nevertheless, no studies mentioned those factors. Moreover, with limited data on comorbidities, the severity of ADHD, and the parents' understanding and practicing of mindful parenting skills, these possible confounding factors could not be controlled. This could have affected the outcomes of each of the 6 studies and the meta-analysis, as well as the generalizability of the results of the meta-analysis.

There were several limitations of this review. Firstly, the studies recruited in this review were published in Thai or English from 3 databases, so some relevant studies might not have been included in this review. In addition, all of the studies had small sample sizes. Moreover, there was heterogeneity in the outcome measures, the interventions, and the designs of the studies. All of those factors could affect the accuracy and generalizability of the meta-analysis results.

The findings from this study may have an important implication for the treatment of children with ADHD. Our experience in conducting a parent training program with parents of young patients with ADHD found that parenting stress hindered the effectiveness of their parenting skills they have gained. Therefore, a mindfulness-based parenting program, which may be able to reduce parenting stress, could be an effective parent training program for parents of children with ADHD, leading to a better treatment outcome in this patient population.

To conclude, the effectiveness of mindfulness-based parenting programs in reducing the parenting stress in parents of children and adolescents with ADHD is still inconclusive, although promising. More studies on this topic are needed.

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Age-Related Changes in Signal Intensity Ratio of Normal Clivus Bone Marrow on Magnetic Resonance Imaging

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ABSTRACT

Objective: To evaluate the association between the signal intensity ratio of clivus bone displayed on magnetic resonance (MR) imaging and ages.

Materials and Methods: A retrospective cohort study of 268 patients underwent brain MR imaging during January 2015 to October 2019. We qualitatively and quantitatively assessed bone marrow signal intensity of clivus bone that were performed on T1-weighted sagittal images. In qualitative assessment, the signal intensities of clivus were visually graded from Grade I to III according to the proportion of low and high signal intensity areas occupying the clival marrow region. In quantitative assessment, we evaluated the association between the signal intensity ratio of clivus to pons and age categorized by decades in multivariable Gaussian regression analysis.

Results: Of 268 patients, the ratio of males to females is 1:1. Grade I clivus was found about 35% of the age 1-9 years, whereas Grade 3 clivus was more frequent (more than 13%) in the ages over 30 years. There were statistically different in the mean values of clivus/CSF and clivus/pons signal intensity ratios by grades. The mean values of clivus/CSF and clivus/pons signal intensity ratios were increased by ages in both sexes, but slightly higher in males. In regression analysis after adjustment for sex, the differences in mean values of clivus/pons signal intensity ratios were larger by increasing age, using the age 1-9 as a reference group.

Conclusion: The present study confirms that signal intensity ratios of clivus to pons on T1-weighted sagittal MR images is increased with ages.

Keywords: Clivus bone marrow; pons; signal intensity ratio; magnetic resonance imaging (Siriraj Med J 2022; 74: 381-387)

Abbreviation

MR : Magnetic resonance
CSF : Cerebrospinal fluid
ROI : Region-of-interest
SD : Standard deviation.

INTRODUCTION

The clivus is located centrally between foramen magnum and dorsum sellae of the skull base and clearly seen on T1–weighted sagittal MR images of the brain. It is an important site for evaluating bone marrow signal intensity.[1-4] Using magnetic resonance (MR) imaging has shown advantages in wide range of radiologic research including to detect of disease severity[5], to grade/stage pathologic conditions[6] and to assess bone structures and its components, for instance. Since MR is a sensitive and

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noninvasive tool, it is superior to other devices used for evaluating bone marrow and detecting pathologic changes. The device can differentiate fat from other tissues on T1-weighted images without contrast-enhanced materials. On MR imaging, the yellow marrow has a high signal intensity, whereas the red marrow has almost an intermediate signal intensity. Previous research showed that the signal intensity of the marrow on T1-weighted images can be used to detect age-related changes of the clivus bone in normal people, in that the value was increased with age which reflect the change from red to yellow marrow.[7–10]

Alteration of the signal patterns of clivus bone marrow on MR imaging should be assessed because the information may indicate whether bone maturation completely corresponds with age and it suggests marrow abnormalities before morphologic bone changes. Often, age-related abnormalities of bone marrow signal intensity is the only sign of bone diseases detected on MR imaging. Although many previous studies have shown that the signal intensity of clivus bone is associated with age, all studies were mainly conducted in non-Asian population, and did not take confounding factors into account.[1,2]

Therefore, the purpose of this study was to qualitatively and quantitatively evaluate of bone marrow signal intensity of clivus bone and to assess whether clivus bone marrow signal intensity on MR images is related to age.

MATERIALS AND METHODS

This was a retrospective study that was approved by the institutional ethics committee and did not require informed consent.

From January 2015 to October 2019, the medical records were examined. The study comprised patients who had had brain MR imaging at Naresuan University's Radiology department in Phitsanulok, Thailand. Patients who were (1) younger than 1 year old due to immature myelination, (2) older than 79 years old due to aging brain or abnormal brain imaging such as abnormalities of clivus and pons structure, and (3) diagnosed with known diseases involving the skull base, as well as those who had systemic diseases such as hematopoietic diseases, lymphoproliferative disorder, and hematogenous metastases or had previous radiation therapy, chemotherapy, or intracranial surgery, were excluded. We used stratified random sampling to divide the age groups into decade groups (i.e., 1-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, and 70-79 years). Each age category had a sample size of around 30% of the original age categories. The MR appearance of clivus on T1-weighted sagittal images was studied in a total of qualified 268 patients.

Imaging procedures

A 1.5-T MR scanner (Philips Ingenia, Philips Medical Systems, Best, the Netherlands) was used for all MR exams. Standard spin-echo T1-weighted midsagittal images (TR = 550 msec, TE = 15 msec, 5 mm section thickness, 200 mm field-of-view, number of signal acquisitions = 1, and a 196x196 matrix size) were used as part of the imaging technique. For this study, T1-weighted midsagittal cranial images were used. Midline features such as the clivus, pons, and fourth ventricle are seen on the same plane in this image. In individuals without disease involving the brain, the pons and the cerebrospinal fluid (CSF) were chosen as reference landmarks with stable MR signal intensity values. Three radiologists (W.G., N.O., S.T.) were blinded to the information connected to the images, such as the patients' name, age, and gender, and examined both qualitative and quantitative MR imaging assessments.

Assessments of clivus signal intensities

The signal intensities of clival bone marrow were visually rated from Grade I to III based on the proportion of low and high signal intensity areas inhabiting the clival marrow region for the qualitative assessment. This grading system was previously utilized by Kimura et al.[3] Grade I denotes a predominantly low signal intensity, occupying more than 50% of the clivus, Grade II denotes a low-signal-intensity portion occupying less than 50% but greater than 20% of the clivus, and Grade III denotes a predominantly high signal intensity, with some low signal intensities, occupying less than 50% but greater than 20% of the clivus (Fig 1). We arrived at a grading that was agreed upon by three radiologists. When there was a disagreement between radiologists' readings, the consensus-based debate was held.

The signal intensity values for the area of interest (ROI) in the clivus, pons, CSF, and background noise were employed for the quantitative assessment. The signal intensity values measured from the clivus, pons, and CSF were subtracted from the background noise represented by air next to the vertex at a level comparable to the clivus. The circular ROI was placed and verified by one of our radiologist team (N.O.). The three main locations of ROI were specified at the center of clivus, pons, and the fourth ventricle. The size of the area to be measured was set to 0.10 cm^2 to prevent including the cortical bone in the ROI (Fig 2). The signal intensity ratios of (1) clivus to CSF (clivus/CSF) and (2) clivus to pons (clivus/pons) were calculated using this data.

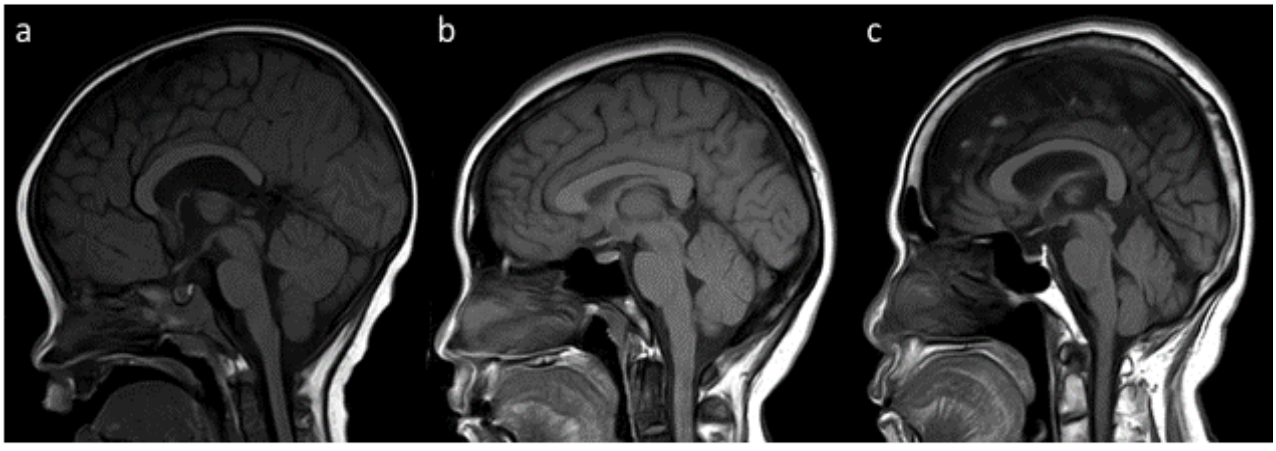

Fig 1. Midsagittal T1-weighted MR imaging of normal clivus bone marrow on qualitative assessment. (a) Grade I in 1-year-old boy (b) Grade II in a 32-year-old female (c) Grade III in a 75-year-old female.

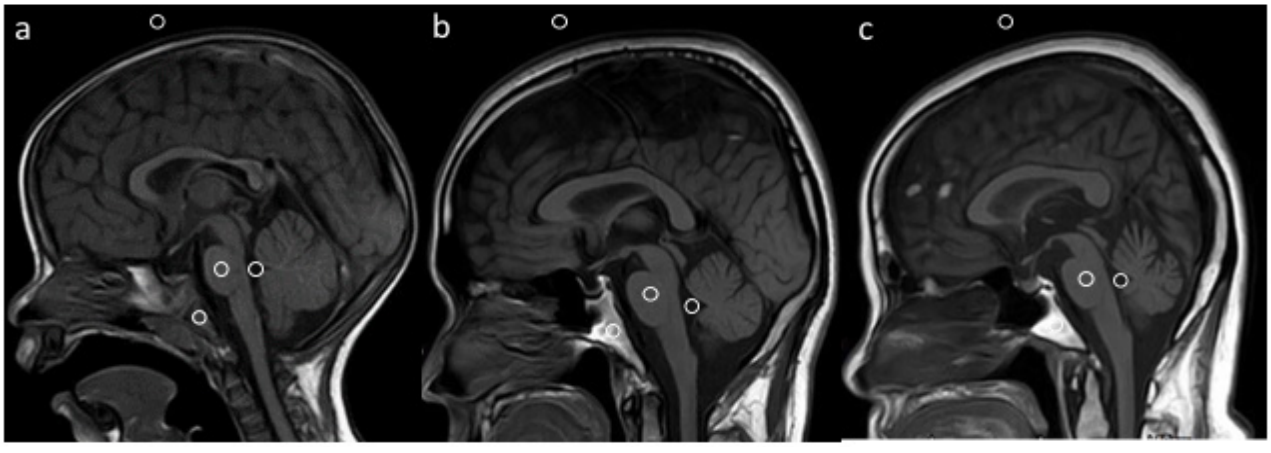

Fig 2. Midsagittal T1-weighted MR imaging of normal clivus bone marrow on quantitative assessment, measured by placing the white circle at the region of interest (clivus, pons, CSF, and the background noise). (a) In a 1-year-old girl (b) In a 46-year-old male (c) In a 75-year-old female.

Statistical analysis

Descriptive statistics for categorical variables were presented in the form of frequencies and proportions. Mean and standard deviation (SD) were used to summarize continuous variables. Using one-way ANOVA with equal variances, we compared the mean values of clivus/CSF and clivus/pons signal intensity ratios by grading intensity. Barrett's test was used to determine the equality of the variances. The relationship between the mean values of clivus/pons signal intensity ratios and age groups was investigated using multivariable Gaussian regression analysis. In the regression analyses, the age group of 1 to 9 years was chosen as the reference category. The difference in the mean values of signal intensity ratios was represented by the beta-coefficients (β) from the regression model. Stata version 12.1 and R Studio version 4.0.2 were used for all statistical analyses. The significance level (α) was set at < 0.05.

All brain imaging were checked and reviewed by three radiologists. We reported a good inter-observer agreement on MRI reading in our previous research.[9]

RESULTS

Table 1 showed the distribution of sex and age of the study patients by the MR signal intensity grading of normal clivus bone marrow. The percentage of Grade I decreased with increasing ages, and particularly was found less than 10% in age groups over 40 years. The highest percentage was found at the first decade (approximate 36%). Grade I was not found in patients over the age of 70. In contrast, the percentage of Grade III increased with age and was more frequent than 10% in each age group over the age of 30 where the highest proportion (27.9%, n=17) was at the age of 60-69. At the first decade, Grade III was not found. Over the age of 40, Grade I and Grade III became more different in proportions. There

TABLE 1. Distributions of sex and age by the Graded MR Signal Intensities of Normal Clivus Bone Marrow.

	Total (N=268)	Grade I (n=45) n (%)	Grade II (n=162) n (%)	Grade III (n=61) n (%)
Sex				
Female	132	24 (53.3)	82 (50.6)	26 (42.6)
Male	136	21 (46.7)	80 (49.4)	35 (57.4)
Age (years)				
1-9	33	16 (35.6)	17 (10.5)	0 (0)
10-19	31	8 (17.8)	19 (11.7)	4 (6.6)
20-29	30	5 (11.1)	22 (13.6)	3 (4.9)
30-39	36	6 (13.3)	19 (11.7)	11 (18.0)
40-49	36	4 (8.9)	24 (14.8)	8 (13.1)
50-59	36	4 (8.9)	22 (13.6)	10 (16.4)
60-69	36	2 (4.4)	17 (10.5)	17 (27.9)
70-79	30	0 (0)	22 (13.6)	8 (13.1)

were different in proportion between males to females in Grade I (46.7% and 53.3%) and Grade III (57.4% and 42.6%) was different, whereas the proportion of males to females in Grade II was nearly equal.

Table 2 showed the mean values of clivus/CSF and clivus/pons signal intensity ratio by grading. The mean values of clivus/CSF measured in Grade I to III were 2.99 (SD= 0.83), 4.60 (SD=1.05), and 5.89 (SD=1.08) respectively. There were statistically significant (P< 0.001) of the mean values between the grades. The mean values of clivus/pons signal intensity ratios also increased by the respective grades. The mean values of clivus/pons measured in Grade I to III were 1.22 (SD= 0.32), 1.94 (SD=0.41), and 2.47 (SD=0.43) respectively, and were statistically different (P< 0.001). The mean values of clivus/CSF signal intensity ratio were higher than clivus/pons in all grades.

Table 3 showed the mean values of clivus/CSF and clivus/pons signal intensity ratios stratified by sex. The mean values of clivus/CSF and clivus/pons signal intensity ratios increased with age in both males and females. Males had slightly higher mean values in both measurements than females in all age groups. Irrespective to sex, the mean values of clivus/CSF were higher than clivus/pons in all age groups. For example, the mean values of clivus/CSF and clivus/pons signal intensity ratios were 5.12 (SD=1.06) and 2.13 (SD=0.40) in males aged 30-39 years, and the respective mean values were 4.54 (SD=1.00) and 1.86 (SD=0.44) in females in the same age group.

TABLE 2. Descriptive Values of clivus/CSF and clivus/pons Intensity Ratios in All Individuals According to the Grades.

	Grade I (n = 45) Mean ± SD	Grade II (n=162) Mean ± SD	Grade III (n=61) Mean ± SD	P-value
clivus/CSF	2.99 ± 0.83	4.60 ± 1.05	5.89 ± 1.08	<0.001*
clivus/pons	1.22 ± 0.32	1.94 ± 0.41	2.47 ± 0.43	<0.001*

* One-way ANOVA with equal variances

TABLE 3. Descriptive Values of clivus/CSF and clivus/pons Intensity Ratios Comparatively for Each Age Group in Males and Females.

Age groups	clivus/CSF, Mean ± SD		clivus/pons, Mean ± SD	
	Female, (n =132)	Male, (n = 136)	Female, (n = 132)	Male, (n =136)
1-9	2.65 ± 0.58	3.13 ± 0.72	1.12 ± 0.29	1.28 ± 0.30
10-19	3.89 ± 1.10	4.03 ± 1.13	1.59 ± 0.41	1.63 ± 0.46
20-29	4.14 ± 0.89	4.24 ± 1.08	1.66 ± 0.34	1.74 ± 0.39
30-39	4.54 ± 1.00	5.12 ± 1.06	1.86 ± 0.44	2.13 ± 0.40
40-49	4.53 ± 1.34	4.71 ± 0.99	1.89 ± 0.43	2.05 ± 0.47
50-59	5.19 ± 1.06	4.81 ± 1.17	2.18 ± 0.43	2.06 ± 0.42
60-69	5.68 ± 1.08	5.84 ± 1.41	2.39 ± 0.41	2.44 ± 0.59
70-79	5.72 ± 1.16	5.43 ± 0.94	2.41 ± 0.41	2.36 ± 0.36

In crude analysis, there were statistically differences in the mean values of clivus/CSF and clivus/pons signal intensity ratios increasing with age groups, using the age of 1-9 years as the reference group. For example, the mean values of clivus/CSF signal intensity ratios at age 30-39 years was 1.91 (95%CI: 1.40, 2.41) and clivus/pons was 0.78 (95% CI: 0.58, 0.97) higher than that of the reference group. After adjustment for sex in the regression analysis, the beta-coefficients were similar in terms of magnitude and its direction to the crude analysis. For example, the mean values of clivus/CSF and clivus/pons signal intensity ratios at age 30-39 years were 1.91 (95%CI: 1.41, 2.42) and 0.78 (95%CI: 0.58, 0.98) higher compared to the reference group (Table 4).

TABLE 4. Crude and adjusted analysis for the differences in mean ratio of clivus/CSF and clivus/pons across age groups.

Parameters	clivus/CSF		clivus/pons	
	Crude Mean Difference, β (95%CI)	Adjusted Mean Difference*, β (95%CI)	Crude Mean Difference, β (95%CI)	Adjusted Mean Difference*, β (95%CI)
Age (years)				
1-9	Ref	Ref	Ref	Ref
10-19	1.03 (0.51, 1.56)	1.05 (0.52, 1.58)	0.40 (0.19, 0.60)	0.41 (0.19, 0.61)
20-29	1.27 (0.73, 1.80)	1.28 (0.74, 1.81)	0.48 (0.27, 0.68)	0.49 (0.28, 0.69)
30-39	1.91 (1.40, 2.41)	1.91 (1.41, 2.42)	0.78 (0.58, 0.97)	0.78 (0.58, 0.98)
40-49	1.68 (1.17, 2.19)	1.70 (1.19, 2.21)	0.75 (0.54, 0.94)	0.76 (0.56, 0.95)
50-59	2.06 (1.55, 2.57)	2.07 (1.55, 2.57)	0.90 (0.70, 1.09)	0.90 (0.71, 1.10)
60-69	2.84 (2.33, 3.35)	2.85 (2.34, 3.36)	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)
70-79	2.65 (2.12, 3.18)	2.66 (2.13, 3.19)	1.17 (0.96, 1.37)	1.17 (0.96, 1.38)

* Multivariable linear regression model adjusted for sex

DISCUSSION

Normal marrow conversion process represents the gradual replacement of red marrow to yellow marrow. During infancy period, red marrow is predominant in both appendicular and axial skeletons and has converted to yellow marrow by the time. In adults approximately 25 years old, the red marrow residuals remain in the axial skeletons.[7–10,12–15]

Red marrow consists of 40% fat, 40% water and 20% protein, whereas yellow marrow consists of approximately 80% fat, 10–15% water, and 5% protein.[7,8,12–14] MR imaging is superior to other imaging devices to detect bone marrow conversion and related diseases. On T1-weighted images, yellow marrow has a high signal intensity, while red marrow has intermediate signal intensity.[2,4,8]

The clivus is an important site to evaluate bone marrow abnormalities because it is located centrally in the skull base and can be seen on routine sagittal T1–weighted MR images.[1,3]

The present study showed that, in the qualitative assessment of clivus, Grade I was more observed in young ages, whereas Grade III was more in old ages. In the quantitative assessment, the mean values of clivus/CSF and clivus/pons signal intensity ratios were increased with age in both female and male. The mean values of signal intensity ratios of both measurements in males were slightly higher than females. After adjustment for sex in the regression analysis, the mean values of clivus/CSF and clivus/pons signal intensity ratios remained the same and slightly higher than unadjusted analysis in some age groups, but the differences in mean values were also increased with age. The mean values of clivus/CSF were greater than that of clivus/pons irrespective of age.

Comparison to previous studies

In the qualitative assessment, the distribution of sex and age by the visual gradings (Grade I to III) of MR imaging clivus observed in our study was consistent with previous research.[1,3,16] A study by Okada et al.[17] evaluating the relation of marrow conversion with ages in normal patients under 25 years old showed that Grade I was more frequently observed in the age of 0-2 years old, whereas Grade III was more observed in the older ages. Grade I was not observed after the age of 6 years old. From this study, it may imply that abnormal infiltrative marrow lesions should be concerned when Grade I was detected after this age. In our study, however, we still observed Grade I after the age of 6. The discrepancy may be because of the difference in the classification criteria of the visual grading of clivus on MR imaging. The previous study used the criteria that is more subjective to grade clivus bone (Grade I = uniformly low signal intensity, relatively isointense to muscle, Grade II = mixed low and high signal intensity portion, and Grade III = almost uniformly high signal intensity, relatively isointense to subcutaneous fat) than the criteria used in our study. We estimated the percentage of the components of bone marrow signal intensity according to a study by Kimura et al.[3] (Grade I = predominantly low signal intensity, occupying more than 50% of the clivus; Grade II = low-signal-intensity portion occupying less than 50% but greater than 20% of clivus; Grade III = predominantly high signal intensity, occupying less than 20% of the clivus). In addition, the early marrow conversion process may be different across study populations in terms of genetic and environmental factors which contribute to the discrepancies between studies.

In quantitative assessment, our findings were also consistent with previous studies[1,2] that showed the age-related pattern of the mean values of clivus/pons signal intensity ratios. The pattern can be explained by the physiologic change of normal marrow conversion as it was detected from signal intensity on T1-weighted images. A study by Bayramglu et al.[2] reported that the mean value of clivus/pons signal intensity ratio in males was slightly higher than that in females. However, this information indicates that the association of the mean values of clivus/pons signal intensity ratio and ages observed in this study may be confounded by sex. In our study, the association of the mean values of clivus/pons signal intensity ratio and ages remained unchanged although the effect of sex was adjusted in the regression analysis. Thus our findings confirmed that there is an association between the mean values of clivus/pons signal intensity ratio and ages. In all studies, the mean value of clivus/CSF signal intensity ratio was higher than that of clivus/pons. It is due to the fact that the signal intensity of CSF was lower than pons that yield the lower ratio of clivus/pons relative to clivus/CSF. In addition to statistical significance of age-related change of clivus in our study, both clivus/pons and clivus/CSF signal intensity ratio have shown clinical implication in practice since the homogeneous property of pons is a good landmark to provide more details on sagittal T1–weighted MR images of the brain. Although clivus/CSF does not much carry potential information, it is needed to be estimated as to evaluate the abnormalities of clivus.

Strengths and limitations

Our research has some potential strengths. First, the

sample for our study was derived by stratified random sampling by age from a large cohort of subjects who had undergone MR imaging and had no abnormalities of the clivus bone marrow in our radiology department over a four-year period. This sample was a good representation of the general population in our settings. As a result, our findings can be generalized to Thai population. Second, three radiologists independently assessed the MR imaging. In the event of disagreement, the values of MR imaging measures and visual grading of the clivus bone were determined by consensus. This may lead to more precise grading of clivus bone marrow. Third, the effect of gender on the association between clivus signal intensity ratios and age was excluded. Our present study confirms the age-related change of clivus on MR imaging. However, some methodological concerns must be addressed. The interpretation of the high signal intensity from clivus could be hampered by the limited window setting image presentation used for MR imaging of the brain. Furthermore, because we only employed a single T1-weighted midsagittal cranial image to evaluate the visual grading, we were unable to determine the precise percentage component of signal intensity in clivus marrow. However, we assume the results will be the same if we use another single clivus parasagittal image.

Implication to clinical practice

The present study suggested that the signal intensity of clivus bone Grade I should not be detected on T1-weighted of brain MR imaging in the old ages. If it is present, abnormal infiltrative marrow lesions could not be excluded. In addition, the signal intensity ratio of clivus bone marrow is a good indicator to evaluate the abnormalities of bone marrow since the value is related to ages.

CONCLUSION

The present study confirms that there is an association of signal intensity of clivus to pons ratio and age where the relationship is independent of gender.

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Comparison of Primary Patency Rate between Drug-Coated Balloon and Plain Balloon Angioplasty in Hemodialysis Access

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ABSTRACT

Objective: Hemodialysis adequacy in end-stage renal disease patients plays a crucial role in their quality of life. Repeated stenosis at the anastomotic site of arteriovenous fistula and synthetic arteriovenous graft are a major cause of access failure resulting in hospitalization, catheter usage, and contributing substantially to increased health care costs. Although standard plain balloon angioplasty (PBA) is successful, the patency rate over time is often poor. Drug-coated balloons (DCB) delivering an anti-restenosis agent, Paclitaxel, may improve patency. In this study, we aimed to investigate whether there is an increase in primary patency rate in drug-coated balloon angioplasty compared to conventional plain balloon angioplasty.

Materials and Methods: We performed a retrospective analysis of 55 patients with stenotic arteriovenous fistulas (AVF), and arteriovenous grafts (AVG) treated with DCB or PBA. Thirty-five patients were treated with drug-coated balloons, while twenty patients were treated with the standard plain balloon angioplasty. Follow up assessment was scheduled at three months, six months, and nine months. Our primary outcome was the primary patency rate, defined as the interval from the time of intervention until hemodialysis inadequacy.

Results: There were 55 patients including twenty-one males and thirty-four females participated in the study. The average age of the 55 patients was 65.43 ± 12.89 years. Thirty (54.5%) patients were diabetes mellitus and 40 (72.7%) patients had hypertension. Seven patients (12.7%) had dyslipidemia. Eight patients (14.5%) had ischemic heart disease. And four patients (7.3%) had hyperparathyroidism. No significant differences in patency rate were found between gender, age group and patients' underlying diseases. The proportion of primary patency rate comparing between the DCB and PBA treatment was 96.3% versus 73.9% at 6 months (P=0.017) and 92.6% versus 40% at 9 months (P<0.001). After multivariable analysis was performed (adjusted for sex, age, and underlying diseases), we found that stenosis was more likely to occur in patients who had undergone plain balloon angioplasty rather than drug-coated balloon angioplasty (HR 15.75; 95% CI 2.5%-99.1%, P=0.003).

Conclusion: Drug-coated balloon angioplasty, when compared with plain balloon angioplasty, achieves a more desirable primary patency rate at 6 months and 9 months after the procedure.

Keywords: Arteriovenous fistula (AVF); Arteriovenous graft (AVG); Paclitaxel, Drug-Coated Balloon (DCB); Plain Balloon Angioplasty (PBA); primary patency; hemodialysis access (Siriraj Med J 2022; 74: 388-394)

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INTRODUCTION

The prevalence of chronic kidney disease (CKD) is significantly rising globally. Its association with major morbidity and mortality demands distinct attention as one of the growing public health concerns. Currently, amongst Thais, there are nearly 12 million people affected with CKD and roughly 6 million people with advanced stage CKD. Over one hundred thousand patients require dialysis.[1] The Thailand renal replacement therapy (TRT) noted that an addition of 15,462 new patients on hemodialysis, 3,598 new patient on peritoneal dialysis and 719 new patients performed kidney transplant in 2020, has brought the total number to 19,722 patients.[2] For these patients, hemodialysis is the preferred treatment to substitute for kidney function and ensure their survival.

Presently, two techniques have been used to facilitate hemodialysis: these are arteriovenous fistula (AVF) and arteriovenous graft (AVG). The **K**idney **D**isease **O**utcomes **Q**uality **I**nitiative (KDOQI) vascular access guideline prefers AVF due to ease of care and has suggested AVG only when AVF is unattainable. Nevertheless, both artificial vasculatures often come with complications such as repeated stenosis which led to hemodialysis failure, hospitalization and even death. The primary failure rate of AVF is approximately 20% higher than that of AVGs.[3]

The first line of approach to hemodialysis failure, caused from stenosis of hemodialysis access, is balloon angioplasty. Plain balloon angioplasty (PBA) is currently the procedure most commonly performed. However, repeated stenosis occurs regularly. Alternate techniques, such as bare metal stents, have been investigated to combat the obstruction but none have had promising results.[4] Recently, one multicenter randomized trial found that a drug-coated balloon (DCB) appeared to reduce the occurrence of stenosis. The drug, paclitaxel, when applied to the balloon, caused the reduction of vessel wall remodeling and fibromuscular hyperplasia, and prevented neointimal hyperplasia from causing stenosis.[5,6]

In this study, we aimed to investigate whether there is an increase in the primary patency rate of AVF or AVG stenosis treated with drug-coated balloon angioplasty (DCB) with AVF or AVG stenosis treated with plain balloon angioplasty (PBA).

MATERIALS AND METHODS

Study design

This retrospective cohort study was conducted in chronic kidney disease patients suffering from primary patency failure of either AVF or AVG at the department of surgery, Burapha University, Thailand duration between August 2016 to October 2019. A total of 55 patients were enrolled. The inclusion criteria were the patient with chronic kidney failure stage 5 and at least 15 years of age diagnosed with the first episode of hemodialysis access failure. The diagnosis criteria of hemodialysis access failure were; 1) inadequate blood flow rate on the dialysis chart 2) presence with clinical of venous hypertension (high venous pressure more than 200 mmHg, arm swelling, upper extremity superficial vein dilatation) and 3) thrombosed of hemodialysis access. The diagnosis was confirmed with CT venography or venous duplex ultrasound, or intra-operative venography. The reduction of intraluminal more than 50% of actual diameter was defined as a significant stenosis lesion. This study aimed to investigate and compare the efficacy of both PBA and DCB in repairing stenosis and maintaining stenosis-free arteriovenous shunts in short- and mid-term scenarios.

Patient allocation and data collection

After informed consent, patients were given information about plain balloon angioplasty and drug-coated balloon angioplasty. Patients were allowed to choose which treatment they preferred. All patients were followed up every three months to evaluate hemodialysis adequacy and restenosis (failure of primary patency rate). The venipuncture site was assessed for prolonged bleeding and the general condition of the arm. The hemodialysis chart was reviewed. The protocol of patient's participation was approved by the Burapha University ethics committee (IRB Issue#280/2562) and was accomplished according to the Declaration of Helsinki and WHO guidelines. There was no external financial support provided.

Procedures

For the patient with clinical of inadequate blood flow rate or present with clinical of venous hypertension, CT venogram or duplex ultrasound was used to confirm the stenotic lesion which more than 50% luminal diameter reduction concerned significant stenosis. The procedure was performed under local anesthesia with monitor anesthetic care (MAC). PBA or DCB did the balloon angioplasty with actual venous diameter. The procedural success was dilatation of stenotic lesion to 80-100% of the actual venous diameter.

Graft thrombectomy was performed with forgarty catheter under local anesthesia with monitor anesthetic care (MAC) for those with graft thrombosis. After successful thrombectomy, intra-operative venography was performed to figure the stenosis portion. PBA or DCB did the balloon angioplasty with the actual size of the stenosis vein. The

final venogram was evaluated the operative result. The operative success was an enlargement of stenosis portion increased up to 80-100% of the actual venous diameter.

Post-operative surveillance

During the follow-up at 3, 6, and 9 months, the circuit pressure while hemodialysis in hemodialysis chart was reviewed to determine proper blood flow during dialysis (adequate arterial flow ≥ 300 ml/min and venous pressure < 200 mmHg). Primary patency rate is defined as the interval from the time of intervention (DCB or PBA) until the time of hemodialysis inadequacy. These following situations ended the primary patency; inadequate blood flow, thrombosed hemodialysis access, high venous pressure (more than 200 mmHg), recurrent arm swelling, or upper extremity superficial vein dilatation and confirmed with CT venography, venography, or duplex ultrasound.

Statistical analysis

The calculation of the sample size was based on two independent proportions formula references from Katsanos study.[8] Results are presented using descriptive statistics. The mean and standard deviations are represented for the continuous data. The comparison between groups was using the chi - square test for the categorical variables. While the continuous variables were compared with the student t-test. The Kaplan-Meier analysis was used to compare the event-free survival. All the statistics were calculated by SPSS, version 19.0 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of fifty-five patients were enrolled in this study. Twenty patients were assigned to the control group (plain balloon angioplasty) (PBA), while 35 patients were assigned to the drug-coated balloon angioplasty (DCB) group. The overall average age was 65.43 ± 12.89 years. Baseline patient demographic data are shown in Table 1. Although there are more patients with diabetes mellitus and ischemic heart disease in the control group, there are no significant differences in baseline demographics between the two groups.

All participants completed the nine-month follow-up examination. At three months, the data displayed no significant differences in post-intervention primary patency rate between both groups (95% for the PBA group and 100% for the DCB group; p=0.192). However, a distinction between the two groups appeared at the six months and 9-months follow-up. At six months, the DCB group exhibited a significantly higher patency rate than the PBA group, 96.3% and 73%, respectively (Fig 1A). And even more evident at nine months, achieving up to 92% for the DCB group versus 40% for the PBA group (Fig 1B).

The chi-squared test showed in Table 2 indicated that sex, age, underlying (HT, DM, DLD, IHD, and hyperparathyroidism) were no effective defenses of patency rate. The restenosis was occurred in a patient with PBA than DCB within nine months (p-Value < 0.001)

Cox regression analysis was accomplished on all variables shown in Table 3. As expected, no significant

TABLE 1. Baseline patient demographics.

	Plain balloon (n=20)	Drug coated balloon (n=35)	P-value
Sex			
Male	5 (25%)	16 (45.7%)	
Female	15 (75%)	19 (54.3%)	0.128
Age (year)	66.63 ± 13.11	64.75 ± 12.91	0.607
Underlying conditions			
Hypertension	15 (75%)	25 (71.4%)	0.775
Diabetes mellitus	14 (70%)	16 (45.7%)	0.082
Dyslipidemia	1 (5%)	6 (17.1%)	0.194
Ischemic heart disease	5 (25%)	3 (8.6%)	0.096
Hyperparathyroidism	1 (5%)	3 (8.6%)	0.624
Follow up time (days)	7.64 (3.74, 13.15)	13.31 (5.74, 17.48)	0.172

Value presented as mean ± SD. or median (IQR) and n (%). P-value corresponds to independent t-test or Mann-Whitney test and Chi-square test.

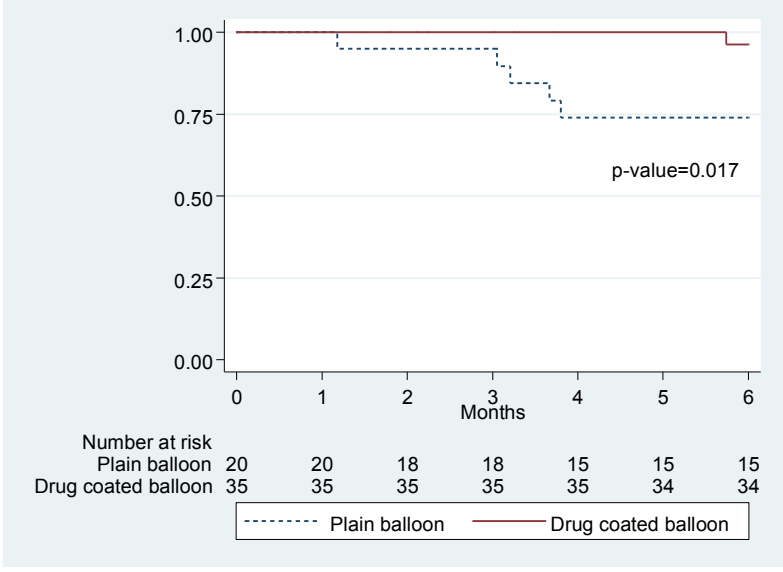

Fig 1A. Kaplan-Meier Curve of PBA group vs DCB group at 6 month follow up (p-value by log rank test)

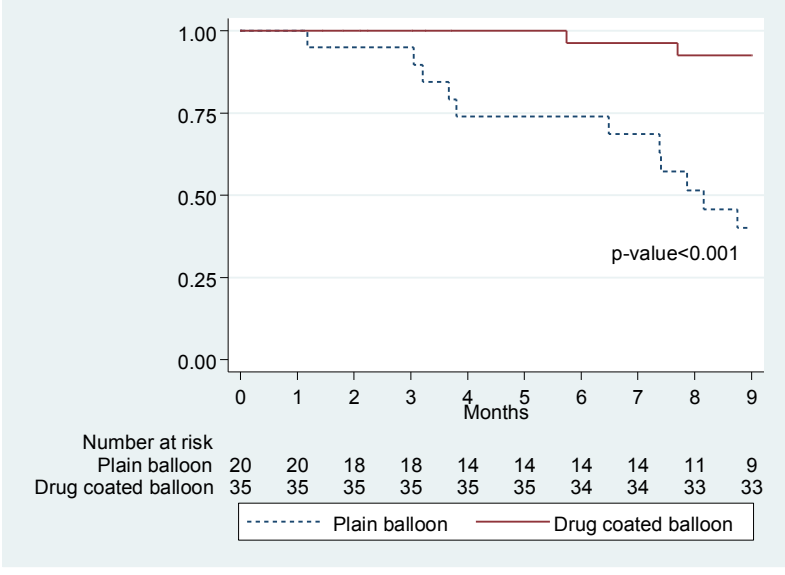

Fig 1B. Kaplan-Meier Curve of PBA group vs DCB group at 9 month follow up (p-value by log rank test)

TABLE 2. Categorical variables associated with patency at 9 months compared by chi-squared test.

	Patency (n=42)	Stenosis or occlusion (n=13)	P-value
Sex			
Female	26 (61.9%)	8 (61.5%)	0.981
Male	16 (38.1%)	5 (38.5%)	
Age (year)	65.26 ± 13.7	65.99 ± 10.31	
Underlying			
Hypertension	30 (71.4%)	10 (76.9%)	0.697
Diabetes mellitus	21 (50%)	9 (69.2%)	0.224
Dyslipidemia	6 (14.3%)	1 (7.7%)	0.533
Ischemic heart disease	4 (9.5%)	4 (30.8%)	0.058
Hyperparathyroidism	3 (7.1%)	1 (7.7%)	0.947
Treatment			
Plain balloon	9 (21.4%)	11 (84.6%)	<0.001*
Drug coated balloon	33 (78.6%)	2 (15.4%)	

TABLE 3. Univariates and multivariate cox regression analysis between two groups.

	Univariate		Multivariate	
	HR (95%CI)	P-value	Adj HR (95%CI)	P-value
Sex				
Female	1.04 (0.34, 3.19)	0.941	1.25 (0.32, 4.93)	0.75
Male	Reference	1	Reference	1
Age (year)	1 (0.96, 1.05)	0.948	0.98 (0.92, 1.03)	0.407
Underlying				
Hypertension	1.69 (0.46, 6.16)	0.425	2.17 (0.43, 10.97)	0.35
Diabetes mellitus	1.95 (0.6, 6.34)	0.267	1.5 (0.37, 5.99)	0.57
Dyslipidemia	0.85 (0.11, 6.54)	0.874	5.73 (0.44, 74.48)	0.183
Ischemic heart disease	2.79 (0.86, 9.08)	0.088	4.21 (0.76, 23.41)	0.101
Hyperparathyroidism	0.91 (0.12, 7.02)	0.929	3.52 (0.27, 45.8)	0.336
Treatment				
Plain balloon	11.71 (2.58, 53.08)	0.001*	15.75 (2.5, 99.1)	0.003*
Drug coated balloon	Reference	1	Reference	1

differences in patency rate were connected to age, sex, and underlying diseases. Nonetheless, after multivariable analysis was performed (adjusted for sex, age, and underlying diseases), we found that restenosis was more likely to occur in patients treated with PBA than DCB within nine months (HR 15.75; 95% CI 2.5%-99.1%, P=0.003) (Table 2).

DISCUSSION

There are currently two types of long-term hemodialysis access, arteriovenous fistulas (AVFs), and arteriovenous grafts (AVGs).[7] According to the Kidney Disease Outcomes Quality Initiative (KDOQI) vascular access guidelines, they recommended placement of AVF over AVG due to the low rate of infection and ease of care.[3] Praditsuktavorn demonstrated that the 12-months primary patency of a snuffbox arteriovenous fistula is roughly about 60%.[8] Although the primary patency rate of the AVFs is lower than AVGs, the long-term patency is superior to AVGs.[3] Two major publications compared the failure rate between AVFs and AVGs. The failure rate of AVFs and AVGs were approximately 40% and 20%, respectively. Conversely, with the long-term patency, AVFs were superior to AVGs (5 versus 2 years).[9,10] In the thrombosed AVG group, Puangpunngam et al. showed no difference in patency between endovascular or open thrombectomy.[11]

Numerous factors induce early AVF failure: small vessel diameter; wall damage during a surgical procedure; newly-developed accessory veins after placement; fluid shear stress at anastomosis; genetic predisposition to vasoconstriction neointimal hyperplasia; pre-existing venous neointimal hyperplasia; and preceding venipunctures.[12] Late AVF failure is usually caused by fibromuscular hyperplasia (fibrotic lesion formation) due to increased shear stress in the thin-walled outflow vein. Venous neointimal hyperplasia (VNH) is characterized by stenosis and subsequent thrombosis, which is a majority of the pathology of graft failure.[13] Roy et al. demonstrated that VHL was characterized by 1) Presence of smooth muscle cell/myofibroblast, 2) Accumulation of extracellular matrix component, 3) Angiogenesis within the neointimal and adventitia, and 4) Presence of an active macrophage cell layer lining graft material. This leads to blood flow reduction or stasis and subsequent thrombosis formation.[12]

Although PBA has been the conventional method to revise failing vascular access, the procedure itself initiates local inflammatory and proliferative repair responses. This consequently increases the rate of short-term restenosis, lowering the clinical efficacy of PBA.[14,15] Even with drug-eluting stents (DES), this obstacle is still present. A potential solution has been presented with the use of drug-coated balloon (DCB) technology in other settings such as in-stent restenosis in coronary artery disease or enhancing the patency of the treatment in peripheral arterial disease. This has led to the use of DCB for the revision of dialysis access failures.[5,16,17]

To further specify, the drug widely used to coat these balloons is called paclitaxel. A substance that is both lipophilic and cytotoxic, initiating local anti-proliferation of human arterial smooth muscle cells (haSMCs) and causes inhibition of access restenosis.[18] It is also selected to treat hemodialysis patients due to its pharmacokinetic properties. Paclitaxel renal clearance is very minimal (approximately 1-8%), making it relatively easy and safe to use and requiring no dosage modification for renal impairments. Paclitaxel is metabolized via other routes, such as hepatic, biliary, and fecal elimination.

Several randomized controlled trials have compared DCB and PBA efficacy in the treatment of failing vascular access.[17,19-22] A study by Katsanos et al. found that the primary patency of the DCB group was almost 3 times that of the PBA group. Hence, repeated procedures' requirement rate was lower in the DCB-treated lesions than the PBA (25% vs. 70%, p=0.002). The study also showed DCB had better mid-term primary patency than PBA.[20]

Similar results were also demonstrated by Yanqi Yin et al. where DCB demonstrated a higher primary patency rate at 6 months without evidence of unfavorable side effects.[14] However, the result suggested otherwise in another trial by Trerotola O et al. Where DCB showed no increase in effectiveness at six months compared to the conventional PBA.[17] This study has raised uncertainty among physicians trying to determine the role of DCBs in treating hemodialysis access stenosis.

The significant improvement of short- and mid-term secondary patency of hemodialysis access in DCB-treated angioplasty was proved in a recent meta-analysis by Chen et al.[19] However, further studies on long-term side effects are needed to investigate the safety of paclitaxel-coated angioplasty in patients with end-stage renal disease. A meta-analysis by Chenyu Liu et al., published by the journal of the American Heart Association in 2021, was derived from multiple randomized controlled trials comparing the safety and efficacy of these two methods. The results showed that DCB angioplasty was superior in maintaining target lesion primary patency and further showed no increase in the risk of mortality when compared with PBA.[21]

To the best of our knowledge, this is the first study in Thailand that compares traditional PBA and new DCB angioplasty for the treatment of failing dialysis vascular access circuits. Furthermore, although our study was a retrospective study, it is the first step in our effort to prove our hypothesis.

Study limitations

There are two core limitations in this study that could be noted for future research. First, the study is based on existing data from only one hospital, creating a possible bias from being non-blinded and single centered. Secondly, the patient sample size was less than initially calculated due to time constraints. Fortunately, some results are statistically significant. Drug-coated balloon angioplasty may show compelling results at three months with larger sample size.

CONCLUSION

This article is the first retrospective study in Thailand that shows that drug-coated-balloon angioplasty using paclitaxel-coated balloons has better long-term patency results when compared to standard plain balloon angioplasty. Blood vessel patency was improved at 6 and 9 months after the initial procedure. However, further studies are needed to assess the cost-effectiveness and mortality of end-stage renal disease patients.

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The Safety of Food and Drink Consistencies Based on a Fiberoptic Endoscopic Evaluation of Swallowing Study Results in Stroke Patients with Dysphagia

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ABSTRACT

Objective: Knowing such dysphagic stroke patients' ability to swallow various food consistencies from instrumental investigations will help the medical staff choose the appropriate and safe food consistencies, and lead to a better swallowing outcome. This study aimed to determine the safety of food textures and drink consistencies in stroke patients with dysphagia.

Materials and Methods: Stroke patients who failed the small-volume water swallow test (WST) and underwent fiberoptic endoscopic evaluation of swallowing (FEES) at the Department of Rehabilitation Medicine from 2017 to 2020 were reviewed. The patients' characteristics and safe food textures and drink consistencies from their FEES results were collected. They were given a bolus test, which included four modified food textures and three varying drink consistencies, as adapted from the International Dysphagia Diet Standardization Initiative. The sequence of bolus test was adjusted by participants' swallowing abilities individually. Moreover, their compensatory techniques were reviewed.

Results: Forty-three participants were recruited. Most of them (81.3%) could safely swallow one consistency of drink. Twenty-five (58.1%) could safely swallow a mildly thick liquid. About 20% of them could not safely swallow any food textures. Most participants (76%) who safely swallowed a mildly thick liquid could also safely swallow at least one kind of food texture. About half of them (53%) used the chin-tuck technique during the FEES testing.

Conclusion: Half of stroke patients with dysphagia who failed small-volume WST could safely swallow with a mildly thick liquid with compensatory techniques. Therefore, they should be referred to dysphagia specialists for comprehensive evaluation and management.

Keywords: Diet modification; stroke; dysphagia; fiberoptic endoscopic evaluation of swallowing study (Siriraj Med J 2022; 74: 395-400)

INTRODUCTION

Stroke is the leading cause of death and long-term disability worldwide[1], especially in developing countries[2] and Thailand.[3] To date, appropriate stroke management and rehabilitation intervention[4-5] have been established to reduced mortality rate and disabilities. However, previous studies[6-7] reported lack of knowledge and awareness about stroke and its risk factors were leading to delayed

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treatment and poor outcome in developing countries. Moreover, comprehensive stroke units that incorporate rehabilitation have not been settled yet. Hence, stroke is a major public health leading to multiple disabilities[8-9] and impact their quality of life.[10]

Post-stroke dysphagia (PSD) is found in approximately 55% of acute stroke survivors.[11] PSD was associated with an increased 12-months-mortality, develop aspiration pneumonia and poorer functional outcomes.[12] Performing swallowing screening among individuals with stroke is recommended.[12-13] According to the dysphagia management guidelines[12,14-15], stroke survivors who fail the swallowing screening should be referred to dysphagia experts and/or consider instrumental investigations, including a videofluoroscopic swallowing study and a fiberoptic endoscopic evaluation of swallowing (FEES) to confirm their swallowing pathology and to prescribe safe modified diet, and compensatory techniques.[16-17] Both interventions have demonstrated excellent agreement in detecting laryngeal penetration (89.58%), tracheal aspiration (96.69%), pharyngeal residue (84.38%) and also diet recommendation (100%).[17]

In clinical practice, the water swallow test (WST) is approved as a standard to detect aspiration risk[12,18] and widely used. The small volume WST (1-5 mL) has sensitivity of 63%-78% and specificity of 86%-93% and large volume WST (90-100 mL) has sensitivity of 89%-93% and specificity of 51%-55%.[18] Therefore, stroke survivors who fail small volume of WST were assumed at high risk of aspiration and may be recommended for NG tube-feeding and then be referred to a dysphagic specialist.[12,14] In developing countries, there are not enough dysphagia specialists, and the instrumental investigations require trained specialists, are costly and not generally accessible. This can lead to an unnecessarily prolonged nothing per oral period which can decondition the swallowing function.[19]

Swallowing rehabilitation[20] consists of an indirect swallowing therapy (oromotor stimulation and exercise) and a direct swallowing therapy (swallowing training with a modified diet and/or compensatory techniques). Direct-swallowing therapy follows the principles of neuromuscular rehabilitation to facilitate increased muscle strength.[21] Dietary modification is a crucial treatment for dysphagia and can reduce the risk of aspiration.[22] According to systematic review[23], show a reduction in the risk of penetration–aspiration with liquids, as they progress from the thin to the very thick end of the viscosity continuum. Benjapornlert P, et al[24] reported thin liquid with large volume (10 mL) showed the highest risk of penetration and aspiration in the healthy elderly with dysphagia risk. However, a small amount of moderately thick liquid (4 mL) was the safest.

However, there is no consensus evidence whether stroke survivors with dysphagia especially in whom failed a small volume of WST should be NPO until they meet dysphagia experts or receive instrumental assessment or try to start training with diet modification.[25] Knowing such patients' ability to swallow various food consistencies from instrumental investigations will facilitate an earlier direct swallowing therapy, help the medical staff choose the appropriate and safe food consistencies, and lead to a better swallowing outcome.

The objective of this study is to find the safe food textures and drink consistencies for individuals with stroke who fail the small- volume WST based on their FEES results.

MATERIALS AND METHODS

This retrospective study was conducted in stroke survivors who failed the small-volume WST and underwent the FEES procedure at the Department of Rehabilitation Medicine from 2017 to 2020. The patients who had a history of surgery or cancer in the head or neck or other neurological diseases affecting the swallowing function, such as Parkinson's disease or brain tumor were excluded.

Demographic data and the FEES result, including the safe food and drink consistencies and compensatory technique, were reviewed from medical records.

The research protocol was approved by the Siriraj Institutional Review Board (Si 752/2019). The clinical trials registry number is TCTR20200322002.

The water swallow test (WST)

The small volume of WST (5 mL) were done 3 attempts by physiatrists. The presence of abnormal signs including coughing, a vocal change, or a decrease in oxygen saturation of more than 2% at any attempts, were considered as failing the WST.

The fiberoptic endoscopic evaluation of swallowing (FEES)

The FEES was performed by dysphagia specialists who had experience in the procedure at least 50 cases.

The definition of a "safe swallow" of each consistency tested when performing the FEES was determined by penetration-aspiration scale[26-27] ≤ 2 and his or her not having a residual content of more than 25%. Otherwise, the swallows were determined to be "unsafe."

Each subject was tested with various consistencies of food and drinks which were adapted from the International Dysphagia Diet Standardization Initiative (IDDSI).[28]

The three drink consistencies consisted of a thin liquid, a mildly thick liquid, and a moderately thick liquid. The four food textures consisted of a pureed, minced and moist, soft and bite-sized, and regular diet.

The FEES protocol, participant swallowed a 5-mL of each drink and food consistency and 2 times for each consistency. The FEES protocol began with a mildly thick liquid. If it was safe, then a thin liquid would be tested. If that failed, then a moderately thick liquid would be tested. The food textures were tested if the patient passed one of liquid-consistency test. A pureed item was initially tested, and then the patient progressed to minced and moist, soft and bite-sized, and finally, a regular diet. The test was stopped at the consistency which was considered unsafe. Finally, the endoscopists determined the food and drink consistency which the patient could safely swallow.

Statistical analysis

The data were analyzed using the IBM SPSS statistics, version 23.0 (IBM corporation). The subjects were categorized into two groups based on their FEES results: 1) indirect- swallowing therapy (IT): These patients could not safely swallow any consistency of food or drink, and 2) direct-swallowing therapy (DT): These individuals could swallow at least one consistency of food or drink.

Quantitative data, including age, BMI and stroke onset, were reported by mean and standard deviation or median and interquartile range. Qualitative data, including demographic data, ability to swallow various drink consistencies and food textures, compensatory techniques used were reported by number or percentage. The Fisher's exact test was used to compare the categorical variables. The independent t-test or Mann-Whitney U-test was used to compare the continuous variables. A multivariate logistic regression analysis, with an adjustment for potential confounding factors, was used to estimate the adjusted odds ratio. A P-value <0.05 was considered statistically significant.

RESULTS

Forty-three patients were included for analysis.

The duration of the days between WST and FEES procedure, mean ± SD was 5.9 ± 5.5 days. Table 1 shows the number and percentage of subjects who could safely swallow various drink consistencies. Most participants (81.3%) could safely swallow one consistency of drink. Twenty-five participants (58.1%) could safely swallow a mildly thick liquid. Six participants (13.9%) could safely swallow liquid. Eight (18.6%) were not allowed to swallow any consistency of drink. More than half (60%) of the patients could safely swallow at least one kind of food consistency. About 40% were not allowed to swallow any food textures.

Twenty-five subjects who could safely swallow a mildly thick liquid could safely swallow pureed, minced and moist, and soft and bite-sized items, at a percentage of 40%, 24%, and 12%, respectively. It was determined that 76% of the subjects who could safely swallow a mildly thick liquid could safely swallow at least one kind of food consistency.

Four subjects who could safely swallow moderately thick liquid, 25% (1/4) could safely swallow pureed and others were unable to swallow any food consistency.

Table 2 summarizes the demographic and clinical characteristics of the subjects in the IT and DT groups. Infratentorial lesion, a history of pneumonia, and a younger age significantly characterized the IT group. Other factors were not significantly different between the two groups.

According to the univariate analysis, the three variables associated with the severity of dysphagia were infratentorial lesion (p=0.022), a history of pneumonia (p=0.028), and a younger age (p=0.023). By multivariate analysis using the stepwise logistic regression, the strongest independent risk factor for the severity of dysphagia was infratentorial lesion (adjusted OR 9.33, 95% CI 1.50-58.01), as shown in Table 3.

TABLE 1. The participants' final abilities to safely manage various drink consistencies and food textures

Drink consistencies and food textures*	N (%), (n=43)
Drink	
Thin liquid	6 (14.0)
Mildly thick	25 (58.1)
Moderately thick	4 (9.3)
Unable to drink any drink consistencies	8 (18.6)
Food	
Pureed	11 (25.6)
Minced and moist	12 (27.9)
Soft and bite-sized	3 (7.0)
Regular	0 (0)
Unable to eat any food textures	9 (20.9)
Not tested	8 (18.6)

Most of participants (83.7%) used at least one compensatory technique. One fourth of them used 2 compensatory techniques and 16 % of them used more than 2 compensatory techniques. The multiple swallows were the most common technique used, at about 53%, followed by the chin tuck, at about 20%.

TABLE 2. Demographic data.

Characteristics	Subjects (n=43)	IT[1] (n=8)	DT[2] (n=35)	*P*-value
Age (years), mean ± SD	68.5 ± 13.6	58.75 ± 13.26	70.74 ± 12.9	0.023*
BMI[3] (kg/m^2), mean ± SD	20.4 ± 3.8	19.37 ± 3.31	20.71 ± 3.9	0.383
Duration of stroke (days), median (range)	118 (65-318)	77.5 (51-503)	120 (71-292)	0.502
Male gender, n (%)	26 (60.5)	7 (87.5)	19 (54.3)	0.119
Stroke type: Infarction, n (%)	32/42 (76.2)	7/8 (87.5)	25/34 (73.5)	0.655
Lesion location: Infratentorial, n (%)	8/39 (20.5)	4/7 (57.1)	4/32 (12.5)	0.022*
Recurrent stroke, n (%)	10 (23.3)	1 (12.5)	9 (25.7)	0.655
History of aspiration pneumonia, n (%)	12 (27.9)	5 (62.5)	7 (20)	0.028*
On tracheostomy, n (%)	2 (4.7)	0 (0)	2 (5.7)	1.000
Bedside-swallowing evaluation, n (%)				
Abnormal gag reflex	19 (44.2)	3 (37.5)	16 (45.7)	1.000
Presence of aphasia	6 (14)	1 (12.5)	5 (14.3)	1.000
Tongue weakness	28 (65.1)	4 (50)	24 (68.6)	0.419
Abnormal laryngeal excursion	39 (90.7)	8 (100)	31 (88.6)	1.000
Tube feeding, n (%)				
No tube feeding	1 (2.3)	0 (0)	1 (2.9)	N/A
NG[4] tube	41 (95.3)	7 (87.5)	34 (97.1)	N/A
PEG[5]	1 (2.3)	1 (12.5)	0 (0)	N/A

*A *p*-value <0.05 indicates statistical significance

[1]IT, indirect swallowing therapy (subject was not safe to swallow any consistency of food or drink); [2]DT, direct swallowing therapy (subject was safe to swallow at least one consistency of food or drink); [3]BMI, body mass index; [4]NG, nasogastric; [5]PEG, percutaneous endoscopic gastrostomy, Values are represented as mean ± SD or median ± IQR or n (%)

TABLE 3. Factors associated with poor ability to safely swallow.

Characteristics	Crude odds ratio	Adjusted odds ratio
Age	0.94 (0.88, 0.99)	-
History of aspiration pneumonia	6.66 (1.27, 34.84)	-
Infratentorial lesion	9.33 (1.50, 58.01)	9.33 (1.50,58.01)

DISCUSSION

Ours is the first study to elucidate such patients' ability to swallow various consistencies of food and drinks. This knowledge will help clinicians to choose the appropriate consistency for each individual, and this will improve the efficacy and safety of the swallowing therapy.

This study showed that most participants could safely swallow one kind of drink, and about half of them could safely swallow a mildly thick liquid such as any liquid or juice with thickener, drinkable yogurt, skimmed milk. The IDDSI[28] recommends to measure how thick a liquid by the flow test measures. For mildly thick liquids, the 4-8 mL remaining in a 10 mL syringe after 10 seconds of flow should observe. It might be an option to start swallowing- training and closely monitor the aspiration under experienced healthcare providers. However, the authors suggest that those patients should be referred to dysphagia expert for comprehensive evaluations.

Furthermore, if patients fail to swallow a moderately thick consistency such as honey or smoothies, then no drinks or food will be allowed for the training. If our subjects could safely swallow a mildly thick liquid, most of them could also safely swallow one kind of food consistency. These might be useful to precede the swallowing training.

Kagaya et al.[29] demonstrated that body position, such as chin down, head rotation, etc., can also minimize aspiration. In our study, half of the patients were recommended to use the multiple swallow technique, and 20% were encouraged to use the chin tuck position. Thus, the study results were affected not only by the modified textures or consistencies, but by the compensatory techniques. Ultimately, compensatory techniques should be used along with a modified diet as dysphagia management.

In the present study, some participants were not allowed to swallow any food. Those included 1.) Patients who were not safe after swallowing mildly and then moderately thick consistencies of drink, and who then did not test with any food. According to the IDDSI[28], a moderately thick liquid consistency is comparable to a liquidized texture of food (the first level of food texture). If they were not safe with this consistency, they would not be safe for food testing. 2.) Patients were not safe after any food-texture testing. However, 13.9% of the subjects could safely swallow a thin liquid. These findings may be due to a false positive of the WST but also from the false negative in FEES. Moreover, compensatory techniques were applied while performing the FEES.

Daniel SK et al.[30] showed that infratentorial lesion has a significantly higher likelihood of an abnormal PAS score, when compared to those in the right hemisphere. This is because the cranial nerve nuclei, the nerve tract, and the reticular interneurons which are responsible for the swallowing function within the brainstem structures are clustered.[31] This is consistent with our study. History of aspiration pneumonia was found more in IT group (62.5%) than DT group (20%). However, this factor did not show a significant association, it might be due to small sample size in IT group.

This study has some limitations. First, this is retrospective study, so there was a high risk of bias and missing data. The FEES did not perform in the same day of WST. In addition, this FEES protocol did not test all the drink consistencies and food textures in all the participants. The endoscopists tested with drink consistencies first and then progressed to food textures, as described in the study method. Therefore, each patient was not tested with the same FEES protocol.

To conclude, half of stroke patients with dysphagia who failed small-volume of WST could safely swallow with a mildly thick liquid with compensatory techniques. Thus, they should be referred to dysphagia specialists for comprehensive management as soon as possible. Infratentorial lesion proved to be a factor associated with poor ability to safely swallow.

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Health Innovation Development by Using Design Thinking in Pharmacy

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ABSTRACT

Nowadays, innovation plays a critical role in business operation. Design thinking is a useful tool to create innovations, including health innovation. It can be applied to various fields of pharmacy to satisfy the needs of its patients. This article presents the idea of design thinking and its process which consists of five stages: empathize, define, ideate, prototype, and test. The first two steps, empathizing and defining, are the most important steps that help identify what users really need. Next, ideas are generated, gathered together, and used to develop a prototype. Then, the prototype is tested, improved, and eventually the innovation is developed successfully. In summary, design thinking can be used in pharmacy to create health innovation with the purpose of the users' fulfillment and long-term benefits to pertinent organizations.

Keywords: Design thinking; pharmacist; innovation (Siriraj Med J 2022; 74: 401-408)

INTRODUCTION

It is quite common for business operations to be challenged by uncertain situations due to new technology, economics, and society. These factors result in more complex consumer behavior. Competition drives organizations to be stronger making it one of the most important factors that can sustain businesses. Therefore, organizations have to develop innovation to cope with changes to solve problems in order to satisfy users' demands. The higher number of innovations they develop to satisfy users, the greater is their competitive power.

According to the Cambridge Dictionary, innovation is 'a new idea or method, or the use of new ideas and methods'.[1] In economics, this definition refers to 'invention', and innovation contributes strength to those inventions or existing products or services.[2]

Innovation can be classified as product innovation, process innovation, positioning innovation, and paradigm innovation. **Product innovation** is a new physical product or an upgraded product which has improved its quality. **Process innovation** refers to new operating processes or services which developed their efficacy and effectiveness. Innovation can also be described as repositioning the customer's perception of an existing product or process which is defined as **Position innovation**. The change of an organization's culture or basic conceptual framework is considered as **Paradigm innovation**.[3]

Wherever health care providers, as researchers, apply this design thinking approach to their departments and generate problem-solving innovation, innovation is recognized as an important competency among health care organizations.[4]

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Correspondingly in health systems, users, which refer to patients in this article, have higher demands which are also more complicated than in the past. Thus, the design of health services to deliver unexpected experiences to patients is crucial. **Design thinking**, which is the concept of architectural design process, has been applied to health innovation development as part of the human-centered approach and creativity to design an innovation.

Currently, Design thinking plays a more important role in the healthcare system to innovate effective and functional interventions[5] and to solve traditional issues. Pharmacy, which is a part of the healthcare system, is developing design thinking within community pharmacies, hospital pharmacies and independent pharmacies. The aim of this study is to address design thinking techniques amongst pharmacists to initiative health innovation.

What is design thinking

'Design thinking' was first mentioned by Professor Bruce Archer in 1976[6], and then it was renowned by Tim Brown in *Harvard Business Review*, 2008.[7] From Brown's statement, Design thinking is a discipline which addresses human-centered design to create a business strategy that can turn into market opportunity and customer value. At present, however, many businesses are more concerned with consumers' desires, and thus researchers have to create not just physical products, but innovations.[7] Innovations could be products, processes, or services, which they can match to users' needs by using design thinking.[7]

There are three major phases in Design thinking; Inspiration, Ideation, and Implementation[7]. Some organizations such as Stanford may develop to five stages of Design thinking: empathize, define, ideate, prototype, and test (Fig 1).[8]

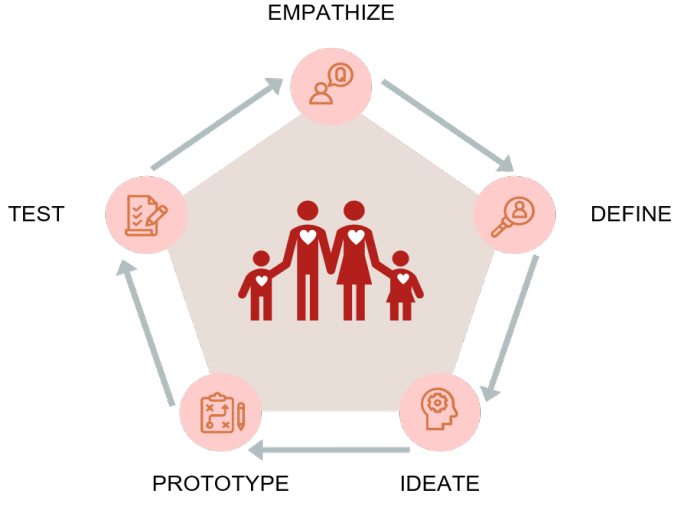

Fig 1. Five stages of design thinking.

In the entire process of Design thinking, 'Inspiration' is the most significant step with its objective being to identify the actual problems by a multidisciplinary team.[7,9] In this phase, team members spend time **emphasizing** patients' thoughts through interviews, observations, and other strategies to approach their experience.[8,9] Teams interview patients by using open-ended questions and frequently use 'Why?' to identify problems behind their stories.[8] Teams observe target patients' customers' behaviors since existing problems may not always coincide with what they mentioned. Tools helping empathize users include customer segmentation and persona.[10,11]

Customer segmentation might divide people according to geographic, demographic, psychological or behavioral characteristics. Examples of customer segmentation include work by Kevrekidis et al.[11] who studied factors affecting the patients decision about pharmacy and OTC medicine selection. Close-ended and multiple-choice structured questionnaires were used to identify customer segments in order to develop the community pharmacy strategies. The patients were divided into 3 segments as presented in Table 1.

Persona creation is applied when researchers seek to understand the needs of diverse and large target patients. It presents the insight of target patients and helps researchers to provide satisfied intervention to the patients. Haldane et al.[10] studied the persona design for mHealth intervention to support medication adherence among elderly Atherosclerotic cardiovascular disease (ASCVD) patients. The target patients were segmented based on their characteristics such as use of technology, adherence factors, and preferences, and then created five personas as reflections of the target group as shown in Table 2. For instance, according to the study, researchers would initially focus on the socializers because they are more accessible compared to other groups. The Busy Grandparent and The Hard-to-Reach personas incline to trust their health care providers, thus, the design to create mHealth intervention should be introduced through their trusted provider.

Customer segmentation is related to persona and could be done to classify the target group and then use persona to empathize patients' insight or vice versa.

After using the empathize tools to collect data, hospital businesses could then **define** the problems or 'pain points' of patients. A challenge in this step is focusing on the insight of patients and to identify the type of targeted patients, as not everyone has the same pain point. It is important to get patients' insights and address their needs. **Define** process could be done by a service blueprint (Fig 2A), P.O.I.N.T tool (Fig 2B),

TABLE 1. Customer segmentation.[11]

	Demographic characteristics	Selection of pharmacy	OTC medicine purchases
Cluster 1	Younger clients (43.5±16.5 yrs) Can be either working people or students High education Maybe low or high income	Purchase from multiple pharmacies A formal relationship is expected from staff **Key factors of selection:** location and business hours	Know approximately what they need when buying OTC medicines **Key factors of purchase:** the pharmacists' opinion and experience of previous use
Cluster 2	Mainly retirement age (57.0±18.7 yrs) Low to moderate education Moderate income	Always purchase from a single pharmacy Prefer informal relationship with the staff **Key factors of selection:** environment and location, pharmacy staff and product range	Know exactly what they need when buying OTC medicines **Key factors of purchase:** the pharmacist's opinion, experience of previous use, and the origin of medicines
Cluster 3	Mainly retirement age or unemployed (56.4±19.4 yrs) Low to moderate education Low income	Visit and purchase only what they need **Key factors of selection:** business hours and pharmacy's location	Unlikely to buy unplanned OTC medicines **Key factors of purchase:** the pharmacist's opinion, experience of previous use, and price

TABLE 2. Personas overview.[10]

Persona	Level of interest in mHealth	Overview
1. The Quiet Analog	Low	This persona favored face-to-face communication with health care providers due to unfamiliarity with technology as well as health-related problems such as poor eyesight.
2. The Busy Grandparent	Low	The busy grandparents tended to use mobile phones more than the quiet analog. But they may not be interested in mHealth unless it is a trusted source.
3. The Socializer	Intermediate	The socializers used their mobile phones habitually and were interested in using mHealth. Although they were more likely to use mHealth, the language was still a matter of concern.
4. The Newly Diagnosed	High	This persona referred to the patients who were newly diagnosed with ASCVD. They may need help and think that mHealth is a useful tool.
5. The Hard-to-Reach	Intermediate	The Hard-to-Reach was low-literacy and mobile use. They paid attention to mHealth but only for the short message service to remind them about their appointment.

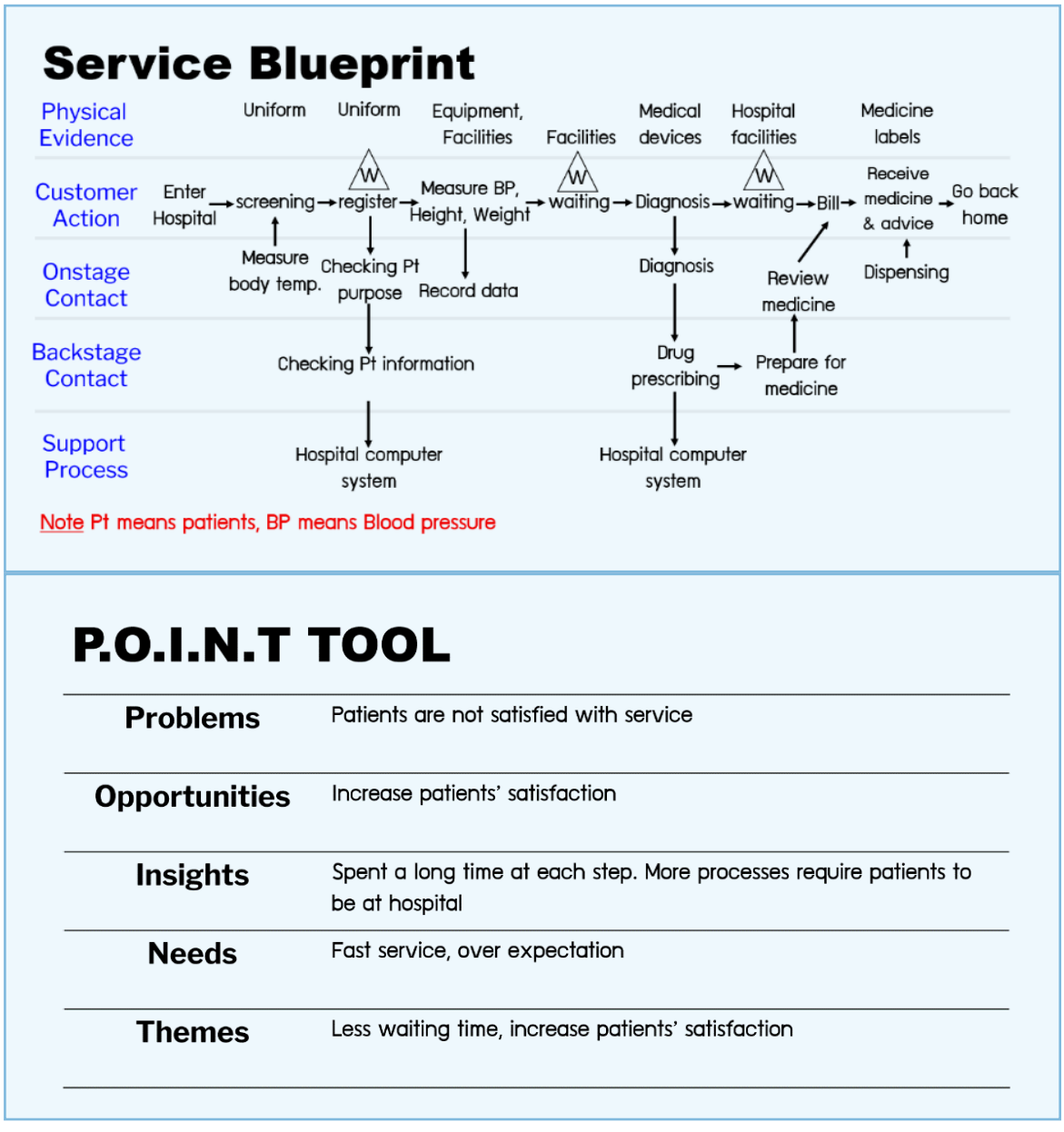

Fig 2. Shows tools used in 'Define' step of design thinking
Fig 2A. (top) Service blueprint, **Fig 2B.** (bottom) P.O.I.N.T Tool

customer segment profile, value proposition map, and etc.[12-14] These tools could assist researchers to interpret pain points of patients.

The service blueprint provides an entire patient journey in both patients and provider aspects, so researchers could spot weaknesses of the whole process. P.O.I.N.T tool stands for Problem, Opportunity, Insight, Needs, and Theme which frames data from the empathy step into recognizing the pain point. The customer segment profile and value proposition map are usually done together to define what patients want by way of the customer segment profile and relate it to what researchers should create from the value proposition map.

Perspectives of patients may differ from what we thought.[9] So, it is necessary to be aware of every single detail in this phase to prevent misinterpreting the information. When real 'needs' could not clearly be identified, time and resources are wasted in the following steps. The researcher should create not only 'invention' but 'innovation'.

During the **'Ideation'** phase, divergent thinking is one of the most crucial tools to encourage innovative ideas. Divergent thinking is an ability to discover creative ideas by merging information in diverse ways and getting novel opinions.[15,16] Brainstorming or mind mapping various types of ideas with an emphasize on quantity over

quality[9] is useful. Avoid judging other ideas, using 'yes, and...' instead of 'yes, but...' when offering an opinion.[9] After exploring ideas which fulfill patients' pain point, it is helpful to extract and narrow scattered ideas, and then use convergent thinking to gain consensus by voting, developing a feasible solution and then making a low-fidelity **prototype** (Fig 3).[7,9] Factors concerned while choosing a solution are human-centered, business viability and technology feasibility. Rapid prototypes can be photo, video clip, mock up, model, and etc. which is readily understandable and tangible.[16] Making it quickly can reduce expenses and use fewer resources.[8]

Subsequently, develop an iterative prototype as far as the final version. The 'implementation' phase uses a prototype to get responses from target patients and improve it throughout the process to resolve patients' needs. This is, again, empathizing with users to get insight from their feedback. For a physical prototype, allow users to **test** it in their situation. In contrast, if the prototype is in the form of experience, design a scenario in which users can approach the prototype similarily to a real situation.[8] Refining can always occur even though the prototype is on its way to becoming an innovation and being launchedin the market.[9]

The feedback capture grid is a tool for gathering feedback from patients, divided into four quadrants of paper: worked, changed, question, and idea as shown in Fig 4. Patients wrote positive feedback in the 'worked' quadrant and put negative feedback in the 'changed' quadrant. Collect all questions in the 'question' quadrant, along with questions which researchers acquired during the last phase. The last quadrant is the 'idea'. Write down all ideas that were mentioned while testing prototypes.[18] The feedback capture grid uses tools such as 'I like, I wish, and What if' in this phase.[17] 'I like, I wish, and What if' are basically a feedback capture grid tool. 'I like' raises positive feedback from clients whereas 'I wish' addresses problems or concerns that patients experienced. 'What if' inspires other comments which may further improve existing prototypes.[19]

One of the most popular innovations from design thinking is mobile application. Besides that, there are many innovations in the healthcare system i.e., smart gadgets (Smartwatch, smart camera, smart glasses, smart headband, Smart Glucometer[20]), and messaging apps (Line, Facebook).

Fig 3. Example of low-fidelity prototype, Smartwatch, is used to estimate waiting time to increase patients' satisfaction

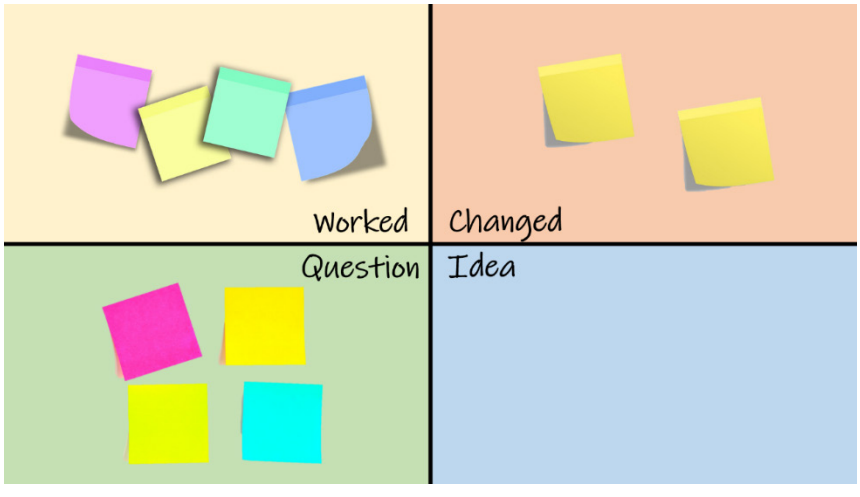

Fig 4. Feedback capture grid, a tool in 'test' phase, collects comments to further improve prototype.

Application of design thinking in pharmacy

In the Google Play Store, 53,054 healthcare applications were active in the first quarter of 2021 with gradually increasing trends[21] which reflect that people are interested in innovations. Meanwhile in Thailand, there are more than 60 health applications available for users.[22] Apart from the number of mobile applications in Thailand, there are only a few of them that are related to pharmacy.

An example of the innovations available in Thailand is **PharmaSee**, a mobile drug identification application. The pain point of this innovation started from numerous medicines in Thailand, not only original brands but also generic brands, which can confuse pharmacists who have to identify patients' current medicines.[23] The other example is the **'ALL Pharmasee'** application which has a different purpose from the previous one. Social distancing and self quarantine triggered this idea, when few people wanted to go outside because of the pandemic. This mobile application allows patients to receive advice from community pharmacists via an online chat or a video call.[24] There are some mobile applications facilitating hospital pharmacists, for example, PharmaSafe and Diamate. By the way, there are lots of interventions are on developing process, such as Punsook, an application for recording a voiding volume for patients on catheter.[25]

To represent design thinking in pharmacy thoroughly, HealthEir is an example of a mix **process-product innovation** prototype created by the design thinking approach. This case study was done by M.Flood et al.[12] in Ireland. The objective of this project is to increase preventative care in community pharmacy and primary care through implementing patients to take good care of themselves. First step, the multidisciplinary researchers made a journey mapping touchpoints. Journey mapping (or service blueprint) visualizes the entire process of patients from a physical and an emotional perspective. The researchers then empathized patients and community pharmacists in real practice by using telephone interviews to deeply understand existing conditions to find the most proper activity that is able to integrate innovative service. Based on the 5As techniques (Ask, Advise, Assess, Assist, Arrange), patients would complete 3As (Ask, Advise, Assess) by using tablet devices and then engaging with health care providers to complete the other 2As (Assist, Arrange) to receive add-on consultation about preventative care. Therefore, they digested data and developed prototypes.

The HealthEir project contained both process and physical innovations. For the physical innovation, the researchers made a 'click-through' prototype and allowed patients to test it and provide feedback before repeatedly refining the prototype, until they developed the most suitable one. Problems during refinement were, for instance, the prototype was too text-heavy, and the username registration should be provided after filling in some service information. These details are examples of patients' 'insights' that provided researchers with information with which they might not have considered. The last phase is evaluation by real patients. However, there was no feedback reported in the research due to the COVID-19 situation.[12]

The other case study is medicine label designing in a community hospital in Thailand. This project applied design thinking to create an innovation for patients. A pharmacist in primary care in Nakhon Phanom province, Thailand, noticed that some elderly patients could not take medicines correctly, some had problems with their eyes and vision, and some were illiterate. The empathize step was done by interviewing patients with open-ended questions such as, 'Do you have problems about taking medicines?' or 'What do you do when you do not know how to take medicine?' Patients then shared their stories and were asked the reason 'Why?' .

Furthermore, problem statements were used to identify the 'where and when' of target users' needs. In this case, target patients were elderly patients who needed an item (or something) to support their medicine routine properly. Patient insights revealed that they wanted to be able to control their disease and take as little medicine as possible.

An innovation adopted in this COVID-19 situation, 'aerosol box' is widely use in the real practice. Aerosol box is a clear acrylic box covering upper body to prevent viral transmission and droplets spread. It uses as an extension of personal protective equipment (PPE).[26]

The ideate step was done by brainstorming to generate ideas without focusing on having an answer. After making a decision, the most suitable idea was making colored medicine labels which easily describe when patients have to take their medicine (Fig 5). Next, create a low-fidelity prototype, open for comments from colleges and patients, and get feedback to improve the prototype. In the final step, generate medicine labels and ask for feedback, again, from patients in the hospital. By asking for feedback, use 'I like, I wish, What if' tools to gain suggestions to further improve an invention. This innovation is used in real practice in Nakae Hospital.[27]

Dilemmas in health design thinking

Altman et al.[5] stated that four problems are related in health design thinking. The first one is conflicts between what researchers think and what patients want, since the researchers do not find 'insight' from patients but believe

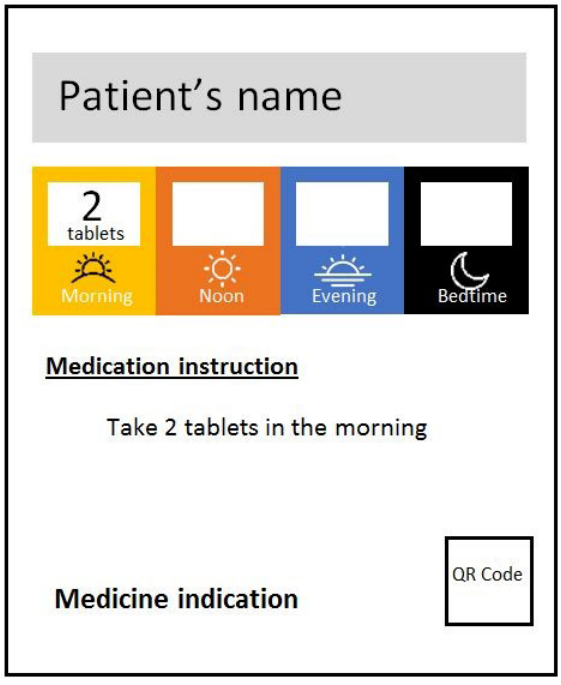

Fig 5. A low-fidelity prototype of colored medicine labels[27]

that their understanding from research is beneficial for patients.

Next is the difference of needs assessment and evidence-based literature. Some researchers are not concerned about the 'insight' of patients from observations or interviews as there is existing research available. So by skipping the emphasize steps the 'pain point' is not detected.

By the way, design thinking by itself does not own these two dilemmas, but researchers usually do not follow the whole process of design thinking. Therefore, the 'inspiration' phase should not be left out in any case.

The third dilemma is controlling the balance between the design thinking method and the traditional research method. Most health care researchers are meticulous when using statistics, thus, balance a qualitative approach (e.g., design thinking method) with a quantitative approach.

The last problem is during the prototype process in that low-fidelity prototypes might cause a high risk of severe outcomes; for instance, longer hospitalization or death. Use of physical rapid prototypes is infrequent because some innovations are related with patient's morbidity and mortality.[5]

Another challenge is when innovations are novel, both healthcare providers and patients are unfamiliar with the innovations, and they are not well managed so this can also lead to unsuccessful innovations.[12]

These problems could affect the success of design thinking as there are many challenges with which healthcare providers have to cope.

CONCLUSION

This study provides an overview of design thinking, especially in the pharmacy profession. Using design thinking to build an innovation focuses on a user-centered perspective. The innovation can be successfully developed and fulfill patients' needs if the researchers are able to comply with the entire process of design thinking. The crucial steps that researchers need to be concerned about in design thinking are empathizing and defining as these steps help characterize the target group of patients and identify what they really need. This study also summarizes problems that frequently occurred during the design thinking process and might be the cause of unsuccessful innovations.

For pharmacists, design thinking is very useful. For example, the development of innovation to improve patients' medication adherence and enhance user satisfaction which might result in patients' loyalty. Moreover, it could facilitate a working process for healthcare providers.

In conclusion, the implementation of design thinking in health innovation development may be a blockbuster which could transform health systems and enhance patients' well-being as well as benefit relevant organizations.

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