E-ISSN 2228-8082

Volume 73, Number 10, October 2021

SMJ

Siriraj Medical Journal

The world-leading biomedical science of Thailand

MONTHLY

By Taya Kitiyakara, et al.

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Siriraj Medical Journal SMJ

Volume 73, Number 10, October 2021

ORIGINAL ARTICLE

REVIEW ARTICLE

Effect of Diabetes Self-Management Education (DSME) with and without Motivational Interviewing (MI) on Glycemic Control among Children and Adolescents with Type 1 Diabetes Mellitus: A Randomized Controlled Trial

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ABSTRACT

Objective: Type 1 diabetes mellitus (T1DM) is a chronic disease that is difficult to control. Motivational interviewing (MI) is a collaborative style of communication that was designed to strengthen a person's motivation and commitment to change and improve. We hypothesized that applying MI to diabetes care would lead to improved glycemic control and improved diabetes self-care behavior.

Materials and Methods: Subjects were T1DM patients aged 10-18 years with HbA_{1C} ≥8% that were recruited from the Outpatient Diabetes Clinic during October 2016 - March 2017. Subjects were randomized into the diabetes self-management education (DSME) or DSME plus MI groups. HbA_{1C} levels, diabetes knowledge test, and diabetes self-care behavioral questionnaire were performed.

Results: Thirty-five patients (17 DSME, 18 DSME + MI) completed the study. Baseline HbA_{1C} was not significantly different between groups. At the end of the study, HbA_{1C} levels were not significantly different within or between groups. From pre-intervention to post-intervention, diabetes knowledge scores were significantly increased, and self-care behavioral scores were significantly increased for dietary control and medical taking. Transition to the stages of change *action* stage was increased from 0 to 12 persons.

Conclusion: The effectiveness of MI on glycemic control was not found to be statistically significant at 6 months. However, continuation of DSME in T1DM patients is necessary for improving diabetes knowledge and care. Further study in a larger sample size with longer duration of MI and follow-up is needed to conclusively establish the value of MI on glycemic control in pediatric T1DM.

Keywords: T1DM; motivational interviewing diabetes; self-management education; glycemic control (Siriraj Med J 2021; 73: 635-643)

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http://dx.doi.org/10.33192/Smj.2021.82

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a complex and chronic disease that requires lifelong insulin injections, psychological support, and lifestyle changes. To optimize glycemic control, regular and frequent self- monitoring of blood glucose (SMBG) is required. Ziegler R, et al. found one additional SMBG per day to be associated with a decrease in HbA_{1c} of 0.20%.[1] Miller KM, el al. also found a higher number of SMBGs per day to be strongly associated with a lower HbA_{1c} level.[2] The numbers of SMBGs per day in the patients at our outpatient clinic[3] was 2.7-3.3 times per day, which are less than the four to six times per day recommended by ISPAD clinical practice consensus guidelines.[4] A possible reason for the inadequate number of SBMGs per day among our patients may be due to the high cost of the glucose test strips. For this reason, in 2015 our hospital organized "The Universal Coverage (UC) provided free glucose strips project for patients with T1DM". However, fifteen months after initiation of this program, HbA_{1C} was improved only in some patients in our clinic.

Another factor in addition to SMBG that contributes to good glycemic control is motivation. Motivational interviewing (MI), which was developed by Miller WR. and Rollnick S., is a proven approach for working through ambivalence and facilitating change of behavior.[5] MI has been widely used in adults to improve control of addictive behaviors, such as reducing illicit drug use[6] and promoting smoking cessation.[7,8] During the last decade, MI has been used in pediatric practice to promote adherence to recommended treatment, including diabetes management with variable results in reducing HbA_{1C}.[9-12]

MI is a brief, goal-directed, patient-centered counseling approach that was designed to help patients increase intrinsic motivation and strengthen commitment to change and improve via the exploration and resolution of ambivalence. Patients are encouraged to develop and recite their own self-motivational statement (SMS) by facilitators. The six stages of change in MI are described, as follows. The initial stage, which is labeled *pre-contemplation*, is when the person is not yet considering change. The next stage is the period of *contemplation*, during which the person evaluates the reasons for and against change. The third stage is when the person reaches a state of *determination* where plans for change are formulated. The person then takes *action* in the fourth stage to effectuate the identified change in behavior. If the change in behavior is successful, the person then moves into the fifth stage, which is a state of *maintenance* to sustain the change in behavior for the long term. The last of the six stages occurs if and when the patient *relapse*, which is defined as a return to any of the previous behavior stages[12]

Thus we conducted a 6-month randomized controlled trial to evaluate the effectiveness of MI on glycemic control, as measured by HbA_{1C}. The primary outcome was HbA_{1C} at the 6-month follow-up. The secondary objective was to evaluate diabetes knowledge and self-care behavior. The secondary outcomes were the scores of the diabetes knowledge test and the self-care behavior questionnaire. We hypothesized that MI would improve glycemic control, diabetes knowledge, and self-care behavior in T1DM patients.

MATERIALS AND METHODS

Design and participants

Following randomization, participants received either diabetes self-management education (DSME) or DSME plus MI. Clinical staff and participants were both aware of the group assignment. Participants were recruited from the Outpatient Diabetes Clinic of the Division of Endocrinology and Metabolism, Department of Pediatrics, Siriraj Hospital during October 2016 to March 2017. Subjects were T1DM patients aged 10-18 years with HbA_{1C} ≥8% that were receiving free glucose strips for at least 3 months. Patients who were receiving medications that effect glycemic control, such as steroids and switching of insulin regimen during this study, were excluded.

Randomization was generated by random permuted blocks with mixed block size. Group allocation results were sealed in sequentially numbered opaque envelopes. The person generated the allocation scheme had no additional role in the study. The protocol for this randomized controlled trial was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (COA no. Si 538/2016). Assent and written informed consent was obtained from patients and their parents/guardians, respectively.

The frequency of SMBG was assessed by downloading glucometer data using accu-check 360º software. The information received were total numbers of SMBG in the past 3 months and average numbers of SMBG per day. Baseline characteristics and diabetes-related data including age, gender, insulin regimen, carbohydrate counting method, diabetes chronic complication, hypertension and dyslipidemia were collected. HbA_{1C} levels were measured prior to entering the study and then at 3 and 6 months after entering the study.

Motivational interviewing (MI)

MI sessions were conducted by 3 interventionists, including 2 pediatric endocrinologists and a pediatric endocrinology fellow) and a diabetes education nurse. All interventionists were trained by experienced pediatric and adult psychiatrists from Department of Pediatrics and Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University. The initial training in MI includes hours of lecture, role play, case scenarios, and practicing with actual patients in individual and group sessions. Monthly discussion and supervision among interventionists and a psychiatrist was continued throughout the study.

MI in group session was performed at the beginning of the study, and at 3 months after entering the study. The length of the two MI sessions was 45-60 minutes each. MI by telephone call was performed individually at 1, 2, 4, and 5 months. Session dialogue included awareness building, making choices, alternatives, goal-setting, problem solving, and avoidance of confrontation. During MI sessions, interventionists encouraged patients to express self-motivational statements. The interventionists would respond to patients according to their stage of change. Interventionist responses included giving information and feedback for the *pre-contemplation* stage, discussion about pros and cons of undesired behavior for the *contemplation* stage, giving menu and promoting patient self-efficacy for the *determination* phase, encouraging compliance and adherence for the action stage, relapse prevention for the *maintenance* stage, and recovery process for the *relapse* stage. The MI manual was created by a pediatric psychologist. All MI sessions were documented, and all documentation was reviewed with a psychologist experienced in MI.

Diabetes self-management education (DSME)

DSME in group session was performed at the beginning of the study, and 3 months later in both the DSME and DSME plus MI groups. The session was designed as an interactive lecture and workshop, with a length of 60-90 minutes, and there were 8-10 patients in each class session. DSME consists of a diabetes knowledge component that was performed by physicians and a nurse, and a nutritional component that was performed by a nutritionist. Diabetes knowledge content included basic knowledge about diabetes, self-monitoring blood glucose, exercise with diabetes, hypo/hyperglycemia management, insulin action, sick-day management, and diabetes complications. Nutritional knowledge content included healthy food, carbohydrate-containing food, carbohydrate counting, food-exchange, and nutrition facts. Food models were used for food exchange and nutrition fact practice. Patients were encouraged to participate in class by asking questions, giving examples, and using case scenarios. We also focused on individual problem-solving skills and insulin self-adjustment at home.

Diabetes knowledge test

Diabetes knowledge test was performed at the beginning and end of the study. We modified a multiple choice test using 30 questions from the diabetes knowledge test administered at the Siriraj Diabetes Camp.[13] Questions covered 7 topics, including basic diabetes knowledge, nutritional management and carbohydrate counting, self-monitoring blood glucose, exercise with diabetes, hypo/hyperglycemia management, insulin treatment, and sick-day management.

Diabetes self-care behavior questionnaire

Diabetes self-care behavior questionnaire was given at the beginning and the end of the study. A 38-question standardized questionnaire that was developed by Tachanivate P.[14] was used. The questionnaire covers 8 topics, including personal hygiene care, dietary control, medical taking, physical activity, self-monitoring blood glucose, problem solving, stress management, and reducing risk of diabetes complications. The score was reported as percentage of the mean, which was calculated using the following equation: % of mean = (actual sore/maximum score) x 100. A higher score indicates better diabetes self-care behavior.

Statistical analysis

All data analyses were performed using SPSS Statistics (SPSS, Inc., Chicago, IL, USA). Patient characteristics were summarized using descriptive statistics. Categorical data were compared using chi-square test, and the results are presented as frequency or percentage. Normally distributed continuous data was compared using independent *t*-test, and the results were presented as mean ± standard deviation (SD). Non-normally distributed continuous data were compared using Mann-Whitney U-test, and the results were given as median and range (min, max). A *p*-value of less than 0.05 was considered statistically significant for all tests.

RESULTS

A flow diagram of the study protocol is shown in Fig 1. Of the 94 patients who received free glucose strips from the UC program, 39 were eligible for this study. Those patients were randomized into either the DSME

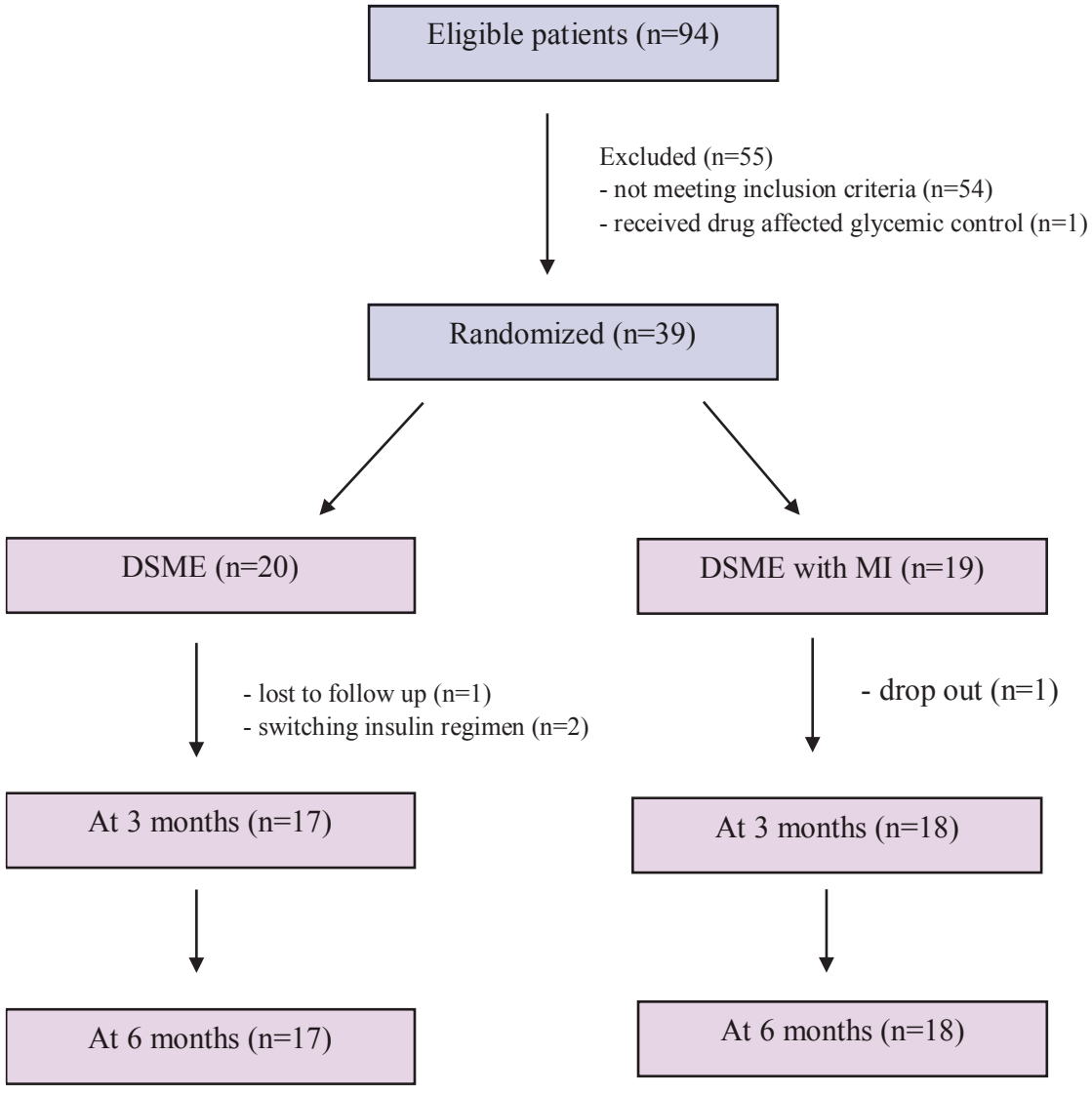

Fig 1. Flow diagram of the study protocol.

group (n=20) or the DSME plus MI group (n=19). One patient in DSME group was lost to follow-up. One patient in the DSME plus MI group declined to participate after randomization, before the first visit. Two patients in the DSME group were excluded due to the fact that they switched insulin regimen during the study. The remaining 35 patients (17 DSME, and 18 DSME plus MI) completed the study.

Demographic characteristics

Patients in the DSME and DSME plus MI groups were well matched for age (14.18±2.02 *vs.* 14.06±2.88 years, respectively), age at diagnosis (8.25±2.86 *vs.* 8.53±3.83 years), duration of diabetes [5.25 (0.83, 13.33) vs. 5.08 (1, 14) years], and HbA_{1c} [10.3% (8.4, 14) *vs.* 9.45% (8, 14.6)]. There were no significant differences between groups for age, age at diagnosis, duration of diabetes, or HbA_{1c}, as shown in Table 1. Counting carbohydrate in grams was 30% and 22%; using basal bolus regimen was 58% and 38% in the DSME and DSME plus MI groups respectively.

Primary outcome: HbA_{1C}

Baseline HbA_{1C} in the DSME and DSME plus MI groups was 10.3 (8.4, 14) and 9.45 (8, 14.6), respectively (p=0.204). At the end of the study, HbA_{1C} in the DSME and DSME plus MI groups was 9.8 (7.4, 16.8) and 9.35 (7.8, 13.2), respectively (p=0.234). No significant difference was observed for HbA_{1C} in each group compared between pre-intervention and post-intervention (Table 2).

Diabetes knowledge score

Diabetes knowledge score compared between baseline and 6 months increased significantly in both the DSME and DSME plus MI groups [19 (7, 24) to 21 (6, 25); p=0.012, and 18.5 (13, 24) to 21 (15, 28); p=0.001 respectively] (Table 3).

TABLE 1. Baseline characteristics.

	DSME (n=17)	DSME + MI (n=18)	*p*-value
Age* (years)	14.18 ± 2.02	14.06 ± 2.88	0.892
Age at diagnosis* (years)	8.25 ± 2.86	8.53 ± 3.83	0.810
BMI * (kg/m^2)	20.70 ± 3.70	20.66 ± 3.04	0.971
Total daily dose* (units/day)	1.26 ± 0.33	1.25 ± 0.35	0.934
Duration of DM**(years)	5.25 (0.83, 13.33)	5.08 (1, 14)	0.766
SMBG** (times/day)	2.00 (0.1, 4)	3.2 (0.07, 4.9)	0.013
HbA1C** (%)	10.3 (8.4, 14)	9.45 (8, 14.6)	0.204
Gender# male/female	10/7	9/9	0.600
Insulin regimen# basal bolus/non-basal bolus	10/7	7/11	0.472
Carbohydrate counting# grams/portion	5/12	4/14	0.627
Lipohypertrophy# yes/no	6/11	6/12	0.903
Diabetic nephropathy# yes/no	1/16	1/17	0.967
Diabetic retinopathy# yes/no	17/0	17/1	0.324
Hypertension# yes/no	0/17	0/18	-
Dyslipidemia# yes/no	8/9	13/5	0.129

* Independent *t*-test; mean ± SD, ** Mann-Whitney U-test; median (min, max), # Chi-square test

Abbreviations: DSME, diabetes self-management education; MI, motivational interviewing; BMI, body mass index.

TABLE 2. HbA_{1c} levels compared between groups at baseline, 3 months, and 6 months.

	DSME (n=17)	DSME + MI (n=18)	*p*-value*
HbA_{1c} at baseline	10.3 (8.4, 14)	9.45 (8, 14.6)	0.204
HbA_{1c} at 3 months	10.1 (7.4, 17.6)	9.35 (7.8, 14.5)	0.095
HbA_{1c} at 6 months	9.8 (7.4, 16.8)	9.35 (7.8, 13.2)	0.234
p-value**	0.813	0.459	

*Compared between DSME and DSME + MI, **Compared between pre-intervention and post-intervention

Data expressed as median (min, max)

Abbreviations: DSME, diabetes self-management education; MI, motivational interviewing

TABLE 3. Pretest and post-test diabetic knowledge test results compared between groups.

	DSME (N=17)	DSME + MI (N=18)	*p*-value*
Pretest score	19 (7, 24)	18.5 (13, 24)	0.816
Post-test score	21 (6, 25)	21 (15, 28)	0.326
p-value**	0.012	0.001	

*Compared between DSME and DSME + MI, **Compared between pre-intervention and post-intervention
Data expressed as median (min, max)
Abbreviations: DSME, diabetes self-management education; MI, motivational interviewing

Self-care behavioral score

The self-care behavioral score was significantly different at 6 months compared between the DSME and DSME plus MI groups for the dietary control domain [48.97 (32.65, 73.47) *vs.* 60.20 (30.61, 77.55); p=0.024], and the medicine taking domain [52.38 (28.57, 78.57) *vs.* 67.86 (47.62, 80.95); p=0.016] (Table 4). There was no significant difference between groups at 6 months for the personal hygiene care, physical activity, self-monitoring, problem solving, stress management, or reducing risk of diabetes complications domains.

Stage of MI

In DSME plus MI group, at the beginning of the study, there was 1 patient in pre-contemplation, 8 in contemplation, 9 in determination, and 0 in the action, maintenance, and relapse stages. At the end of the study, there were 12 patients in the action stage. (Table 5)

TABLE 4. Self-care behavioral score compared between groups post intervention.

Topics	DSME (% of mean)	DSME + MI (% of mean)	*p*-value
Personal hygiene care	71.43 (28.57, 100)	69.04 (33.33, 100)	0.765
Dietary control	48.97 (32.65, 73.47)	60.20 (30.61, 77.55)	0.024
Medication taking	52.38 (28.57, 78.57)	67.86 (47.62, 80.95)	0.016
Physical activity	57.14 (19.05, 90.48)	64.29 (9.52, 85.71)	0.337
Self-monitoring	39.29 (17.86 , 78.57)	51.79 (28.57 , 67.86)	0.068
Problem solving	48.21 (23.21, 78.57)	50.89 (30.36, 71.43)	0.895
Stress management	47.62 (0, 71.43)	40.47 (0, 71.43)	0.640
Reducing risk of diabetes complications	57.14 (35.71, 71.43)	55.36 (35.71, 71.43)	0.973

Data expressed as median (min, max)
Abbreviations: DSME, diabetes self-management education; MI, motivational interviewing

TABLE 5. Stages of change in the motivational interviewing group (n=18).

Stage of Change	Sessions (months)					
	0	1	2	3	4	5
Pre-contemplation	1	1	1	-	-	-
Contemplation	8	6	5	2	-	3
Determination	9	6	3	15	6	3
Action	-	5	9	1	12	12
Maintenance & relapse prevention	-	-	-	-	-	-

SMBG

Baseline SMBG frequency in the DSME and DSME plus MI groups was 2 (0.1, 4) and 3.2 (0.07, 4.9) times/day, respectively (p=0.013). At the end of the study, SMBG frequency in the DSME group and the DSME plus MI group was 2 (0, 4) and 3 (0, 4.7) times/day, respectively (p=0.053). SMBG frequency data was downloaded from the glucometer at baseline, 3- and 6-month time points.

DISCUSSION

We found no significant different in HbA_{1C} between the DSME and DSME plus MI groups at the end of the study, as well as between pre- and post-intervention. Diabetes knowledge score in both groups was significantly increased at the end of study. Self-care behavioral score showed significant improvement in 2 domains (dietary control and medicine taking) in the DSME plus MI group. Transition to the *action* stage increased from 0 to 12 patients, and the transition occurred at approximately 4 months.

T1DM is a complex and chronic illness that requires consistent adherence to treatment, psychological support, and changes in lifestyle. Optimal glycemic control is not easy to achieve, requires commitment to change, and depends on multiple factors. Accurate carbohydrate counting is crucial for precise insulin calculation. The DAFNE Study Group reported significant improvement in HbA_{1C} at 6 months (p<0.0001) after training patients how to match their insulin dose to their food choice.[15] As demonstrated by Spiegel G, et al., T1DM patients overestimated and underestimated carbohydrate content, especially in mixed meals.[16] Moreover, less than half of our patients were counting carbohydrates as grams, not portions (Table 1). Calculating insulin dose according to carbohydrate portion size may yield a loser insulin dose than calculating according to gram weight. This may result in a suboptimal dose of insulin and poor glycemic control. Intensive patient education in carbohydrate counting and encouraging patients to count carbohydrates accurately may result in accurate insulin calculation and improving of glycemic control.

Non-intensive insulin regimen could be a barrier to achieving tight glycemic control. The American Diabetes Association (ADA) recommends that individuals with T1DM receive multiple daily insulin injections (three or more injections per day of prandial insulin, and one to two injections of basal insulin) or CSII.[17] Hathout EH, et al. reported improvement in glycemic control with intensive therapy as compared with conventional insulin regimens.[18] Only 58% and 38% of our patients in the DSME and DSME plus MI groups, respectively, used intensive insulin therapy, so tight glycemic control may be difficult to achieve. Likitmaskul S, et al. reported that Thai patients with T1DM had unsatisfactory glycemic control, with a mean HbA_{1C} of 9.3±2.5%.[19] Achieving good glycemic control in Thai patients may be challenging due to the fact that intensive diabetes treatment requires glucose test strips, and glucose strips are not available to all patients.

At the end of the intervention, the patients in the DSME plus MI group did better in the dietary control and medicine taking domains of self-care behavior than those in the DSME group, however, the HbA_{1C} levels in the DSME plus MI group did not improved. This may be explained by the complexity of diabetes self-care, which requires multiple tasks of management. Their self-care behavior scores in other domains e.g. self-monitoring, problem solving, stress management, etc. were relatively low. No increase in frequency of SMBG and the fact that majority of patients in DSME plus MI group were treated with non-intensive insulin regimen might partly explain the lack of improvement in glycemic control. Moreover,

psychological issue might be another factor. The burden of having type 1 diabetes and the demands in managing daily diabetes-related tasks can lead to negative emotions or diabetes distress and depressive symptoms[20] which can impact the glycemic control.

The duration of this study may have been too short to observe the effect of MI. In the present study, transition to the *action* stage of MI was observed at 4 months, so measurement of HbA_{1C} at 6 months may be too early to observe the effect of action that recently took place. Channon S, et al. conducted a randomized controlled trial that showed significant reduction of HbA_{1C} in the MI group compared to the control group at 12 months and 24 months, but not at 6 months.[21] In our study, HbA_{1C} was not significantly decreased in any comparison. On the other hand, MI may not affect glycemic control. Walter G. suggested that verbal indices of MI to change do not necessarily translate to actual change in response to treatment if the patient does not also have the ability to change, and that patient declarations should be regarded as reflecting the patient's intent to change at that moment as opposed to being considered a predictor of real change in behavior.[22]

Diabetes knowledge score was significantly improved in both groups, which is similar to the finding reported by Santiprabhob, et al. at 6 months post-DSME at diabetes camp.[23] Despite improving of diabetes knowledge score but the HbA_{1C} levels did not improved may be due to the patients know the theory but did not apply the knowledge gained to daily life problem solving. From International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendation and guidelines, educational interventions in children and adolescents with diabetes have a beneficial effect on both glycemic control and psychosocial outcomes.[24] However, it is important to evaluate patients' ability to apply their knowledge to their daily self-care.

The limitations of this study are short duration of intervention, infrequency of motivation intervention sessions and small sample size. Increasing the duration, intensity, and frequency of MI sessions, as well as focusing on individual ambivalence, may have positive impact on MI stage progression and actual change. It should also be considered that our small sample size may have given our study insufficient statistical power to identify all significant differences in HbA_{1C}.

CONCLUSION

In conclusion, this study demonstrated that applying MI to diabetes care does not lead to improvement in glycemic control. However, diabetes knowledge was improved in both groups, and self-care behavior score was improved in some topics. The process and methods for instilling and integrating diabetes knowledge, daily diabetes management, and self-care behavior, as well increasing the patient's intrinsic motivation to change and improve, requires further study. Further study should also include a larger sample size, motivation that is focused on individualized specific issues, and a longer follow-up period.

ACKNOWLEDGEMENTS

The authors wish to thank the T1DM patients and their families that participated in this study, Julaporn Pooliam and Kanokwan Sommai for statistical analysis, and Hathaichanok Tirapongporn and Sriwan Thongpang for nutritional teaching. This study was supported by a Siriraj Routine to Research Fund, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (grant no. R015935055).

Conflict of interest: The authors hereby declare no personal or professional conflicts of interest relating to any aspect of this study.

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Vaginal Tablets of Metronidazole (750 mg) plus Miconazole Nitrate (200 mg) versus Oral Metronidazole (2 g) for Bacterial Vaginosis: A Randomized Controlled Trial

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ABSTRACT

Objective: To compare the cure rates, side effects, satisfaction, and recurrence rates of bacterial vaginosis (BV) in women having vaginal tablets of metronidazole (750 mg) plus miconazole (200 mg) - the "NPF group" - versus oral metronidazole (2 g) - the "MET group."

Materials and Methods: This September 2019–March 2020 trial enrolled symptomatic women aged 18-45 years diagnosed with BV based on Amsel's criteria. Excluded were women who were immunocompromised; allergic to metronidazole or miconazole; had BV episodes during the preceding 3 months; or had abnormal vaginal bleeding. After randomization with a ratio 1:1, another vaginal swab was done for Nugent scoring. Two weeks later, the evaluation using Amsel's criteria and Nugent scores was repeated. Also, symptom resolution, side effects and satisfaction were evaluated. Symptomatic resolution referred to 75% improvement in discharge, irritation, itching, odor, and coital pain. At one and three months, subjective symptomatic recurrence was assessed by telephone.

Results: Data on 70 participants were analyzed (NPF, N=34; MET, N=36). Their average age was 32.3±7.9 years (NPF, 34.1±8.1; MET, 30.6±7.3). Without statistical significance, NPF had higher symptom resolution (67.7% vs 58.3%; P=0.420), cure rate by Amsel criteria (82.4% vs 77.8%; P=0.632), and cure rate by Nugent scoring (35.3% vs 16.9%; P=0.075). Both groups reported high satisfaction (NPF, 8.5±1.4; MET, 7.9±2.0; P=0.125). Side effects were comparable, including appetite loss, metallic taste, nausea, and dizziness.

Conclusion: For BV treatment, both vaginal ovules containing metronidazole (750 mg) plus miconazole nitrate (200 mg) and oral metronidazole (2 g) show comparable efficacy and side effects.

Keywords: Bacterial vaginosis; metronidazole; vaginal tablet (Siriraj Med J 2021; 73: 644-651)

INTRODUCTION

Bacterial Vaginosis (BV) is the most common cause of abnormal vaginal discharge in women of childbearing age.[1] It is a polymicrobial clinical syndrome characterized by a profound change in vaginal microbiota from a *Lactobacillius*- dominant state to anaerobic bacteria of high diversity including *Gardnerella vaginalis, Atopobium vaginae, Mobiluncus spp, Prevotella spp*, and

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Received 5 July 2021 Revised 18 August 2021 Accepted 19 August 2021
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http://dx.doi.org/10.33192/Smj.2021.83

other BV-associated bacteria (BVAB).[2,3] This change is accompanied by a rise in vaginal pH and increased amines which produce typical odor. BV increases the incidence of gynecologic and obstetric diseases, including of spontaneous abortion, premature labour, chorioamnionitis, and postpartum endometritis and pelvic inflammatory disease (PID).[4,5] Also, it associates with a 2-3 fold increased risk of acquiring sexually transmitted diseases (STDs) such as chlamydial infection, gonorrhea, genital herpes and human immunodeficiency virus (HIV) infection.[6-8]

The recommended treatment is metronidazole or clindamycin.[9] In Thailand, oral metronidazole is more commonly prescribed for BV. However, the metronidazole 400 mg oral tablet taken 3 times day commonly elicits adverse events such as a metallic taste, nausea and vomiting resulting in poor compliance.[10] A single oral dose of metronidazole 2gm has comparable efficacy with a 7-day course[10] and previous studies demonstrated less gastrointestinal side effects.[11-13] Therefore, the 2 g metronidazole regimen is included in the treatment guideline provided by the Australian Sexual Health Alliance.[14]

A novel vaginal ovule containing metronidazole 750 mg plus miconazole nitrate 200 mg (Neo-penotrans Forte®; NPF, Exeltis, Thailand) may be an alternative treatment modality. Previous studies showed that an oral metronidazole tablet can be used intravaginally for treating women with BV.[10-11] The novel vaginal ovule, which dissolves more readily, had been reported to have high efficacy against BV, trichomoniasis and fungal infection: 75-96%, 100%, and 82-90%, respectively.[15,16] Also, NPF can effectively cure mixed infection.[15,16] A monthly 7-day course of NPF for up to 3-8 months was found to prolong remission period among women with recurrent BV.[17] Another benefit of this vaginal suppository is that there have never been any serious adverse events reported.[16,18] However, with different backgrounds of the users, the efficacy is yet to be validated in Thai women. The present study aims to compare the cure rate and symptomatic recurrence rate between a 7 day-course of vaginal metronidazole 750 mg plus miconazole nitrate 200 mg (NPF®) and a single oral dose of 2 g oral metronidazole in treating BV. Side effects of treatment and the women's satisfaction were also evaluated.

MATERIALS AND METHODS

This prospective open label randomized clinical trial was carried out at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, during September 2019 – March 2020. The ethical approval was obtained from the Siriraj Institutional Review Board (Si 222/2019). The trial was registered at the Thai Clinical Trials Registry (TCTR20200902002).

Participants

All women who aged 18-45 years and were diagnosed with BV by Amsel's criteria were invited to participate in the study. The diagnosis based on Amsel's criteria required at least 3 of the following criteria: thin white/grey homogenous discharge, pH>4.5, fishy (amine) odor and the presence of clue cells.[19] The exclusion criteria were women who: had a history of allergy to metronidazole or miconazole, were immunocompromised, had previous episodes of BV within 3 months, had taken medications that could disrupt the vaginal ecosystem e.g. anti-parasitic drugs, oral antibiotics, any vaginal medications, anti-coagulant, or disulfiram within the previous month, had co-incidental other STIs or cervical pre-cancerous or cancerous lesions, was currently pregnant or lactating, or had abnormal uterine bleeding.

Intervention

All women who presented with abnormal vaginal discharge at the Clinic were informed about the study before entering examination rooms. Then, they underwent history-taking, pelvic examination and wet preparation as a part of routine practice. The initial evaluation using a microscope took around 5 minutes for diagnosing BV based on Amsel's criteria. The eligible participants were explained in detail about the study by a study nurse and signed the informed consent. After that, another high vaginal swab was collected for gram stain and consequently Nugent's scoring system. Demographic data, as well as pre-treatment symptom evaluation, were then collected by the study nurse.

The randomization was computer-generated using block-of-four with a ratio 1:1. Each participant was allocated to receive either a 7-day course of vaginal ovules containing metronidazole 750 mg plus miconazole nitrate 200 mg (Neo-penotrans Forte®; NPF, Exeltis, Thailand) or a single dose of oral 2gm metronidazole (Metrolex®, Siam Bheasach Co., Ltd., Thailand).

The participants who were assigned to use vaginal tablets were trained to perform a proper self-insertion of vaginal tablets using a manikin. The single oral dose of metronidazole was given 45 minutes following the oral consumption of domperidone 10 mg at the Clinic on the recruitment day. All participants were asked to comply

with the following prohibitions: no sexual activity, no vaginal douching or cleansing, and avoiding alcoholic beverages for one week following treatment.

All participants were scheduled for a 2-week follow up visit. Clinical response, wet preparation and gram stain for Nugent scoring system were done by an investigator (Chayachinda C). Satisfaction and side effects were evaluated by a study nurse. Those who had persistent BV were treated with metronidazole 400 mg per oral thrice a day for 7 days; or who had other diagnosis were treated accordingly. At 1-month and 3-month post-treatment, all participants were telephoned asking about symptomatic recurrence and/or additional treatment.

Outcome measures

At 2-week follow-up, outcome measures were clinical response, cure rate by Amsel's criteria, cure rate by Nugent's scoring system, satisfaction and side effects. Five key symptoms which were evaluated by a study nurse including vaginal discharge, irritation, itching, odor and coital pain, were graded into 0 (no/absent), 1 (mild), 2 (moderate) and 3 (severe). This results in the ranging score from 0-15. At least 75% reduction of the scores was defined as 'clinical response'. Satisfaction and side effects were also evaluated by the study nurse; and being reported using 0-10 from 'no' to 'maximum'.

The diagnosis of BV based on Amsel's criteria (Chayachinda C) required at least 3 of the following criteria: thin white/grey homogenous discharge, pH > 4.5, fishy (amine) odor and the presence of clue cells.[19] The Nugent scoring was assessed by a blinded microbiologist. The gram-stained slides, two for each participant (first visit and follow-up visit), were labeled using code numbers; and were sent to the microbiologist all at once. The scoring system was done by looking for *Lactobacillus spp., Gardnerella/ Bacteroides spp.*, and curved gram variable rods. The scores ranged from 0-10 and are categorized into 3 groups: score 0-3 (normal), score 4-6 (intermediate flora) and score 7-10 (BV).[20] Cure rate was defined as the conversion of BV to non-BV, including reduction of Amsel's criteria from ≥3 to <3 criteria or that of Nugent score from ≥7 to <7.

At 1-month and 3-month post-treatment, the telephone interview regarding current symptoms, symptomatic recurrence and additional treatment was done by a study nurse who was blinded to the allocation.

Sample size calculation and statistical analysis

Data analyses were carried out with STATA (version 12.0; Stata Corp., College Station, Texas, USA). To describe the characteristics of the participants, mean ± standard deviation, n (%), and median with range were used. For categorical variables, comparisons were performed using the chi-squared test or Fisher's exact test. The distribution of each continuous variable was tested using the Shapiro–Wilk test. Parametric continuous variables were compared with Student's t-test, while nonparametric continuous variables were analyzed with the Wilcoxon rank-sum test. Univariate and multivariate logistic regression were used to determine treatment efficacy. A *P*-value of < 0.05 was deemed statistically significant.

The sample size calculation was undertaken using a formula that compares 2 proportions. A study by Chaithongwongwatthana et al. showed that the efficacy of a single dose of 2 g metronidazole to treat BV was 78.6%[12], whereas another study by Regidor showed that the cure rate in women using NPF was 98.1%.[16] The required sample size was determined to be 30 per group (power, 70%; alpha, 0.05). As a lost-to-follow-up rate of 30% was expected, 40 participants needed to be recruited to each group.

RESULTS

Of 84 eligible participants, 70 came for the two-week follow-up and were included in the analysis. (NPF N=34, MET N=36) Sixty-nine and 60 were contacted at one-month and three-month respectively (Fig 1). The average age and body mass index (BMI) were 32.3±7.9 years and 21.6±3.8 kg/m^2. Around half of all participants reported regular external vaginal cleansing after urination and 8.6% reported ever vaginal douching. Ten participants reported history of sexually transmitted diseases (STD), including 5 genital warts, 3 genital herpes and 2 PID. (Table 1)

All treatment outcomes at two weeks are shown in Table 2. After adjusting for age, sexual experience and number of lifetime sex partners, both NPF and MET had comparable efficacy. Improvement of each symptom is demonstrated in Table 2. Table 3 shows clinical score, Amsel's criteria and Nugent's scores before the intervention and 2-week post treatment. There was no difference between NPF and MET except that the total Nugent's score in NPF group was significantly lower at 2-week follow-up (5.4±1.9 vs 6.8±1.9, p=0.004). At the two-week follow-up, four participants were diagnosed with vaginal candidiasis (NPF 1/34, 2.9% vs MET 3/36, 8.3%, p=0.331); and none had BV.

Both groups reported high satisfaction (NPF 8.5±1.4 vs MET 7.9±2.0, p=0.125). No drug allergy was reported but the side effects were as the followings: loss

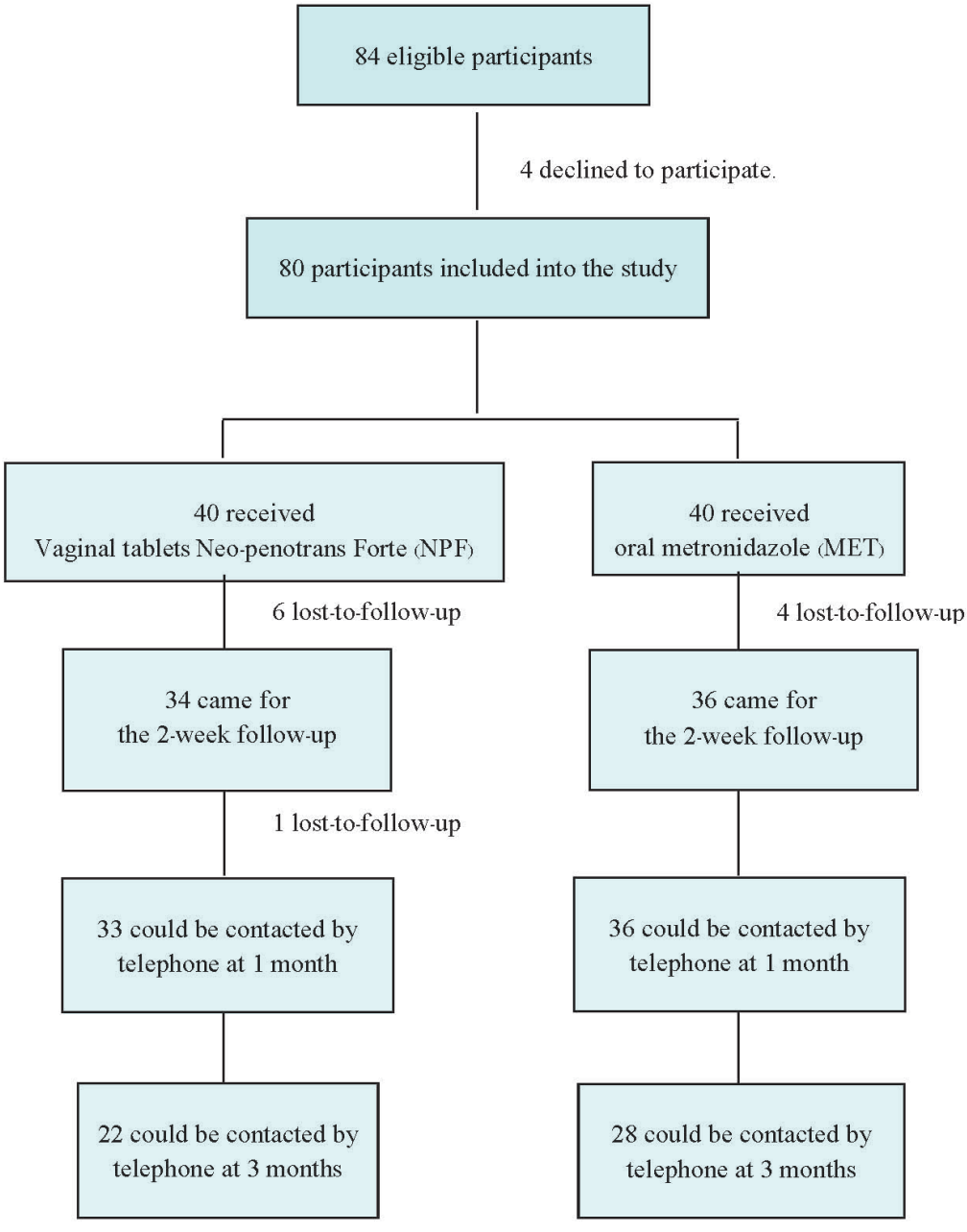

Fig 1. Flow of the participants.

of appetite/metallic taste (NPF 5/34, 14.7% vs MET 6/36, 16.7%, p=0.822), nausea (NPF 3/34, 8.8% vs MET 6/36, 16.7%, p=0.327), dizziness (NPF 4/34, 11.8% vs MET 5/36, 13.9%, p=0.791), vaginal irritation (NPF 3/34, 8.8% vs MET 6/36, 16.7%, p=0.327) and pelvic pain/diarrhea (NPF 2/34, 5.9% vs MET 1/36, 2.8%, p=0.522). No symptomatic, recurrent episode of BV was reported at one-months and three-month telephone follow-ups.

DISCUSSION

Both vaginal tablets containing metronidazole (750 mg) and miconazole nitrate (200 mg) and a single dose of oral metronidazole (2 g) for treating women with BV demonstrate comparable clinical cure and laboratory-based cure rate. The high efficacy demonstrated by NPF in the current investigation was consistent with a meta-analysis done by Lugo-Miro VI et al.[10] Our findings support the potential of this medication as a first-line treatment for BV. Given that oral metronidazole has remarkable side effects of gastrointestinal irritation when BV is localized dysbiosis of the vaginal ecosystem, topical treatment modality appears promising. Moreover, a vaginal biofilm of *G. vaginalis* may limit the treatment efficacy of oral metronidazole[21] whereas vaginal metronidazole may better disrupt such protective factor.

TABLE 1. Characteristics of the participants (N=70).

Total (N=70)	Total (N=70) NPF (N=34)	NPF (N=34) MET	MET (N=36) (N=36)
Age (years)	32.3±7.9	34.1±8.1	30.6±7.3
<25	15 (21.4)	4 (11.8)	11 (30.6)
25-35	32 (45.7)	16 (47.1)	16 (44.4)
>35	23 (32.9)	14 (41.2)	9 (25.0)
Body mass index (kg/m^2)	21.6±3.8	21.5±3.7	21.7±3.8
<18	10 (14.3)	6 (17.7)	4 (11.1)
18- <25	47 (67.1)	21 (61.8)	26 (72.2)
≥25	13 (18.6)	7 (20.6)	6 (16.7)
Being a mother	31 (44.3)	15 (44.1)	16 (44.4)
Abortion	13 (18.6)	5 (14.7)	8 (22.2)
Contraception			
No	23 (32.9)	15 (44.1)	8 (22.2)
Condom	16 (22.9)	4 (11.8)	12 (33.3)
Oral contraceptive pill	21 (30.0)	9 (26.5)	12 (33.3)
Implant/ injectable contraception	4 (5.7)	3 (8.8)	1 (2.8)
No sexual experience	14 (20.0)	10 (29.4)	4 (11.1)
Number of lifetime sex partners	2 (0-4)	1 (0-4)	2 (0-4)
Vaginal hygiene			
Cleansing	37 (52.9)	17 (50.0)	20 (55.6)
Douching	6 (8.6)	3 (8.8)	3 (8.3)
History of sexually transmitted diseases	10 (14.3)	3 (8.8)	7 (19.4)

*Wilcoxon Ranksum test

Abbreviations: NPF = neo-penotrans forte, MET = metronidazole

TABLE 2. Treatment outcomes (N=70).

	Total	NPF	MET	P	cOR (95% CI)	aOR* (95% CI)
Clinical cure rate	44/70 (62.9)	23/34 (67.7)	21/36 (58.3)	0.420	1.49 (0.56-3.97)	1.35 (0.46-3.99)
Amsel cure rate	56/70 (80.0)	28/34 (82.4)	28/36 (77.8)	0.632	1.33 (0.41-3.43)	5.79 (0.88-37.99)
Nugent cure rate	18/70 (25.7)	12/34 (35.3)	6/36 (16.9)	0.075	2.73 (0.89-8.39)	2.73 (0.83-8.96)

*adjusting for age, sexual experience, number of lifetime sex partners

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole, cOR = crude odd ratio, aOR = adjusted odd ratio

TABLE 3. Comparison of symptoms at each visit.

	Before treatment (N=70)			2 weeks (N=70)			1 month (N=69)			3 months (N=60)		
	NPF (n=34)	MET (n=36)	P	NPF (n=34)	MET (n=36)	P	NPF (n=33)	MET (n=36)	P	NPF (n=22)	MET (n=28)	P
Vaginal discharge												
0	0	0	0.252	14 (41.2)	11 (30.6)	0.214	12 (36.4)	10 (27.8)	0.683	7 (31.8)	10 (35.7)	0.870
1	9 (26.5)	6 (16.7)		18 (52.9)	18 (50.0)		16 (48.5)	20 (55.6)		11 (50.0)	14 (50.0)	
2	15 (44.1)	23 (63.9)		2 (5.9)	7 (19.4)		5 (15.2)	5 (13.9)		2 (9.1)	3 (10.7)	
3	10 (29.4)	7 (19.4)		0	0		0	1 (2.8)		2 (9.1)	1 (3.6)	
Vaginal irritation												
0	1 (2.9)	0	0.397	27 (79.4)	22 (61.1)	0.114	25 (75.7)	29 (80.6)	0.964	17 (77.3)	22 (78.6)	0.248
1	7 (20.6)	8 (22.2)		7 (20.6)	11 (30.6)		5 (15.2)	4 (11.1)		4 (18.2)	3 (10.7)	
2	10 (29.4)	16 (44.4)		0	3 (8.3)		2 (6.1)	2 (5.6)		0	3 (10.7)	
3	16 (47.1)	12 (33.3)		0	0		1 (3.0)	1 (2.8)		1 (4.6)	0	
Vaginal itching												
0	8 (23.5)	8 (22.2)	0.962	26 (76.5)	24 (66.7)	0.325	28 (84.9)	29 (80.6)	0.613	17 (77.3)	22 (78.6)	0.627
1	10 (29.4)	11 (30.6)		8 (23.5)	10 (27.8)		5 (15.2)	6 (16.7)		5 (22.7)	5 (17.9)	
2	12 (35.3)	14 (38.9)		0	2 (5.6)		0	0		0	1 (3.6)	
3	4 (11.8)	3 (8.36)		0	0		0	1 (2.8)		0	0	
Malodorous discharge												
0	22 (64.7)	17 (47.2)	0.311	29 (85.3)	32 (88.9)	0.579	33 (100)	33 (91.7)	0.238	21 (95.5)	26 (92.9)	0.662
1	7 (20.6)	8 (22.2)		4 (11.8)	2 (5.6)		0	2 (5.6)		1 (4.6)	1 (3.6)	
2	2 (5.9)	7 (19.4)		1 (2.9)	2 (5.6)		0	1 (2.8)		0	1 (3.6)	
3	3 (8.8)	4 (11.1)		0	0		0	0		0	0	
Coital pain												
0	4 (11.8)	6 (16.7)	0.651	30 (88.2)	32 (88.9)	0.562	31 (93.9)	31 (86.1)	0.238	20 (90.9)	26 (92.9)	0.249
1	12 (35.3)	14 (38.9)		4 (11.8)	3 (8.3)		0	3 (8.3)		2 (9.1)	0	
2	7 (20.6)	9 (25.0)		0	1 (2.8)		2 (6.1)	2 (5.6)		0	1 (3.6)	
3	11 (32.4)	7 (19.4)		0	0		0	0		0	1 (3.6)	
Total score	8(1-12)	8(3-11)	0.795	1(0-5)	2(0-8)	0.218	1(0-6)	1(0-9)	0.852	2(0-7)	1(0-8)	0.263

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole

TABLE 4. Clinical score, Amsel's criteria and Nugent's score before intervention and at 2-week follow-up (N=70).

	Before intervention			2-week follow-up		
	NPF (n=34)	MET (n=36)	P	NPF (n=34)	MET (n=36)	P
Sum of clinical scores Amsel's criteria	8(1-12)	8(3-11)	0.795	1(0-5)	2(0-8)	0.218
Homogeneous whitish discharge	17 (50.0)	22 (61.1)	0.350	11 (32.4)	11 (30.6)	0.871
pH >5	34 (100)	36 (100)	1.000	7 (20.6)	15 (41.7)	0.058
Positive whiff test	29 (85.3)	34 (94.4)	0.202	6 (17.7)	8 (22.2)	0.632
Presence of clue cells	34 (100)	35 (97.2)	0.328	7 (20.6)	11 (30.6)	0.340
Total	3 (3-4)	3 (3-4)	0.342	1 (0-3)	1 (0-3)	0.902
Nugent's score						
Normal (score <4)	0	0	0.653	8 (23.5)	4 (11.1)	0.032
Intermediate flora (4-6)	5 (14.7)	4 (11.1)		12 (35.3)	6 (16.7)	
Bacterial vaginosis (>6)	29 (85.3)	32 (88.9)		14 (41.2)	26 (72.2)	
Total score	7.6±1.0	7.8±0.9	0.291	5.4±1.9	6.8±1.9	0.004

Abbreviations: NPF = Neo-penotran forte®, MET = metronidazole,

CONCLUSION

Amsel's criteria at two-week follow-up were not different whereas Nugent's scores were. Amsel's criteria partially belonged to clinical-based diagnostic methods when Nugent's scoring system was mainly a laboratory-based method. The latter one was usually used as a gold-standard diagnostic method in research study. Obviously, Nugent's scoring system had a better reflection of vaginal ecosystem as our previous study showed that, based on this method, 20% of asymptomatic pregnant women had BV; and tended to have worse pregnancy outcomes.[22] Therefore, the higher cure rate based on Nugent's scoring system in the present study suggested the better resolution of vaginal dysbiosis following NPF treatment.

Contrasting to previous studies, none of the participants in both groups reported symptomatic recurrence. A longer course of metronidazole results in a lower incidence of recurrence at 1 month.[10] Moreover, a long-term study in Australian women found that over 50% of BV-diagnosed women receiving or not receiving adjuvant treatment reported recurrent BV episodes at their 6-month follow-up.[23] This may be partly explained by the fact that practice to achieve and maintain vaginal hygiene were emphasized during participant counselling, such as avoiding excessive cleansing, vaginal douching, and the wearing of tight garments. Additionally, the follow-up period was short; and BV can also be asymptomatic.

Compatible with previous studies, the combination of metronidazole and miconazole in a vaginal tablet appear not to cause severe adverse events; and mitigate the coincidence of BV and vaginal candidiasis (VC).[15,16] The coincidence of BV and VC and VC as a consequence of BV have been evident. The coincidence was reported in 15.2% of American non-pregnant women[16] and 13.3% of Thai pregnant women.[22] Furthermore, the administration of miconazole (200 mg) vaginal suppositories for 3 days is a recommended regimen for treating women with vaginal candidiasis (VC) treatment guidelines.[9,23] As a consequence, pseudohyphae was detected around three times higher in the MET group at 2-week.

Although none of the participants required additional BV treatment within 3 months post-treatment, a quarter of the participants reported a malodorous vaginal discharge or fishy odor following sexual intercourse. This supports the dynamic and self-heal of vaginal microbiome. Despite the fact that seminal fluid can precipitate the incidence of BV, the resumption of individual participant's normal life is the goal of BV

treatment. As such, other risk factors of BV occurrence should be serious taken into consideration such as excessive vulvar cleansing and vaginal douching.

The strength of this study is its randomized design. Although the participants could not be blinded, the investigators who evaluated the outcome measures and the statistician were. The limitations of the study were its small sample size and short follow-up period. One of the biggest concerns among women with BV is the frequent recurrence of the condition. Only symptomatic recurrence is approached at 1- and 3-month while BV can be asymptomatic. Another limitation was that the administrative route and the duration of treatment period of the two assigned treatment were different. Provide that double-dummy, placebo-controlled design and daily self-record of symptoms had been applied, the study would have had less bias in outcome measurement but probably more advantage of the novel treatment.

In conclusion, for BV treatment, both vaginal tablets containing metronidazole (750 mg) plus miconazole nitrate (200 mg) and oral metronidazole (2 g) show comparable efficacy and side effects.

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Prevalence and Factors Associated with Antepartum Depression: A University Hospital-Based

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ABSTRACT

Objective: This study aimed to assess the prevalence of and factors associated with antepartum depression among Thai women.

Materials and Methods: All pregnant women attending the Antenatal Care Clinic at Songklanagarind Hospital from June to August 2020 were invited to participate and evaluated through self-administered questionnaires. Multivariate logistic regression models were used for the data analysis in order to control for potential confounders.

Results: 435 women were in their first, second, and third trimester of pregnancy (20.2 %, 39.5 %, and 40.2 %, respectively). The majority of them reported normal Rosenberg's Self-esteem Scale scores (83.4 %) and a high level of perceived social support (74.5 %). Moreover, according to the Edinburgh Postnatal Depression Scale (EPDS) scores, the prevalence of antepartum depression was 10.6 %. A multivariate logistic regression analysis showed that factors associated with antepartum depression were second trimester of pregnancy, survival and below-survival levels of income, unintended pregnancy, and low level of self-esteem.

Conclusion: One-tenth of pregnant Thai women suffered from depression. Advanced gestational age, low income, unintended pregnancy, and low self-esteem were significant factors associated with antepartum depression.

Keywords: Antepartum; associated factors; depression; pregnancy; prevalence (Siriraj Med J 2021; 73: 652-660)

INTRODUCTION

Depression is a common psychiatric disorder.[1,2] The World Health Organization (WHO) reported depression as the third cause of global burden of disease in 2004 and the second cause in 2020, and it estimates depression will be the leading cause of "lost years of healthy life" worldwide by 2030.[1] Women are twice as likely to develop depression, especially during pregnancy, due to the physical, physiological, and hormonal changes they undergo.[3]

Antepartum depression is characterized by depressive symptoms like low mood or sadness, feeling of worthlessness, loss of interest or pleasure, sleep disturbance, and changes in appetite[4]; it affects both the maternal health and family life of women.[5] Moreover, it is often considered to be associated with adverse pregnancy outcomes such as preterm birth and low birth weight.[6-8] Untreated antepartum depression leads to postpartum depression[9], resulting in malnourishment and a poor relationship between mother and child.[10]

Systematic reviews have estimated the overall prevalence of antepartum depression at around 6.2 - 9.2 % in high-income countries and 19.2 - 23.5 % in low-to middle-income countries.[11-13] The onset of antepartum depression most commonly occurs during the third trimester.[14] The potential risk factors of antepartum

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Received 18 May 2021 Revised 19 August 2021 Accepted 19 August 2021
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http://dx.doi.org/10.33192/Smj.2021.84

depression can be categorized into four aspects-the personal background, obstetric, psychological or psychiatric, and social and family aspects. The personal background and obstetric aspects involve factors such as parity[15], advanced maternal age[16,17], unintended pregnancy[18,19], and obstetric complications.[20] In addition, low self-esteem[18], experiencing negative life events[11], history of depressive symptoms[15,21], history of illness during the previous month[22,23], and family history of psychiatric disorders[15], which belong to the psychological or psychiatric aspect, are significant factors associated with antepartum depression.

Moreover, in regards to the social and family aspect, factors such as low socioeconomic status[22], lack of partner support[23] or poor marital relationship[24], history of intimate partner violence[11,12], differences in religion and/or culture between partners[13], having a partner with a smoking and drinking habit[15,18], difficult relationship with the mother-in-law, lack of parenting knowledge[12], and baby gender selection or gender preference due to the family-related circumstances[17,23] are potential risk factors for persistent depression during pregnancy.

The risk factors associated with antepartum depression may differ among countries. Limited data concerning these issues are available from Asian countries. In Thailand, only one study on this topic has been conducted in the past ten years (2010). It reported a 10.3 % prevalence of antepartum depression, but it did not explore its associating risk factors.[25] Therefore, we conducted this study to determine the prevalence of antepartum depression across gestational ages and identify its associating risk factors. This research may provide useful information for both psychiatrists and obstetricians in their efforts to establish antepartum depression screening programs aimed at the early detection, prevention, and timely management of severe depression among pregnant women.

MATERIALS AND METHODS

After approval by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC: 63-083-3-4), this cross-sectional study was conducted at Songklanagarind Hospital, which is an 800-bed university hospital that serves as a tertiary referral center in Southern Thailand. All methods were carried out following relevant guidelines and regulations. Written informed consent was obtained from all participants before enrollment. All pregnant women, who were at least 18 years old and attended the hospital's Antenatal Care Clinic (ANC) from June to August 2020, were invited to participate in this study. We included all the pregnant women who were able to complete all parts of the questionnaires. Those with a self-reported history of psychiatric illness and who did not complete the questionnaires in full, declined to participate in the study, or could not read or write the Thai language, were excluded. The sample size was calculated based on an estimated prevalence (P = 0.1, alpha = 0.05 and d = 0.03); at least 395 participants were deemed necessary for enrollment.

All eligible pregnant women were asked to answer the self-reported questionnaires anonymously. Then the researcher informed the participants about the results immediately after their completion. If they had EPDS scores of greater than or equal to 11, which was considered a positive screening for depression, the psychiatrists in the research team performed in-depth interviews by using DSM-V criteria for definite diagnosis and proper management.

Measures

The data collection tools consisted of the demographic data questionnaire, the Rosenberg's Self-esteem Scale, the Multidimensional Scale of Perceived Social Support

1) The demographic characteristics questionnaire consisted of questions enquiring about the woman's age, gestational age, educational level, occupation, religion, healthcare coverage scheme, marital status, family income, pregnancy intention, gravidity, parity and abortion, obstetric complications, history of substance abuse, underlying medical illness, and family and partner profiles.

2) Rosenberg's Self-esteem Scale-Thai version[26] consisted of 10 questions related to positive and negative feelings about themselves. All items were rated via a 4-point Likert scale ranging from "0" (strongly disagree) to "3" (strongly agree). The total score ranged from 0 - 30; a score greater than 25 indicated a high level of self-esteem, scores in the 15 - 25 range represented a normal level of self-esteem, and the ones less than 15 signified a low level of self-esteem.[27] A Cronbach's alpha coefficient of 0.86 has been reported for this tool.[26]

3) The Multidimensional Scale of Perceived Social Support (MSPSS)-Thai version[28] comprised 12 questions grouped into 3 subcategories: family, friends, and significant others. All items were rated using a 7-point Likert scale ranging from "1" (very strongly disagree) to "7" (very strongly agree). The total score ranged from 12 - 84, and the score of each subpart ranged from 1 to 7; a score of 1 - 2.9 was indicative of low support level, a score in the 3 - 5 range was deemed to represent

moderate-level support, and those from 5.1 to 7 were considered to represent a high level of support.[29] The Cronbach's alpha coefficient for this questionnaire has been reported to be 0.91.[28]

4) The Edinburgh Postnatal Depression Scale (EPDS)-Thai version[30] consisted of 10 questions. All items were rated using a 3-point scale. The total score ranged from 0 - 30; the cut-off score of > 11 was the optimal cut-off points for screening both antepartum and postpartum depression according to previous study.[30,31] The Cronbach's alpha, sensitivity, and specificity values for this tool have been determined to be 0.87, 100.0 %, and 92.6 %, respectively.[30]

Statistical methods

Descriptive statistics, the chi-square test, the Fisher's exact test, and multivariate logistic regression analyses were used in the data analysis. A p-value of < 0.05 was considered to represent statistical significance.

RESULTS

Demographic characteristics

A total of 447 pregnant women attended the Antenatal Care Clinic during the study period, and 435 of them (97.3 %) agreed to complete the questionnaires. Most women were in the third and second trimesters. Overall, the mean (SD) maternal age was 32.0 (5.2) years, and the mean (SD) gestational age was 23.8 (10.3) weeks. The majority of the participants were Buddhist (69.0 %), had a high educational level (72.2 %), had a Bachelor's degree or higher), were employees (36.3 %), and had a low monthly household income (66.9 %). Besides, most women were multigravida (65.3 %) and had planned their pregnancies (77.7 %). About one-fourth of them had experienced pregnancy complications such as gestational diabetes mellitus, fetal anomaly, and threatened abortion during the current pregnancy. However, the majority of participants had no underlying medical illnesses (85.7 %). Moreover, only 10 participants (2.3 %) had a family history of psychiatric illness such as major depressive disorder, persistent depressive disorder, generalized anxiety disorder, and schizophrenia.

Self-esteem

Using the Rosenberg's Self-esteem Scale-Thai version, the mean (SD) total score of self-esteem was 21.4 (3.3). The majority of participants had a normal level of self-esteem (83.4 %); only 6 participants had low self-esteem (1.4 %), and 15.2 % had high self-esteem (Table 1).

Perceived social support

The Multidimensional Scale of Perceived Social Support (MSPSS)-Thai version revealed a mean (SD) total score of 69.3 (9.6) for perceived social support. The majority of participants had a high level of perceived social support (74.5 %), and only 2 participants (0.5 %) reported having a low level of perceived social support (Table 1).

TABLE 1. EPDS, self-esteem, and perceived social support scores categorized by trimester (N = 435).

Questionnaire measures	Total (N = 435)	Trimester; number (%) First trimester (n = 88)	Second trimester (n = 172)	Third trimester (n = 175)	Chi² P-value
EPDS[a]					0.095
< 11	389 (89.4)	81 (92.0)	147 (85.5)	161 (92.0)	
≥ 11	46 (10.6)	7 (8.0)	25 (14.5)	14 (8.0)	
Self-esteem[b]					0.293*
Low	6 (1.4)	2 (2.3)	1 (0.6)	3 (1.7)	
Normal	363 (83.4)	77 (87.5)	139 (80.8)	147 (84.0)	
High	66 (15.2)	9 (10.2)	32 (18.6)	25 (14.3)	
MSPSS[c]					0.530*
Low	2 (0.5)	0 (0)	0 (0)	2 (1.1)	
Moderate	109 (25.1)	19 (21.6)	47 (27.3)	43 (24.6)	
High	324 (74.5)	69 (78.4)	125 (72.7)	130 (74.3)	

Note: [a]EPDS = the Edinburgh Postnatal Depression Scale; [b]Self-esteem = the Rosenberg's Self-esteem Scale; [c]MSPSS = the Multidimensional Scale of Perceived Social Support
* Fisher's exact test

Prevalence of antepartum depression

Using the Edinburgh Postnatal Depression Scale (EPDS)-Thai version, the mean (SD) total score was 5.8 (3.9). The prevalence of antepartum depression according to EPDS was 10.6 %. The prevalence of antepartum depression in the first, second and third trimesters was 1.6 %, 5.7 %, and 3.2 %, respectively. However, after in-depth interviews by psychiatrists using the DSM-V criteria for major depressive disorder, it was revealed that only 3 participants (0.7 %) had major depressive disorder, whereas the remaining 43 participants (9.9 %) had adjustment disorder with depressed mood.

Factors associated with antepartum depression

To identify factors associated with antepartum depression, demographic characteristics, self-esteem, and perceived social support were included in the univariate analysis. Variables with p-values of less than 0.2 from the univariate analysis were included in the final model of the multivariate logistic regression analysis. These factors were trimester of pregnancy, educational level, occupation, health coverage, income, pregnancy intention, complications during current pregnancy, family history of psychiatric illness, partner's educational level, partner's underlying diseases, self-esteem, and perceived social support (Table 2). The multivariate analysis showed that trimester of pregnancy, income, pregnancy intention, and self-esteem level were significant factors associated with antepartum depression (Table 3).

With regard to the factors associated with antepartum depression, women in the second trimester faced a 2.7 times increased risk for antepartum depression compared to those in the first trimester. Likewise, compared to the pregnant women with a high income level, those who reported survival and below-survival levels of income experienced a 3.2 and 5.4 times increased risk for antepartum depression, respectively. Similarly, unintended pregnancy was associated with a 2.3 times higher risk for antepartum depression than intended pregnancy. On the other hand, a normal level of self-esteem was found to exert a protective influence against antepartum depression (Table 3).

DISCUSSION

This study indicated that the prevalence of depression during the antepartum period assessed via EPDS was 10.6 %. Comparing the prevalence of our study with those reported by previous researches, it was similar to the one found by a study from Thailand (10.3 %) even if using the different tools.[25] Thus, we can conclude that for the screening of antepartum depression we can use both EPDS (our study) and Two-question screening for depression, Thai-version (previous study) for screening antepartum depression in ANC. However, our rate was lower than those found in low-to middle-income countries (19.2 - 23.5 %) but higher than those reported in high-income countries (6.2 - 9.2 %).[11-13] These differences might be due to the differences in study instruments, population ethnicity, family background, and gestational age at enrollment. The factors identified to associate with antepartum depression were advanced gestational age, low monthly household income, unintended pregnancy, and low self-esteem. Surprisingly, gestational age in the second trimester has not been reported before as a significant factor associated with antepartum depression. This might be due to a change in appearance and body image, along with quickening of the baby. Moreover, obstetricians can detect fetal abnormalities from ultrasound as well as various pregnancy problems. All these abnormalities can lead to anxiety or stressful in pregnant women.

Regarding family income, compared to pregnant women with a high level of income, those with survival or below-survival income levels had a significantly increased risk of experiencing antepartum depression. This result was similar to the findings reported by previous studies.[18,22] An explanation for this could be the possibility that economic problems can result in stress and anxiety, especially for women who play an important role in family care, provide food for family members, pay for various family expenses and antenatal care, and is expected to shoulder the cost of other medical care in the future. Nevertheless, it was women's point of view which Thai people normally underestimate their income.

Similarly, unintended pregnancy was associated with twice the likelihood of antepartum depression compared to intended pregnancy. This finding was consistent with those of previous studies conducted in Jordan and Kenya.[18,19] Unplanned pregnancies can lead to concerns about oneself, the family, and the baby's future. Furthermore, unintended pregnancy was high in our study because of high ratio of Islamism in Southern Thailand that they cannot do any contraception according to the principles of their religious.

Conversely, normal self-esteem protected pregnant women from antepartum depression. This finding was in line with the results reported by a study conducted in Jordan.[19] Women with a higher level of self-esteem tend to feel more valuable than those with a lower level of self-esteem. Therefore, the women with a normal level of self-esteem may feel less fearful or insecure and also

TABLE 2. Demographic characteristics, self-esteem, and perceived social support categorized by EPDS score (N = 435).

Variables	Total (N = 435)	EPDS[a]; number (%) < 11 (n = 389)	EPDS[a]; number (%) ≥ 11 (n = 46)	Chi² P-value
Age (years)				0.622
< 35	293 (67.4)	264 (67.9)	29 (63.0)	
≥ 35	142 (32.6)	125 (32.1)	17 (37.0)	
Trimester				0.095
First	88 (20.2)	81 (20.8)	7 (15.2)	
Second	172 (39.5)	147 (37.8)	25 (54.3)	
Third	175 (40.2)	161 (41.4)	14 (30.4)	
Educational level				0.197
Below Bachelor's degree	121 (27.8)	104 (26.7)	17 (37.0)	
Bachelor's degree and higher	314 (72.2)	285 (73.3)	29 (63.0)	
Occupation				0.159
Employee/self-employed	199 (45.7)	175 (45)	24 (52.2)	
Government employee	158 (36.3)	147 (37.8)	11 (23.9)	
Housewife/unemployed	78 (17.9)	67 (17.2)	11 (23.9)	
Religion				0.414*
Buddhism	300 (69)	272 (69.9)	28 (60.9)	
Islam	132 (30.3)	114 (29.3)	18 (39.1)	
Christianity	3 (0.7)	3 (0.8)	0 (0.0)	
Health coverage				0.093
Civil Servant Medical Benefit Scheme (CSMBS)	152 (34.9)	140 (36)	12 (26.1)	
Universal Coverage Scheme (UCS)	45 (10.3)	36 (9.3)	9 (19.6)	
Social Security Scheme (SSS)	101 (23.2)	88 (22.6)	13 (28.3)	
Out-of-pocket	137 (31.5)	125 (32.1)	12 (26.1)	
Marital status				0.637*
Single/divorced	13 (3)	11 (2.8)	2 (4.3)	
Married	422 (97)	378 (97.2)	44 (95.7)	
Monthly household income (Baht/month)				0.058
< 30,000; low income	291 (66.9)	254 (65.3)	37 (80.4)	
≥ 30,000; high income	144 (33.1)	135 (34.7)	9 (19.6)	
Standard of living				< 0.001
High	222 (51)	211 (54.2)	11 (23.9)	
Survival	183 (42.1)	156 (40.1)	27 (58.7)	
Below survival	30 (6.9)	22 (5.7)	8 (17.4)	
Family structure				> 0.99
Nuclear	306 (70.3)	274 (70.4)	32 (69.6)	
Extended	129 (29.7)	115 (29.6)	14 (30.4)	
Pregnancy intention				0.002
Unintended	97 (22.3)	78 (20.1)	19 (41.3)	
Intended	338 (77.7)	311 (79.9)	27 (58.7)	
Parity				0.878
Nulliparity	151 (34.7)	136 (35)	15 (32.6)	
Multiparity	284 (65.3)	253 (65)	31 (67.4)	

TABLE 2. Demographic characteristics, self-esteem, and perceived social support categorized by EPDS score (N = 435). (Continue)

Variables	Total (N = 435)	EPDS[a]; number (%) < 11 (n = 389)	EPDS[a]; number (%) ≥ 11 (n = 46)	Chi² P-value
Complications during this pregnancy	84 (19.3)	70 (18)	14 (30.4)	0.068
Number of children				0.568
0 - 1	173 (39.8)	157 (40.4)	16 (34.8)	
> 1	262 (60.2)	232 (59.6)	30 (65.2)	
Complications during previous pregnancies	106 (24.4)	91 (23.4)	15 (32.6)	0.232
Previous miscarriage	89 (20.5)	76 (19.5)	13 (28.3)	0.233
Smoking	3 (0.7)	2 (0.5)	1 (2.2)	0.285*
Alcohol consumption	47 (10.8)	41 (10.5)	6 (13)	0.615*
Underlying medical illness	62 (14.3)	54 (13.9)	8 (17.4)	0.674
Family history of psychiatric illness	10 (2.3)	7 (1.8)	3 (6.5)	0.078*
Self-esteem[b]				< 0.001
Low	6 (1.4)	2 (0.5)	4 (8.7)	
Normal	363 (83.4)	321 (82.5)	42 (91.3)	
High	66 (15.2)	66 (17)	0 (0)	
MSPSS[c]				0.006
Low-to-moderate	111 (25.5)	91 (23.4)	20 (43.5)	
High	324 (74.5)	298 (76.6)	26 (56.5)	
Partner's demographic characteristics (n=432)**				
Educational level				0.166
Below Bachelor's degree	226 (52.3)	197 (51)	29 (63)	
Bachelor's degree and higher	206 (47.7)	189 (49)	17 (37)	
Occupation				0.79
Employee/self-employed	285 (66)	253 (65.5)	32 (69.6)	
Government employee	140 (32.4)	127 (32.9)	13 (28.3)	
Stay-at-home dad/unemployed	7 (1.6)	6 (1.6)	1 (2.2)	
Religion				0.223*
Buddhism	300 (69.4)	273 (70.7)	27 (58.7)	
Islam	130 (30.1)	111 (28.8)	19 (41.3)	
Christianity	2 (0.5)	2 (0.5)	0 (0.0)	
Smoking	191 (44.2)	169 (43.8)	22 (47.8)	0.715
Alcohol consumption	182 (42.1)	163 (42.2)	19 (41.3)	> 0.99
Other substance abuse				
(E.g. Cannabis)	3 (0.7)	2 (0.5)	1 (2.2)	0.287*
Underlying medical illness	27 (6.2)	22 (5.7)	5 (10.9)	0.19*
Psychiatric illness	1 (0.2)	1 (0.3)	0 (0.0)	> 0.99*

Note: [a]EPDS = the Edinburgh Postnatal Depression Scale; [b]Self-esteem = the Rosenberg's Self-esteem Scale; [c]MSPSS = the Multidimensional Scale of Perceived Social Support

* Fisher's exact test; ** There were 3 missing values.

TABLE 3. Factors associated with antepartum depression by multivariate regression analysis.

Factors	Crude OR[a] (95 % CI[b])	Adjusted OR[a] (95 % CI[b])	P-value LR[c] test
Trimester			0.018
First	Ref[d]	Ref[d]	
Second	1.97 (0.82, 4.75)	2.73 (1.04, 7.21)	
Third	1.01 (0.39, 2.59)	1.06 (0.38, 2.95)	
Standard of living			0.001
High	Ref[d]	Ref[d]	
Survival	3.32 (1.6, 6.9)	3.23 (1.5, 6.96)	
Below survival	6.98 (2.54, 19.17)	5.35 (1.78, 16.03)	
Pregnancy intention			0.021
Intended	Ref[d]	Ref[d]	
Unintended	2.81 (1.48, 5.31)	2.3 (1.15, 4.6)	
Self-esteem level			< 0.001
Low*	Ref[d]	Ref[d]	
Normal	0.07 (0.01, 0.37)	0.06 (0.01, 0.39)	
High	0 (0, inf.)	0 (0, inf.)	

Note: [a]OR = odds ratio; [b]CI = confidence interval; [c]LR = likelihood-ratio; [d]Ref = reference category

*We could not use a normal self-esteem value as a reference due to the imprecision of the estimation (the 95 % CI was too wide).

experience less stress or anxiety than those with a low level of self-esteem. Thus, this may serve as an indication for targeting the enhancement of the self-esteem of pregnant women in our country. In addition, screening pregnant women with low self-esteem using Rosenberg's Self-esteem Scale-Thai version during antenatal care might be useful.

Finally, the information provided by our findings might prove useful in establishing a screening program that utilizes EPDS for pregnant women in the future, which can be applied from the first trimester of the antepartum period. The rationale of using the first trimester as a reference point was is based on evidence from a previous study, which demonstrated an increasing risk for antepartum depression with advancing gestational age.[14] Such programs may be especially beneficial for women at risk for antepartum depression, e.g., those with unintended pregnancy, low family income, low self-esteem, and a gestational age of the second trimester onwards. This screening would be very helpful for the early detection, prevention, and timely management of severe depressive episodes among pregnant women. Furthermore, health agencies that play a role in pregnancy care should design and conduct activities aimed at enhancing the self-esteem of pregnant women, their ability to manage stress properly, as well as their problem-coping skills during antenatal visits. In addition, educating family members and other influential persons about the detection, care, and prevention of antenatal depression would be a worthwhile goal. We recommend that the antenatal care book, which is made available as a handout for the general public, should contain essential information regarding the warning signs of depression as well as appropriate self-care to prevent depression during pregnancy. Moreover, for pregnant women with unintended pregnancy, critical socioeconomic problems, and severe psychiatric disorders that are at risk for major depression with suicidal ideation, termination of pregnancy at an early gestational age should be offered as an option. Such strategy may prevent suicide during pregnancy. Additionally, effective contraception, sex education also risks and benefit of multiparity should be provided to women who wish to prevent future unintended pregnancies.

Strengths and limitations

To our knowledge, this is the only study on this topic conducted in Thailand during the past decade, which employed an adequate sample size and covered pregnant women in all trimesters of pregnancy. Another strength of this study is that we identified factors associated with antepartum depression, which can be very useful in detecting pregnant women at risk for this significant health problem. However, our study suffered from some limitations. It utilized self-administered questionnaires; therefore, some misunderstandings regarding the intended meaning of the questions might have occurred. Nevertheless, to minimize this, the questionnaires were validated and showed good reliability (good Cronbach's alpha coefficient values). Another drawback was that our data were collected from pregnant women without any previous history of depression or other psychiatric illnesses in the lower part of Southern Thailand. Hence, this dataset may not represent fairly the situation of pregnant women in the whole country.

Future recommendations and implications

For further study, screening from the first ANC visit until the postpartum period and conducting multi-centric research on this topic are necessary before making a definite guideline for screening depression during pregnancy.

CONCLUSION

One-tenth of Thai women responders were found to suffer from antepartum depression via EPDS screening. Advanced gestation, low income, unintended pregnancy, and low self-esteem were determined to relate to antepartum depression. Future longitudinal studies encompassing the time interval from the first antenatal visit to the postpartum period should be conducted in order to assess the exact onset of depression. Furthermore, multi-centric studies are recommended.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all the participants for their willingness to provide information and the nursing staff of the antenatal clinic for facilitating this study by providing space at the clinic and support to carry out the study. We would like to also acknowledge Associate Professor Hutcha Sriplung, and the research assistants; Nisan Werachattawan and Kruewan Jongborwanwiwat, for their assistance with the data analysis. Moreover, we genuinely appreciate the International Affairs Unit of the Faculty of Medicine for proof-reading the English.

This study was fully supported by the Faculty of Medicine, Prince of Songkla University, Thailand. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure statement: The authors declare no conflict of interest.

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The Perceptions of Roles and Understanding about Forensic Evidence and Crime Scene Preservation of Thai Paramedics

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ABSTRACT

Objective: 1. To study the perceptions of roles and understanding of FECSP of Thai paramedics. 2. To study the problems, obstacles, and solutions for development of Thai paramedics FECSP practices. 3. To study the factors affecting the perceptions of roles and understanding of FECSP in Thai paramedics.

Materials and Methods: Thai paramedics data over the country registered with National Institute for Emergency Medicine (NIEMS) during 1st March – 31st March 2021 was collected in this cross-sectional survey. The questionnaires were sent as Google forms to them by e-mail.

Results: 382 questionnaires were sent, and 281 responses (74%) were obtained. Most were female (61.9%). The average age was 26.09±4.44 years. The most common crime scene experienced was traffic accidents. Most had never had additional training related to forensic science. The perceptions of roles and understanding about FECSP were at the highest level. The most common problem and hindrance about FECSP was no FECSP law and the most common solution for improvement of the FECSP was the standard FECSP guideline development. Hospital level was found to be a factor related to the perceptions of roles of FECSP in Thai paramedics. Average score of a cohort who worked at university hospital was higher than those working at tertiary hospitals 0.220 (B = -0.220, p-value = 0.018). Additionally, hospital level was also a factor concerning the understanding about FECSP of Thai paramedics. The average score of cohorts who worked at university hospitals was greater than those working in primary or secondary hospitals 0.197 (B = -0.197, p-value = 0.022).

Conclusion: The paramedics had the perception of the roles and understanding about FECSP at the highest level. Hospital level was a significant factor related to the perception of the roles and understanding about FECSP. Relevant health institutes should develop standard guidelines and promote FECSP training.

Keywords: Crime scene; forensic evidence; paramedic; role; understanding (Siriraj Med J 2021; 73: 661-671)

INTRODUCTION

Paramedicine is a new profession in Thailand. The most important role of paramedics is to provide pre-hospital advanced life support for emergency patients.[1] Paramedics often need to assist the injured at crime scenes. However, paramedics have not received any official educational sessions or trainings to deal with crime scene management.[2] Currently, the role of paramedics in forensic evidence and crime scene preservation (FECSP) is unclear in Thailand. In the past, the management of

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http://dx.doi.org/10.33192/Smj.2021.85

the evidence and the crime scene depended on individual knowledge and experience. Consequently, paramedics might damage the evidence and crime scene due to a lack of a recognized role and understanding of FECSP and may damage evidence at the crime scene while performing their duties due to not following appropriate handling processes, potentially causing a more complicated inquest, an inconclusive judgement or even a miscarriage of justice.[3]

The aim is to study the perceptions of roles and understanding about FECSP of Thai paramedics as well as factors affecting the perceptions of roles and understanding of FECSP in Thai paramedics.

MATERIALS AND METHODS

The study design was a cross-sectional survey. The sample was composed of Thai paramedics registered with National Institute for Emergency Medicine (NIEMS). The questionnaire data was collected during 1st March – 31st March 2021. Inclusion criteria were being registered with NIEMS and having the intention to renew their 5-year license. Exclusion criteria were incomplete data in NIEMS database, such missing as e-mail addresses, as well as declining participation. The questionnaire was examined using a validity index by three forensic experts. The validity index was 1 for all questionnaires.

The questionnaire was comprised of 4 parts. Part one was comprised of of 9 questions about participants' personal information and included questions about participant sex, age, education level, income, position, employment period, hospital level, crime scene experience and additional forensic training experience. The second and third parts contained 30 questions in total: 15 questions referred to the perception of roles in FECSP of Thai paramedics and another 15 regarding their understanding of FECSP. The questionnaire employed closed questions, with responses structured using 5-point Likert rating scales - 5 being the highest, 4 being high, 3 being neutral, and 2 and 1 being low and lowest respectively. Parts two and three were validated via a tryout, tested by 30 fourth-year paramedic students who had similar characteristics to the sample. Reliability indices were calculated using Cronbach's alpha and were 0.868 and 0.875 for parts two and three respectively, indicating high reliability. The scoring criteria of the questionnaire parts two and three was divided into 5 levels, in accordance with the mean score (Best, 1986). Mean scores of 4.21-5.00, 3.41-4.20, 2.61-3.40, 1.81-2.60 and 1.00-1.80 mean highest, high, neutral, low, and lowest, respectively.[4] Part four contained two questions relating to problems, obstacles, and solutions to improve FECSP. The questionnaires were sent out as Google forms to the paramedics by e-mail. Participants were given 30 days to complete the survey. The definitions of factors were determined, firstly, hospital level regarding geographic information system (GIS), including tertiary, secondary and primary hospitals, as well as university hospital, separated from tertiary hospital. The university hospital was defined as a super tertiary hospital with the highest service capability and treatment readiness as well as provided medical personnel training and medical research. The tertiary hospital was an excellence center dedicated to sub-specialty care. Low, middle and high levels of secondary services were assembled in secondary hospital. The low secondary service level consisted of general practice to in-patient department (cared by general practitioner/ family medicine physician). While the middle level was composed of major sub-specialty care. Both major and minor sub-specialty cares were offered in the high level of secondary service. The primary hospital was a combination of initial and main levels of primary service. The initial primary service level included elementary health promotion, prevention, rehabilitation and treatment (serviced by non-physician personnel). Whereas the main level of primary service comprised preliminary promotion, prevention, rehabilitation and treatment to out-patient department (cared by general practitioner/ family medicine physician, etc.), besides paramedics under local administration were involved. Secondly, the perceptions of roles about FECSP were defined as paramedics' behavior or duty regarding knowledge and profession in FESCP according to emergency medicine. Thirdly, the understanding about FECSP was defined as paramedics' psychological process and evaluation in FECSP.

Statistical analyses

382 paramedics both registered with NIEMS in 2021 and determined to renew their 5-year license responded (NIEMS, 2021). The Taro Yamane formula was used for sample size calculation (Taro Yamane, 1973). The calculated sample size was 196, with an error margin of 0.05. After 20% of sample size was added to compensate for non-responses using the formula $n_{new} = 196 / (1-0.2)$[5], final sample size was 245. However, the questionnaire was sent to every paramedic.

Descriptive statistics were used to analyze the personal data including sex, age, education level, income, position, employment period, hospital level, crime scene experience and additional forensic training experience. For the qualitative data, frequency distribution and percentage were reported. Mean with standard deviation (SD) or

median with interquartile range (IQR) were used for the quantitative data, as appropriate. For the data of perceptions of roles and understanding about FECSP of Thai paramedic, mean with SD were reported, while frequency distribution and percentage were reported for problems, obstacles, and solutions for improvement of FECSP in Thai paramedics. Inferential statistics, multiple linear regression, were utilized for analysis of factors affecting perceptions of roles and understanding about FECSP of Thai paramedics.

IBM SPSS Statistics for Windows, Version 26.0 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY, USA: IBM Corp.) was used. All statistical tests were considered statistically significant at P-value ≤.05.

Ethical approval

This study was approved by the institutional review board of Suan Sunandha Rajabhat University, No. COA. 1-006/2021.

RESULTS

Of 382 questionnaires sent, 281 responded (74%). Most respondents were female (61.9%). The average age was 26.09 ± 4.44 years. The average employment period was 1 year (IQR 1-3 years) for most paramedics. The most common crime scenes experienced were traffic accidents (91.1%), physical assaults (56.6%), and suicide attempts (55.5%). Most Thai paramedics (73%) had never received additional training related to forensic science (Table 1).

Mean of overall perceptions of roles about FECSP of this cohort was at the highest level ($\bar{x}$= 4.27, SD = 0.51). (Table 2)

Mean of overall understanding about FECSP of the sample was at the highest level ($\bar{x}$= 4.28, SD = 0.63). (Table 3)

Most paramedics (99.6%) faced problems and obstacles in FECSP. The most reported problems were: no FECSP law (68.7%), no standard FECSP guideline (64.8%), and lack of forensic evidence preservation equipment and collection systems (61.2%). The most commonly reported solutions to improve the practice of FECSP were: standard FECSP guideline development (83.3%), FECSP training program development (82.9%) and the passing of FECSP related laws (Table 4).

Multiple linear regression analysis revealed hospital level was the key factor related to the perceptions of roles about FECSP of Thai paramedics. The average score of a cohort who worked at tertiary hospitals was less than the cohort working at university hospitals (B = -0.220, p-value = 0.018), after controlling for current position and crime scene experience (physical assault, falls from height, poisoning, occupational accident and suspicious death or suspected homicide) (Tables 5 and 6).

Hospital level was also the factor most related with the understanding about FECSP of Thai paramedics, as shown by multiple linear regression analysis. The average score of cohorts who worked at primary or secondary hospitals was less than that of university hospitals (B = -0.197, p-value = 0.022), after controlling for crime scene experience (falls from height and sexual assault) (Tables 7 and 8).

DISCUSSION

Overall, the perception of roles and understanding of FECSP reported in this study were at the highest level, reflecting a good quality of educational institutions providing training in paramedicine. Presently there are only four institutions, namely Navamindradhiraj University, Mahidol University, Mahasarakham University and University of Phayao that provide education and training about roles and understanding of FECSP, even though, most paramedics in this study did not have additional forensic training. Most paramedics in university hospitals were teachers and teacher assistants which had a higher level of perception of roles and understanding of FECSP than ones in tertiary, secondary and primary hospitals, respectively. Although they mainly didn't have experience in the field, due to their skill and knowledge in forensic science and crime scene, their level of perception of roles and understanding of FECSP was higher. Further, consistent with Khamya's study, emergency medical responders (EMRs) at the Poh Teck Tung Foundation in Bangkok mostly did not have additional forensic training, while overall knowledge and understanding, regard to emergency calls management aspect and crime scene preservation aspect were at the highest level, and forensic evidence understanding was at a high level.[6] In addition, the most common problems and hindrances of FECSP the paramedics faced was a lack of an FECSP law and a lack of standard FECSP guidelines for EMRs, emergency medical technicians (EMTs), advanced emergency medical technicians (AEMTs), paramedics, emergency nurse practitioners (ENPs) and emergency physicians (EPs).[7-8] At this moment, no FECSP guideline has been developed in Thailand, comparable to the study by Asci et al. in which there was no proper guideline relating to forensic patients for emergency medical staff and emergency stations in Turkey.[3] EMRs did not clearly recognize the role as well as confronted problems and obstacles in handling the subject, while overall role perception was at a middle level for personnel, as

TABLE 1. Personal and Employment Information (n = 281).

Variables	No.	%
Sex		
Male	107	(38.1)
Female	174	(61.9)
Age (years), mean ± SD	26.09 ± 4.44	
Education level		
Bachelor degree	275	(97.9)
Master degree	5	(1.8)
Doctoral degree	1	(0.4)
Income (per month)		
Less than 15,000 baht	57	(20.3)
15,001 - 20,000 baht	79	(28.1)
20,001 - 25,000 baht	56	(19.9)
25,001 - 30,000 baht	52	(18.5)
30,001 - 35,000 baht	13	(4.6)
35,001 - 40,000 baht	12	(4.3)
More than 40,001 baht	12	(4.3)
Current position		
Teacher/Teacher assistant	18	(6.4)
University employee/State Enterprise	39	(13.9)
Civil servant/Ministry of Public Health officer	106	(37.7)
Employee/Freelance	114	(40.6)
Other	4	(1.4)
Employment period (year), median (IQR)	1	(1 - 3)
Hospital level		
University hospital	104	(37.0)
Tertiary hospital	65	(23.1)
Secondary hospital	70	(24.9)
Primary hospital	20	(7.1)
Private hospital	10	(3.6)
Local Administration	12	(4.3)
Crime scene experience		
Traffic accident	256	(91.1)
Suicide attempt	156	(55.5)
Physical assault	159	(56.6)
Fall from height	150	(53.4)
Shooting	98	(34.9)
Poisoning	98	(34.9)
Occupational accident	114	(40.6)
Electrical accident	111	(39.5)
Burn	86	(30.6)
Drowning	130	(46.3)
Suspicious death/homicide	94	(33.5)
Sexual assault	37	(13.2)
Incised wound	115	(40.9)
Additional forensic training		
No	205	(73.0)
Yes	76	(27.0)

TABLE 2. The perceptions of Thai paramedics regarding their roles in FECSP.

Questions	mean	SD	Level of Understanding/ Awareness
1. Paramedics always remember that lifesaving is more important than forensic considerations.	4.26	0.79	Highest
2. Paramedics should damage the crime scene as little as possible for forensic evidence preservation.	4.72	0.58	Highest
3. Paramedics and team member should not enter the crime scene until the crime scene is safe and controlled by police.	4.84	0.47	Highest
4. Paramedics have a role in recording details of the crime scene and forensic evidence in the patient record.	3.93	1.09	High
5. Paramedics have a role in giving information and advice regarding critical emergency state to prehospital forensic patient.	4.27	0.84	Highest
6. Paramedics have a duty to examine forensic evidence, especially when recording the medical details of the case.	3.68	1.17	High
7. Paramedics have a role in history taking and recording information of forensic patient at the scene, during delivery, history taking, physical examination, treatment at the scene and vital signs, clearly.	4.60	0.66	Highest
8. Paramedics have a role to contact dispatch center for coordination with police officer or authorities involved in case of forensic patient.	4.54	0.75	Highest
9. Paramedics have a role in explanation of required information regarding crime scene examination to forensic doctor and inquiry official.	4.17	0.92	High
10. Paramedics have a role as an advanced life support team leader and has a duty in security check of the team before entering the crime scene.	4.66	0.72	Highest
11. Paramedics often have a role in assisting forensic patient.	3.89	0.99	High
12. Paramedics have an important role in forensic evidence and crime scene preservation as well as often been related to this activity in daily operation.	4.17	0.91	High
13. Paramedics have a role in Chain of Custody.	3.89	1.08	High
14. Paramedics have a role in assisting forensic patient by applying holistic approach, included physical, mental, social and spiritual aspects, according to emergency medicine theory.	4.25	0.91	Highest
15. Overall, what level of a role in forensic evidence and crime scene preservation does paramedic has?	4.15	0.88	High
Overall perception of roles in forensic evidence and crime scene preservation.	4.27	0.51	Highest

TABLE 3. The understanding of FECSP of Thai paramedics.

Questions	mean	SD	Level of Understanding/ Awareness
1. You must control ambulance parking at the scene to be far from skid marks, tire prints or other evidence.	4.32	0.93	Highest
2. From the ambulance, you must use the same walking route to and from the scene to avoid evidence damage.	4.16	0.93	High
3. You are notified about a body found hanging at home. You are the first team arriving the scene, the body found hanging, slightly faced down with the knot at the posterior. You will cut the rope far from the knot and the hanging loop.	3.95	1.34	High
4. You will avoid touching the weapon or moving the object possible to be a clue for forensic patient except only as needed for patient assistance.	4.70	0.59	Highest
5. You must record patient's state and injured person's character when arriving the scene as well as surrounding.	4.48	0.82	Highest
6. You will cut or tear victim's clothes regarding seam to avoid mark penetrated from object and avoid cutting and tearing at the mark.	4.38	1.02	Highest
7. You will not shake the clothes but collect all the clothes in the paper bag, instead of plastic bag due to evidence change and you will not give the clothes to unknown people, even victim's family.	4.40	0.94	Highest
8. You will preserve tissue or other parts for the benefit of forensic examination.	4.08	1.17	High
9. If you find bullet at the scene, you will put it in the container padded with cotton or protection sheet to prevent any mark on the bullet and you will keep the evidence until giving to the police.	3.63	1.45	High
10. You will record victim's dying declaration and report to EMS director and police officer.	3.96	1.20	High
11. You will make a report recording all the change EMS team make to the scene and physical evidence, to crime scene investigator and police officer.	4.12	1.11	High
12. You will keep all the irrelevant ones away from the patient and the scene.	4.57	0.79	Highest
13. You will not smoke or eat at the scene.	4.77	0.66	Highest
14. You will not make any comment relating the case.	4.63	0.82	Highest
15. What level do you have for overall understanding of forensic evidence and crime scene preservation?	4.12	0.89	High
Overall understanding of forensic evidence and crime scene preservation.	4.28	0.63	Highest

TABLE 4. The problems, obstacles and solutions for improvement of FECSP.

Problems and Obstacles/Solutions	No.	%
Problems and obstacles of forensic evidence and crime scene preservation	280	(99.6)
Not knowing the detail of the role.	103	(36.7)
No standard guidelines for forensic evidence and crime scene preservation.	182	(64.8)
Lack of knowledge, education and training of forensic evidence and crime scene preservation.	143	(50.9)
No law of forensic evidence and crime scene preservation.	193	(68.7)
Insufficient information of forensic evidence and crime scene preservation.	137	(48.8)
Lack of device in forensic evidence and crime scene preservation, systematically.	172	(61.2)
Other problems and obstacles.	7	(2.5)
Solutions for improvement of forensic evidence and crime scene preservation	281	(100.0)
Development of standard guideline of forensic evidence and crime scene preservation.	234	(83.3)
Development of training program of forensic evidence and crime scene preservation.	233	(82.9)
Legislation of forensic evidence and crime scene preservation.	206	(73.3)
Development of connection systems and communication between police officer and EMS team.	193	(68.7)
Other solutions.	6	(2.1)

TABLE 5. Univariable analysis regarding the perceptions of roles about FECSP of Thai paramedic.

Factors	B	SE(B)	β	p-value
Sex				
Male	Reference			
Female	-0.059	0.063	-0.056	0.348
Age (years)	0.003	0.007	0.027	0.650
Education level				
Graduate and above	Reference			
Undergraduate	-0.009	0.212	-0.003	0.965
Income (per month)				
Less than 15,000 baths	Reference			
15,001 - 20,000 baths	0.044	0.089	0.039	0.619
20,001 - 25,000 baths	-0.066	0.097	-0.052	0.493
More than 25,000 baths	-0.062	0.087	-0.056	0.478
Current position				
Teacher/Teacher assistant/ University employee/State Enterprise	Reference			
Civil servant/Ministry of Public Health officer	-0.168	0.084	-0.159	0.046
Employee/Freelance/Other	-0.170	0.082	-0.164	0.040
Employment period (year)	-0.017	0.013	-0.082	0.169

TABLE 5. Univariable analysis regarding the perceptions of roles about FECSP of Thai paramedic. (Continue)

Factors	B	SE(B)	β	p-value
Hospital level				
University hospital	Reference			
Tertiary hospital	-0.172	0.081	-0.142	0.034
Primary/Secondary hospital	-0.113	0.074	-0.103	0.127
Private hospital/ Local Administration	-0.094	0.120	-0.049	0.432
Crime scene experience				
Traffic accident	0.026	0.108	0.014	0.813
Suicidal attempt	0.082	0.061	0.080	0.182
Physical assault	0.136	0.061	0.131	0.028
Falls from height	0.192	0.060	0.187	0.002
Shooting incident	0.038	0.064	0.035	0.557
Poisoning	0.169	0.064	0.158	0.008
Occupational accident	0.169	0.062	0.162	0.006
Electrical accident	0.112	0.062	0.107	0.074
Burn	0.087	0.066	0.078	0.193
Drowning	0.066	0.061	0.064	0.282
Suspicious death/Suspected homicide	0.137	0.064	0.126	0.035
Sexual assault	0.145	0.090	0.096	0.109
Incised wound	0.083	0.062	0.080	0.182
Additional forensic training	0.012	0.069	0.010	0.864

B = Regression coefficient, SE(B) = Standard error of B, β = Standardized regression coefficient

TABLE 6. Multivariable analysis regarding the perceptions of roles about FECSP of Thai paramedic.

Factors	B	SE(B)	β	p-value
Current position				
Teacher/Teacher assistant/ University employee/State Enterprise	Reference			
Civil servant/Ministry of Public Health officer	-0.039	0.098	-0.037	0.692
Employee/Freelance/Other	-0.109	0.086	-0.106	0.204
Hospital level				
University hospital	Reference			
Tertiary hospital	-0.220	0.093	-0.181	0.018
Primary/Secondary hospital	-0.119	0.080	-0.108	0.140
Private hospital/ Local Administration	-0.016	0.121	-0.008	0.897
Crime scene experience				
Physical assault	0.042	0.071	0.041	0.553
Fall from height	0.107	0.071	0.105	0.133
Poisoning	0.073	0.073	0.068	0.318
Occupational accident	0.060	0.075	0.058	0.422
Suspicious death/Suspected homicide	0.097	0.068	0.090	0.154

B = Regression coefficient, SE(B) = Standard error of B, β = Standardized regression coefficient, Constant = 4.255, R^2 = 0.086

TABLE 7. Univariable analysis regarding the understanding about FECSP of Thai paramedic.

Factors	B	SE(B)	β	p-value
Sex				
Male	Reference			
Female	0.111	0.074	0.090	0.134
Age (years)	0.003	0.008	0.020	0.739
Education level				
Graduate and above	Reference			
Undergraduate	-0.004	0.248	-0.001	0.988
Income (per month)				
Less than 15,000 baht	Reference			
15,001 - 20,000 baht	-0.064	0.105	-0.048	0.543
20,001 - 25,000 baht	-0.125	0.113	-0.083	0.272
More than 25,000 baht	-0.059	0.102	-0.046	0.563
Current position				
Teacher/Teacher assistant/ University employee/State Enterprise	Reference			
Civil Servant/Ministry of Public Health officer	-0.036	0.099	-0.029	0.720
Employee/Freelance/Other	-0.003	0.097	-0.003	0.974
Employment period (year)	-0.011	0.015	-0.045	0.456
Hospital level				
University hospital	Reference			
Tertiary hospital	-0.108	0.094	-0.076	0.254
Primary/Secondary hospital	-0.195	0.086	-0.152	0.024
Private hospital/ Local Administration	-0.031	0.140	-0.014	0.823
Crime scene experience				
Traffic accident	0.036	0.126	0.017	0.777
Suicide attempt	0.072	0.072	0.060	0.320
Physical assault	0.134	0.072	0.111	0.063
Fall from height	0.144	0.071	0.120	0.045
Shooting	0.045	0.075	0.036	0.548
Poisoning	-0.004	0.075	-0.003	0.958
Occupational accident	0.104	0.073	0.085	0.155
Electrical accident	0.110	0.073	0.090	0.134
Burn	-0.018	0.078	-0.014	0.814
Drowning	-0.040	0.072	-0.034	0.576
Suspicious death/homicide	0.051	0.076	0.040	0.500
Sexual assault	0.209	0.105	0.118	0.048
Incised wound	0.015	0.073	0.013	0.833
Additional forensic training	0.015	0.081	0.011	0.851

B = Regression coefficient, SE(B) = Standard error of B, β = Standardized regression coefficient

TABLE 8. Multivariable analysis regarding the understanding about FECSP of Thai paramedic.

Factors	B	SE(B)	β	p-value
Hospital level				
University hospital	Reference			
Tertiary hospital	-0.135	0.094	-0.095	0.152
Primary/Secondary hospital	-0.197	0.085	-0.153	0.022
Private hospital/ Local Administration	0.021	0.140	0.009	0.881
Crime scene experience				
Fall from height	0.126	0.072	0.105	0.082
Sexual assault	0.208	0.106	0.118	0.051

B = Regression coefficient, SE(B) = Standard error of B, β = Standardized regression coefficient, Constant = 4.294, R^2 = 0.047

Sadudee reported.[9] Regarding solutions for improving FECSP, the paramedics most wanted development of standard guidelines for FECSP and FECSP training programs, agreeing with the study by Saenkaew showing the best crime scene investigation improvement was annual training and guideline development.[10] To improve emergency nurses' practice, hospitals should focus on and support forensic tasks by providing training in forensic medicine and forensic science, as suggested in Suwanchasri's study.[11] This paper would encourage the National Institute for Emergency Medicine to develop Forensic Evidence and Crime Scene Preservation training course together with launching national standard FECSP law and guidelines. In Thailand, the multidisciplinary team involved with crime scene, including crime scene investigators, forensic medicine doctors, pathologists and forensic anthropologists.[12] Paramedics were required only if there is injury necessary for emergency treatment and hospital admission. Sexual assault was common in Thailand and counted as a criminal case. Sperm detection in specimen collection after male sexual assault was essential in court.[13-14] Therefore, knowledge of forensic evidence preservation in sexual assault case was crucial for paramedics to prevent forensic evidence damage and investigation compromise.

The most important limitation of this study was that of potential insufficient experience on the part of survey respondents, as their average employment period was only 1 year. Hence, information regarding problems, hindrances and solutions for FECSP improvement might not be representative, because they had less experience about problems and hindrances of FECSP. Secondly, no e-mail addresses of the older generation of paramedics was in the database, hence they could not be included in this study. Thirdly, the second and third parts of the questionnaire regarding the perceptions of roles and understanding about FECSP of Thai paramedics were positive questions only because most paramedics might choose without consideration, possibly leading to bias. Hence, the highest levels of the perceptions of roles and understanding about FECSP of Thai paramedics were presented. In the future study, both positive and negative questions should be set to get rid of this limitation.

CONCLUSION

Thai paramedics had overall perceptions of the roles and understanding of FECSP at the highest level. Hospital level was the factor related to the perceptions of the roles of Thai paramedics, with the group working in tertiary hospitals scoring less than those at university hospitals. The factor related to the understanding of FECSP of Thai paramedics was hospital level, as the scores of those working in primary or secondary hospitals were lower than those at university hospitals. The professional council, NIEMS and educational or training institutes should focus on roles of paramedics in FECSP, by developing standard guidelines and FECSP training for paramedics.

ACKNOWLEDGEMENTS

The present study was supported by Assistant Professor Police Lieutenant General Narong Kulnides Ph.D, my thesis adviser, who suggested publication of the

study. The authors thank the experts of the Department of Forensic Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University for validating and improving our research tools; The National Institute for Emergency Medicine for their effort in obtaining the contact information of the certified paramedics used in the study; The Research Facilitation Division, Faculty of Medicine Vajira Hospital, Navamindradhiraj University for statistical analysis guidance as well as providing third and fourth-year paramedicine students who assisted in collecting the data and monitoring questionnaire responses. The authors were grateful to Institute for Research and Development and Suan Sunandha Rajabhat University for proofreading the manuscript regarding universally standard research methodology and ethics and also thanked Aniwat Berpan MD for correcting English for the present study.

Conflicts of interest: There are no conflicts of interest.

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The Predictive Factors Associated with Longer Operative Time in Single-Incision Laparoscopic Cholecystectomy

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ABSTRACT

Objective: The difficult laparoscopic cholecystectomy (LC) is defined as the presence of one of the following conditions including prolonged operative time, conversion to open cholecystectomy or significant blood loss. At present, there is no evidence of predictive factors related to longer operative time in single-incision laparoscopic cholecystectomy (SILC). The aim of this study is to determine predictive factors associated with longer operative time in SILC procedure.

Materials and Methods: A retrospective study was conducted of patients with benign gallbladder disease who underwent SILC in Thammasat University Hospital between October 2014 and December 2020. Patients' records were reviewed. Primary outcomes were preoperative predictive factors associated with DSLC. Secondary outcomes were perioperative and 3-month postoperative adverse outcomes.

Results: 592 SILC procedures were categorized as 80 DSLC and 512 non-difficult SILC (NDSLC). The median (interquartile range) of operative time in all SILC procedure is 48 (38, 62) minutes. The threshold of operative time of difficult SILC was 72 minutes. The multivariate analysis indicated 5 significant predictive factors. Obesity (body mass index > 25 kg/m^2)) and abdominal pain reflected the difficulty of SILC procedures ($p = 0.041$ and $p = 0.009$). Calcified gallbladder showed the highest RR of 14.08 ($p = 0.011$). Contracted gallbladder and chronic cholecystitis were also predictive factors with RR of 13.79 and 3.64, respectively ($p < 0.001$ and $p = 0.007$).

Conclusion: Obesity, abdominal pain, chronic cholecystitis, contracted gallbladder and calcified gallbladder were preoperative predictive factors. Surgeons should perform the SILC procedure carefully when predictive factors are identified.

Keywords: Laparoscopic cholecystectomy; single-incision laparoscopic cholecystectomy; predictive factors; difficult laparoscopic cholecystectomy (Siriraj Med J 2021; 73: 672-679)

INTRODUCTION

Laparoscopic cholecystectomy (LC) can reduce pain and surgical scar after surgery.[1] Single incision laparoscopic cholecystectomy (SILC) is the LC procedure that has the least number of incisions. It was reported for the first time by Navara et al.[2] without difference in the overall rate of complications, including biliary tract injury, bile leakage and wound infection, when compared with conventional LC. The cosmetic result of SILC was superior to that of conventional LC.[3] However, some reports revealed that SILC had a higher incidence of incisional hernia than conventional LC.[4,5] The SILC

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http://dx.doi.org/10.33192/Smj.2021.86

procedure may not be familiar to the surgeon which may take longer operative time and higher perioperative complication rates than conventional LC.[6]

There were a lot of predictive factors of difficult LC in conventional LC procedure.[6-12] However, there was no report about predictive factors of difficult SILC, which may be different from conventional LC due to a different step of the procedure, surgeon's skill and familiarity. The definition of difficult LC is varied by operative time, bile duct injury, vascular injury, open conversion. The operative time is the important determinant to categorized the difficulty of LC procedure.[6,8,11]

The aim of our study was to investigate predictive factors affecting the difficulty of SILC. The predictive factors included baseline characteristic and demographic data, clinical presentation, and preoperative ultrasound finding.[6-20] The predictive factors are beneficial to caution surgeons, especially those in residency training, and to determine the patient's prognosis before SILC surgery.[21]

MATERIALS AND METHODS

Study design and participants

Retrospective data of patients who underwent SILC in Thammasat University Hospital between October 2014 and December 2020 were reviewed. The inclusion criteria were patients who had indications for cholecystectomy, including: (1) symptomatic gallstone, (2) acute cholecystitis, (3) chronic cholecystitis, (4) gallbladder polyp size more than 1 centimeters or increasing size during imaging surveillance,[22] (5) calcified gallbladder,[23] and (6) biliary dyskinesia.[24] The exclusion criteria included: (1) the patients with malignant gallbladder or suspected gallbladder malignancy by preoperative presentation and imaging, (2) an LC procedure which required additional intraoperative procedures, including choledocholithotomy, choledochoscope or cholangiography and, (3) patients who failed to follow up in the 3 months after the SILC procedure. The patient's characteristics, clinical presentation, pre-operative ultrasound finding, and operative time were collected.

The criteria to categorize as difficult SILC procedure and outcomes

The difficult SILC is defined as the presence of one of the following conditions including prolonged operative duration, conversion from LC to open cholecystectomy or significant blood loss, biliovascular injury. The incidence of significant blood loss and biliovascular injury of our study is very low. So, the operative time which is the important determinant to categorize the difficulty of LC procedure were used in this study. SILC procedure was performed as a standard technique by a single surgeon who was highly experienced in the LC procedure (more than 1,000 cases of LC in 10 years). The operative time is the determinant to categorize the difficulty of LC procedure.[6,8,11,13] Difficult LC was identified for each surgeon when the operative time for a procedure exceeded 1.5 times the surgeon's individual base time. Patients were classified into two groups: non-difficult SILC (NDSLC) (operative time <1.5 times the surgeon's individual operative time) and difficult SILC (DSLC) (operative time ≥1.5 times the surgeon's individual operative time).[6]

The primary outcomes objectives were pre-operative predictive factors which included (1) baseline characteristic and demographic data, including old age, male gender, obesity by body mass index ((BMI (kilograms (kgs) per square meters (m^2) ≥ 25 kg/m^2, diabetes mellitus (DM), dyslipidemia (DLP) (2) the clinical presentation, including symptomatic gallstones, suspected acute cholecystitis (acute cholecystitis by clinical diagnosis at the same admission of SILC operation), history of acute cholecystitis (subside cholecystitis), common bile duct (CBD) stone, history of endoscopic retrograde cholangiopancreatography (ERCP), gallstone (GS) pancreatitis, GS cholangitis, acute cholecystitis and (3) preoperative ultrasound findings including thickening of gallbladder wall, definited acute cholecystitis, chronic cholecystitis, gangrenous cholecystitis, adenomyosis, gallbladder polyps, contracted gallbladder, calcified gallbladder, CBD dilatation. Symptomatic gallstones were included dyspepsia and abdominal pain at any time during follow-up before the SILC operation. The dyspepsia was a non-specific pain in the epigastrium area. The abdominal pain refers to dull aching in the upper part abdomen which specific to biliary colic without evidence of pancreatitis, cholangitis, or cholecystitis. The chronic cholecystitis from the ultrasound imaging was used the clinical correlation to establish the diagnosis of U/S. The SILC was performed via transumbilical incision. The Calot's triangle has been identified for the exposed cystic duct and artery to obtain a critical view of safety. After ligating of cystic duct and cystic artery by clip, the gallbladder was dissected from the liver bed and removed through Alexis® retractor. The pathologic studies were confirmed all of the ultrasonographic results reports. Intra-op complications including bile leakage and cystic artery injury were collected as secondary outcomes objectives

Post-operative care and follow-up

In postoperative care, patients were monitored for

postoperative complications. Most of the patients were discharged within 24 hours after surgery and followed up 2 weeks, 6 weeks, and 3 months postoperatively. The post-operative surgical complications, including infected wound surgical site infection (SSI) and incisional hernia were collected and analyzed to identify adverse outcomes associated with difficult SILC which depend on the operative time.[7]

Sample size calculation

The strong predictive factors for difficult SILC including BMI, history of acute cholecystitis and gallbladder wall thickening were used to calculated sample size. Retrospective data of predictors that affected the difficulty of SILC (measured by operative time) were used to calculate the power of the sample size under 0.05 alpha error and 0.02 beta error.[6,7,11,13,15-20] The power calculations were more than 80% at the total number of 592 procedure.[25]

Statistical analysis

The associations between baseline characteristic and demographic data, clinical presentation, and preoperative predictive factors were assessed and presented in percentage or mean with standard deviation (SD). Student's t-test was used for analysis of independent continuous variables and the χ^2 test for dependent categorized variables. The predictors of difficult SILC were tested using multivariate logistic regression. Relative risk (RR) and 95% confidence interval (CI) were reported. P <0.05 was considered significant. All the statistical analyses were performed with STATA/SE 15.1 for Mac (Stata Corp LP, TX, USA). The study process and report follow the strengthening the reporting of observational studies in epidemiology (STROBE) statement on reports of cohort studies.[26]

RESULTS

A total of 592 SILC procedures were included in this study. The mean operative time with SD was 53.44 ± 22.86 minutes. The distribution of operative time data was an asymmetric pattern. The median (interquartile range) of operative time in all SILC procedure is 48 (38, 62) minutes. So, the threshold of DSLC by operative time was 48 x 1.5 = 72 minutes.[6] 512 (86.5%) patients were classified as NDSLC and 80 (13.5%) patients were classified as DSLC.[6] None of the SILC procedures required conversion to open cholecystectomy.

Baseline characteristic and demographic data between NDSLC and DSLC are shown in Table 1. DSLC was more often associated with male gender. (p = 0.015). The DSLC group had higher BMI than the NDSLC group (27.74 ± 5.70 vs 25.31 ± 4.42, p < 0.001). The weight and height parameters were higher in the DSLC group when compared with the NDSLC group. The distribution of clinical presentation is given in Table 2.

Multivariate logistic regression analysis showed 5 significant predictive factors (Table 3). BMI and clinical presentation of abdominal pain were statistically significant predictive factors that influenced the difficulty of SILC procedures (95%CI 0.002 – 0.084, p = 0.041 and RR 2.35, 95%CI 1.236 – 4.466, p = 0.009, respectively). The preoperative ultrasound findings, which were significant predictive factors are presented in Table 3. Calcified gallbladder showed the highest RR of 14.08 (RR 14.08, 95%CI 1.822 – 108.771, p = 0.011). Contracted gallbladder and chronic cholecystitis were also predictive factors with RR of 13.79 and 3.64, respectively (RR = 13.79, 95%CI 14.512 – 42.193, p < 0.001 and RR = 3.64, 95%CI 1.413 – 9.403, p = 0.007, respectively).

The adverse outcomes of SILC procedures were reported in Table 4. The adverse outcomes which were more frequent in DSLC procedure included bile leakage, cystic artery injury and wound infection. At the end of the three-month follow-up period, the complication was a single case (0.2%) of incisional hernia. The intraoperative bile leakage was not associated with wound infection. In addition, the wound infection was not related to incisional hernia.

DISCUSSION

Our study demonstrated high BMI as the one of predictive factor for difficult SILC procedure. Recent studies have reported that high BMI is associated with difficult LC.[7,11,15,17,18] Obesity increases abdominal wall thickness and mesenteric fat volume.[27] Hassan technique for single-port insertion may be difficult when a thick abdominal wall and pendulous abdomen cause the downward displacement of umbilicus to the level of the pubic symphysis. So, longer operating time is required to encounter the thick abdominal wall and the difficulty of abdominal wall closure when compared with thin abdominal wall. The incidence of incisional hernia in SILC at our study was found to be 1 out of all 592 patients (0.17%). Previous studies report incisional hernia following SILC surgery as well as wound infection related to obesity due to a thick layer of fat on the abdominal wall.[28] However, there are only 8 wound infections and 1 incisional hernia reported in our study. There is no correlation between wound infection, incisional hernia, and BMI in our study.

Abdominal pain was found to be associated with

TABLE 1. Comparison of patients' demographic and clinical data between NDSLC and DSLC groups.

	NDSLC (n1 = 512)	DSLC (n2 = 80)	P-value
Age (years ± SD)	58.68 ± 14.16	61.06 ± 15.31	0.167
Male gender	149 (29.1%)	34 (42.5%)	0.015
Weight (kg ± SD)	64.74 ± 13.50	72.46 ± 13.74	<0.001
Height (cm ± SD)	159.57 ± 8.56	161.95 ± 7.09	0.019
BMI (kg/m^2 ± SD)	25.31 ± 4.42	27.74 ± 5.70	<0.001
Underlying disease			
DM	102 (19.92%)	17 (21.25%)	0.782
HTN	203 (39.65%)	36 (45.00%)	0.364
DLP	212 (41.41%)	32 (40%)	0.812
CAD	14 (2.73%)	3 (3.75%)	0.613
Thalassemia	12 (2.34%)	3 (3.75%)	0.456
CKD	10 (1.95%)	2 (2.50%)	0.746
Asthma	9 (1.76%)	1 (1.25%)	0.743
Other	48 (9.38%)	12 (15.00%)	0.121
Blood thinner used			
Antiplatelet	57 (11.13%)	9 (11.25%)	0.975
Anticoagulant	4 (0.75%)	0 (0%)	0.427
Median operative time (minutes)	46	94.5	<0.001

Abbreviations: kg, kilograms; m, meters; cm, centimeters; NDSLC, non-difficult single-port laparoscopic cholecystectomy; DSLC, difficult single-port laparoscopic cholecystectomy; SD, standard deviation; BMI, body mass index; DM; diabetes mellitus; HTN, hypertension; DLP, dyslipidemia; CAD, coronary artery disease; CKD, chronic kidney disease.

the difficult SILC. Abdominal pain is more present in patients who categorized as DSLC (55%). Abdominal pain is known to be symptomatic of gallstones and multiple episodes of cholecystitis.[6,17,18] Recurrent episodes of inflammation can create adhesion around peritoneal cavity which increase the difficulty of the SILC procedure.[6,9,16]

Chronic cholecystitis, contracted and calcified gallbladder were associated with DSLC procedure due to long operative time. These predictive factors which can be identified preoperatively by ultrasound were caused by chronic, repeated episodes of inflammation.[9] Previous studies have reported association between chronic cholecystitis and the difficulty of LC.[29,30] That contracted gallbladder is related to difficult LC procedure has also been reported in previous studies.[31,32] The calcification of the gallbladder wall is a variant of chronic cholecystitis and inflammatory scarring of the wall. Likewise with abdominal pain symptom, the chronic inflammation parameters lead to surrounding adhesion of Calot's triangle and gallbladder wall.[7,11,13,17,18,20] Thus, chronic cholecystitis, contracted gallbladder and calcified gallbladder on preoperative ultrasound finding can predict the difficulty of SILC procedure.

A lot of previous studies have reported relationships between gallbladder wall thickening ≥ 4 mm and the difficulty of SILC.[7,11,13,17,18,20] In our study, we collected data of gallbladder wall thickening and cholecystitis factors. So, we did not compare DSLC procedure with the factor of isolated gallbladder wall thickening without any evidence of inflammation on clinical and imaging results. Previous studies have revealed that cholecystitis is

TABLE 2. Clinical presentation and preoperative ultrasound finding between NDSLC and DSLC groups.

Variables	NDSLC (n1 = 512)	DSLC (n2 = 80)	P-value
Clinical presentation			
Dyspepsia	495 (96.68%)	79 (98.75%)	0.316
Abdominal pain	199 (38.87%)	44 (55.00%)	0.006
History of acute cholecystitis	25 (4.88%)	13 (16.25%)	<0.001
CBD stone	15 (2.93%)	12 (15.00%)	<0.001
History of ERCP	13 (2.54%)	10 (12.5%)	<0.001
GS pancreatitis	6 (1.17%)	4 (5.00%)	0.013
GS cholangitis*	3 (0.59%)	3 (3.75%)	0.009
Suspected acute cholecystitis**	0 (0%)	3 (3.75%)	<0.001
Pre-operative ultrasound finding			
GS	492 (96.09%)	80 (100%)	0.072
Gallbladder wall thickening ≥ 4 mm	51 (9.96%)	21 (26.25%)	<0.001
Definite acute cholecystitis***	2 (0.39%)	2 (2.50%)	0.032
Gangrenous cholecystitis	0 (0%)	1 (1.25%)	0.011
Chronic cholecystitis****	21 (4.10%)	12 (15.00%)	<0.001
Adenomyosis	30 (5.86%)	6 (7.50%)	0.568
Gallbladder polyp	45 (8.79%)	5 (6.25%)	0.447
Contracted gallbladder	7 (1.37%)	15 (18.75%)	<0.001
Calcified gallbladder	2 (0.39%)	5 (6.25%)	<0.001
CBD dilatation	8 (1.56%)	8 (10.00%)	<0.001

*Systemic inflammation (fever and/or chills or laboratory data) + cholestasis (Jaundice or Laboratory data) + imaging (biliary dilatation or evidence of the etiology on imaging), **Clinical diagnosis (local signs of inflammation (murphy's sign or right upper quadrant mass/pain/tenderness) + systemic signs of inflammation (fever or elevated C-reactive protein or elevated white blood cell count), *** Ultrasound finding characteristic diagnosis, ****Gallbladder wall thickening ≥ 4 mm with non-distended gallbladder with clinical diagnosis.

Abbreviations: NDSLC, non-difficult single-port laparoscopic cholecystectomy; DSLC, difficult single-port laparoscopic cholecystectomy; CBD, common bile duct, ERCP, Endoscopic retrograde cholangiopancreatography; GS, gallstones; mm, millimeters.

related to the difficulty of LC procedure.[6,14,16-19] However, the incidence of acute cholecystitis and gangrenous cholecystitis in this study was very low.

The adverse outcomes of the study, which significantly related to DSLC included intraoperative bile leakage and cystic artery injury. The DSLC from adhesion and inflammation of Calot's triangle had a high risk of major biliovascular injury during SILC.[6,7,17] In addition, biliovascular injury may have increased operative time for controlling bile leakage or stopping bleeding. Wound infections were reported more in DSLC procedure but there was no correlation between wound infection and intraoperative biliary leakage. Cystic artery injury and bile leakage can be managed via laparoscopic technique without open conversion. Three-month follow-up demonstrated one patient with incisional hernia without incarceration. Nevertheless, the DSLC procedure was not associated with incisional hernia. The limitations of the study included the bias inherent in the retrospective nature of the design. In addition, the operative time, intraoperative complication and open conversion surgery was related to the surgeon's

TABLE 3. Multivariate analysis of influencing predictive factors on difficulty of SILC procedures.

Variables	Relative risk (RR)	95% Confidence interval (CI)	P-value
Male gender	0.79	0.419 – 1.502	0.477
Weight (kg)	N/A	0.029 - 0.004	0.136
Height (cm)	N/A	0.003 – 0.023	0.131
Obesity (BMI ≥ 25 kg/m^2)	1.72	1.125 – 2.639	0.041[a]
Clinical presentation			
Abdominal pain	2.35	1.236 – 4.466	0.009[a]
History of acute cholecystitis	1.82	0.616 – 5.406	0.277
CBD stone	2.76	0.431 – 17.660	0.283
History of ERCP	0.62	0.063 – 6.029	0.679
GS pancreatitis	2.59	0.286 – 23.399	0.397
GS cholangitis*	2.35	0.235 – 23.524	0.467
Suspected acute cholecystitis**	N/A	N/A	N/A
Pre-operative ultrasound finding			
Gallbladder wall thickening ≥ 4 mm	1.44	0.657 – 3.154	0.362
Definite acute cholecystitis***	N/A	N/A	N/A
Gangrenous cholecystitis	N/A	N/A	N/A
Chronic cholecystitis****	3.64	1.413 – 9.403	0.007[a]
Contracted gallbladder	13.79	4.512 – 42.193	< 0.001[a]
Calcified gallbladder	14.08	1.822 – 108.771	0.011[a]
CBD dilatation	3.92	0.637 – 24.133	0.140

*Systemic inflammation (fever and/or chills or laboratory data) + cholestasis (Jaundice or Laboratory data) + imaging (biliary dilatation or evidence of the etiology on imaging), **Clinical diagnosis (local signs of inflammation (murphy's sign or right upper quadrant mass/pain/tenderness) + systemic signs of inflammation (fever or elevated C-reactive protein or elevated white blood cell count), *** Ultrasound finding characteristic diagnosis, ****Gallbladder wall thickening ≥ 4mm with non-distended gallbladder.

Abbreviations: N/A, not applicable; kg, kilograms; m, meters; cm, centimeters; BMI, body mass index; a P < 0.05, statistically significant

TABLE 4. Adverse outcomes between NDSLC and DSLC groups.

Variables	NDSLC (n1 = 512)	DSLC (n2 = 80)	SUM (n=592)	P-value
Intraoperative complication				
Intraoperative bile leakage	0 (0%)	1 (1.25%)	1 (0.17%)	0.011
Cystic artery injury	0 (0%)	1 (1.25%)	1 (0.17%)	0.011
Other critical adverse events*	0 (0%)	0 (0%)	0 (0%)	
Post-operative complication				
Wound infection	4 (0.78%)	4 (5.00%)	8 (1.35%)	0.002
Incisional hernia	1 (0.20%)	0 (0%)	1 (0.17%)	0.692

*common hepatic duct, common bile duct, hepatic artery proper injury.

Abbreviations: NDSLC, non-difficult single-port laparoscopic cholecystectomy; DSLC, difficult single-port laparoscopic cholecystectomy.

experience (operator dependent). SILC may not be recommended if performed by a relatively inexperienced laparoscopic surgeon or trainee. Three-month follow-up period cannot represent the long-term complications such as incisional hernia.

The significant preoperative predictive factors for DSLC included BMI (obese), abdominal pain symptom, chronic cholecystitis, contracted gallbladder, and calcified gallbladder.

CONCLUSION

DSLC depends on individual operative time and experience of surgeons. The predictive factors which determine the difficulty of SILC procedure were concordant with conventional LC. Obesity, abdominal pain, chronic cholecystitis, contracted and calcified gallbladder were significant preoperative predictive factors for DSLC. Surgeons should perform the SILC procedure carefully by surgeon who was highly experienced in the LC procedure when predictive factors are identified. Wound infection and biliovascular injury were the major adverse outcomes of the DSLC procedure.

ACKNOWLEDGEMENT

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Clinical Outcomes of Extracranial Germ Cell Tumors: A Single Institute's Experience

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ABSTRACT

Objective: To determine the clinical features and treatment outcomes of pediatric extracranial germ cell tumor (EGCT) in Thailand.

Materials and Methods: A retrospective chart review of children under 15 years old with newly diagnosed EGCT who were treated at Faculty of Medicine Siriraj Hospital from January, 2004 to December, 2013 was conducted.

Results: Forty-four patients were included in the study. The median age at diagnosis was 1.74 years (1 day-14.7 years) with the median follow up time of 6.9 years (14 days-15.2 years). Twenty-eight patients (64%) had extragonadal tumor. The most common primary tumor location was the sacrococcygeal area. Majority of the patients (61%) had malignant EGCT; yolk sac tumor was the most common diagnosis. Six patients (14%) had stage IV disease. Forty patients (91%) underwent surgery; 27 patients (61%) received chemotherapy. Thirty-eight patients (86%) achieved remission; 3 patients (7%) subsequently relapsed at a median time of 1 year. Eight patients (18%) died, mostly from tumor progression. The 5-year event-free survival (EFS) and overall survival (OS) rate were 78.3% and 81.1%, respectively. Patients achieving total tumor removal had significantly better 5-year EFS and OS. Cox regression analysis revealed that the adequacy of surgery was the only prognostic factor for survival.

Conclusion: The survival rate of pediatric EGCT in our study was relatively favorable, but still inferior to that of developed countries. Novel therapy may be warranted for those patients who are unresponsive to the current treatment.

Keywords: Extracranial germ cell tumor, EGCT, survival rate, treatment outcome, Thailand (Siriraj Med J 2021; 73: 680-686)

INTRODUCTION

Germ cell tumor (GCT) is a rare tumor, accounting for 3% of childhood cancers.[1] Extracranial germ cell tumor (EGCT) is more common than intracranial germ cell tumor (IGCT), and more than half of EGCT was extragonadal in origin[1]. EGCT can be classified based on histological features into 2 categories: teratoma and malignant GCT. The clinical manifestations are varied, depending on the location of the tumor. EGCT is found to be associated with several genetic syndromes causing gonadal dysgenesis such as Klinefelter syndrome, Turner syndrome, and Swyer syndrome.[2-4] Those with EGCT appear to respond well to the treatment and can attain long term remission. The mainstay of treatment of EGCT is surgery, although chemotherapy may be beneficial in some cases which harbor a malignant component. The

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http://dx.doi.org/10.33192/Smj.2021.87

outcome of EGCT in developed countries was relatively favorable.[5] Previous study in Thailand demonstrated the 5-year overall survival (OS) rate of pediatric germ cell tumor (GCT) of 70.6%; however, this study included both IGCT and EGCT.[6] The clinical information regarding Thai patients with EGCT has been scarce. Our study aimed to determine the clinical features and outcomes of pediatric EGCT in one of the tertiary centers in Thailand.

MATERIALS AND METHODS

This retrospective study was conducted in patients diagnosed with EGCT at the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, from January 2004 to December 2013. All patients with newly diagnosed EGCT during the study period were recruited; those who refuse the treatment were further excluded. The diagnosis of EGCT was established based on clinical features, tumor markers, and radiographic findings. Patients who had normal serum tumor markers must have a histopathology result to confirm a diagnosis of EGCT. The clinical staging of testicular, ovarian, and extragonadal GCT was determined by the Children's Oncology Group staging system.[7,8] Surgery was a primary treatment for resectable tumors. Those who had an unresectable tumor received neoadjuvant chemotherapy consisting of cisplatin, etoposide, and bleomycin (PEB) before surgery.[9] Patients with teratoma were treated with surgery solely. However, those children with immature teratoma (IT) either greater than stage II or grade III tumor may have received PEB upon physician discretions. Among patients with nonteratomatous EGCT, those with stage I testicular GCT did not receive adjuvant chemotherapy after surgery, while other patients were subsequently treated with adjuvant PEB. The responses to the treatment were classified using RECIST guidelines.[10] This retrospective study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 380/2020).

Statistical analysis

The collected data were analyzed using SPSS Statistic version 22.0 for Windows (SPSS Inc., Chicago, IL). Demographic data were described using mean, medians, and percentage. The Kaplan-Meier survival curve was used to demonstrate the OS and event-free survival (EFS) rate of EGCT patients; event was defined as tumor relapse or death. The patients' age at diagnosis, stage, histopathology subtype, site of tumor, and adequacy of surgery were analyzed using the Cox regression analysis to determine the predictors of survival. The adjusted hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. A p-value of <0.05 was regarded as being statistically significant.

RESULTS

Forty-seven patients were diagnosed with EGCT; 3 patients were excluded due to treatment refusal. There were 44 patients included in this study, with the median age at diagnosis of 1.74 years (range 1 day-14.7 year). Twenty-eight patients (64%) had extragonadal tumor; sacrococcygeal area was the most common primary tumor location. Majority of the patients (61%) had malignant EGCT. Yolk sac tumor (YST) was the most common histopathological diagnosis, followed by mature teratoma (MT) and mixed GCT. Of all 10 patients with mixed GCT, MT with a component of YST was the most common diagnosis. The demographic data, clinical features, histopathology and staging of EGCT are presented in Table 1. Three patients had underlying genetic diseases, including 1 Down syndrome (DS) with stage I retroperitoneal IT grade II, 1 DS with stage I ovarian dysgerminoma, and 1 Cornelia de Lange syndrome (CdLS) with stage III sacrococcygeal mixed GCT comprising of MT and YST.

One patient presented with hemophagocytic lymphohistiocytosis (HLH) and subsequently diagnosed with mediastinal germinoma. He ultimately died of infectious complication before receiving treatment for EGCT. Thirty patients (68%) were treated with upfront surgery while 13 patients (29%) received chemotherapy as an initial treatment. Of all 30 patients undergoing upfront surgery, 16 patients did not receive adjuvant chemotherapy since their tumors were completely resected and contained no malignant component. Twenty-four patients (55%) received combination treatment of surgery and chemotherapy, while 16 patients (36%) were solely treated with surgery and 3 patients (7%) received chemotherapy without surgical treatment (Fig 1). Chemotherapy (PEB) was prescribed for 27 patients, including 26 patients with malignant EGCT and 1 patient who had sacrococcygeal IT grade III with lymph node metastasis.

Three patients with a pathological diagnosis of sacrococcygeal IT grade II (1 patient) and III (2 patients) had elevated serum tumor markers, but did not receive chemotherapy. All of them were alive and free of disease at the end of the study.

One patient died before the treatment of EGCT was initiated. Thirty-eight patients (86%) had a complete response; 5 patients who were unresponsive to treatment subsequently died of disease. Relapse occurred in 3

TABLE 1. Demographic data, histopathology and staging of all patients (n=44).

Characteristics		Number (%)
Gender	Male	18 (41)
	Female	26 (59)
Primary site of tumor	Sacrococcygeal area	12 (27)
	Ovary	11 (25)
	Retroperitoneum	6 (14)
	Mediastinum	6 (14)
	Testis	5 (11)
	Mandible	1 (2)
	Bladder	1 (2)
	Vaginal wall	1 (2)
	Stomach	1 (2)
Histopathology results	Teratoma	
	-IT	12 (27)
	-MT	5 (11)
	Malignant germ cell tumor	
	-YST	13 (29)
	-Germinoma	4 (9)
	-Mixed germ cell tumor	
	-MT with YST	5 (11)
	-IT with YST with choriocarcinoma	3 (7)
	-IT with YST	1 (2)
	-Germinoma with choriocarcinoma	1 (2)
Staging	I	17 (39)
	II	3 (7)
	III	18 (41)
	IV	6 (14)

Abbreviations: IT, immature teratoma; MT, mature teratoma; YST, yolk sac tumor

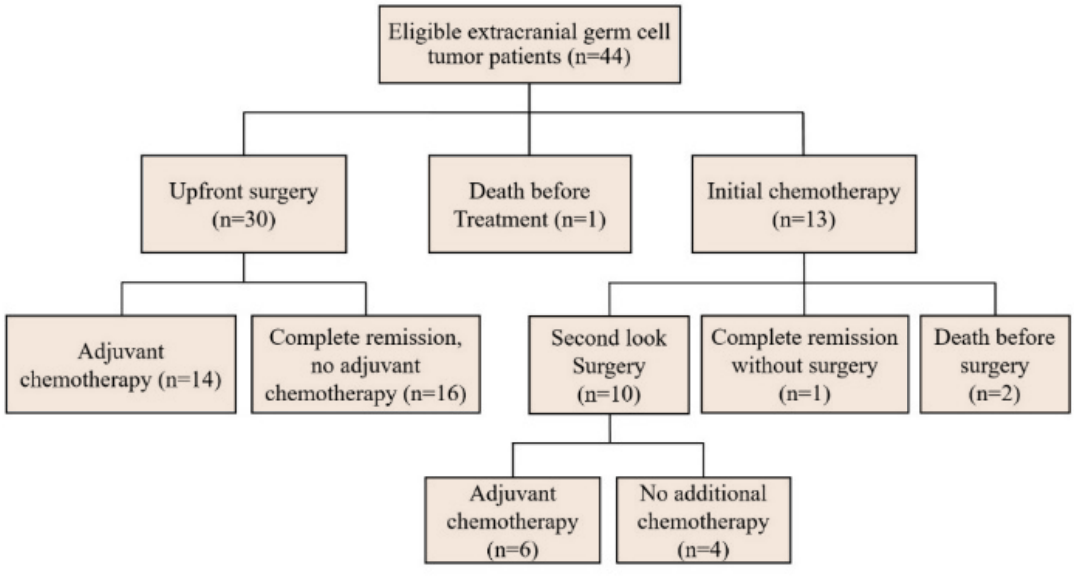

Fig 1. Treatment of patients with extracranial germ cell tumor.

patients, with a median time to relapse of 1 year (range 3.3 months-1.1 years). Of all 3 patients with relapse, 2 patients (1 patient with YST at vaginal wall and the other with IT at mandible) achieved remission after a combination of surgery and chemotherapy, and 1 patient died of disease progression. The mortality of EGCT in this study is detailed in Table 2. Among 27 patients who received chemotherapy, 19 patients (70%) experienced treatment-related toxicity. The most common adverse reaction from chemotherapy were infection (55%) and hematotoxicity (55%), followed by renal toxicity (37%). Two patients with mediastinal mixed GCT had concomitant hematologic malignancies. One of them developed prolonged cytopenias during treatment; his bone marrow aspiration result was compatible with acute megakaryoblastic leukemia. The other patient had tumor progression and subsequently died of disease; the autopsy result revealed a component of myeloid sarcoma within the remaining mediastinal mass with the presence of isochromosome 12p abnormality.

The 5-year EFS and OS were 78.3% (95%CI 10.3-13.9) and 81.1% (95%CI 10.8-14.2), respectively (Fig 2). The median follow-up time was 6.9 years (range 14 days-15.2 years). The comparison of EFS and OS according to clinical factors is demonstrated in Table 3. Cox regression analysis was performed to determine the predictors of mortality; the only factor associated with survival was the adequacy of surgery (HR 8.69, 95% CI 1.44-52.26, *p*-value 0.018).

DISCUSSION

In our study, EGCT was common among patients under 2 years of age, with a female preponderance; this was concordant with other studies.[1,11] Sacrococcygeal area appeared to be the most common primary site, which corresponds with a previous study.[11]

Klinefelter syndrome, Turner syndrome, and Swyer syndrome were found to be associated with EGCT[2-4] but none of the patients in our study harbor those conditions. However, 3 of our patients had underlying genetic diseases including DS and CdLS. Individuals with DS have been reported to have EGCT, but the incidence of EGCT in DS was relatively low compared to that of hematologic malignancies.[12] CdLS is a rare syndrome resulting from mutation in cohesin protein[13], and typically affected craniofacial, gastrointestinal and central nervous systems. Although mutation of cohesin might be associated with the development of cancer, there was no clear evidence that CdLS increased the risk of cancer. Few case reports of CdLS with Wilms tumor and liver hemangioendothelioma have been documented[14], but there was still no report of EGCT in CdLS. Hence, we believe that the finding of EGCT in CdLS in our study might be an incidental finding.

TABLE 2. Mortality of extracranial germ cell tumor patients (n=8).

Patient	Diagnosis	Stage	Treatment	Response of treatment	Cause of death
1	DS with retroperitoneal IT grade II	I	TTR	CR	Infection (not related to cancer treatment)
2	Mediastinal IT grade III	I	TTR	CR, then relapse	Disease progression due to treatment refusal
3	Sacrococcygeal IT grade III	III	TTR with CMT	PD	Disease progression
4	Mediastinal germinoma	III	None	Not evaluable	HLH
5	Mediastinal mixed GCT	III	CMT with TTR	PR	Disease progression
6	Mediastinal mixed GCT	III	CMT	PR, concomitant myeloid sarcoma	Disease progression
7	Mediastinal mixed GCT	III	CMT	PD, concomitant AML	Disease progression
8	Sacrococcygeal YST	IV	CMT	PD	Disease progression

Abbreviations: AML, acute myeloid leukemia; CR, complete response; DS, Down syndrome; GCT, germ cell tumor; HLH, hemophagocytic lymphohistiocytosis; IT, immature teratoma; PD, progressive disease; PR, partial response, TTR, total tumor removal; YST, yolk sac tumor

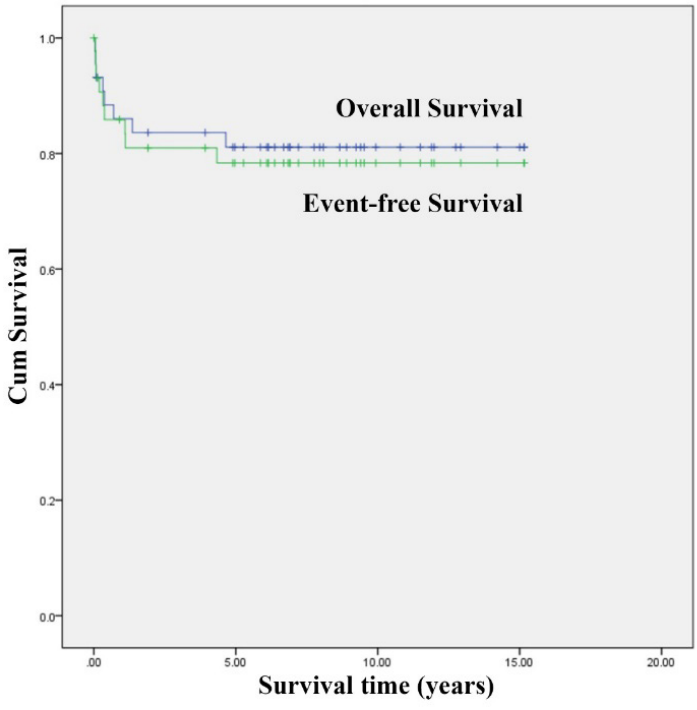

Fig 2. The 5-year event-free survival and overall survival rate of patients with extracranial germ cell tumor.

TABLE 3. Comparison of survival rates according to various clinical factors.

Factors	5-year EFS	*p*-value	5-year OS	*p*-value
Age group at diagnosis				
<11 yr (n=33)	83.8	0.088	87.4	0.056
≥11 yr (n=11)	61.4		61.4	
Site of tumor				
Gonadal (n=16)	100	0.170	100	0.203
Extragonadal (n=28)	65.9		70.5	
Diagnosis				
Teratoma (n=17)	73.7	0.614	80.7	0.961
Malignant germ cell tumor (n=27)	81.1		81.3	
Stage				
I (n=17)	80	0.861	86.7	0.723
II (n=3)	100		100	
III (n=18)	72.2		72.2	
IV (n=6)	80		80	
Adequacy of surgery				
Partial tumor removal (n=3)	33.3	0.023	33.3	0.018
Total tumor removal (n=37)	88.6		91.6	

Abbreviations: EFS, event-free survival; OS, overall survival

Several type of hematologic malignancies, especially acute megakaryoblastic leumemia, were reported in patients with mediastinal GCT.[9,15] Isochromosome 12p might be responsible for the concomitant hematologic malignancies in these patients.[16] Although only one of our patients harbor this abnormal chromosome, we believed that the hematologic malignancies in both of them were related to the mediastinal GCT rather than a secondary malignancy related to cancer treatment since theirs myeloid neoplasms developed very early after the initiation of chemotherapy.

Chemotherapy treatment in IT is controversial, especially in ovarian IT.[17] However, several reports have revealed that chemotherapy might not benefit for other IT patients, even if they have malignant foci or elevated tumor markers.[18,19] In accordance with the aforementioned studies, all 3 IT patients with elevated serum tumor markers in our study survived after having a solely surgical intervention.

Previous reports revealed that teratoma usually had a better outcome than malignant EGCT.[20] In contrast, patients with teratomatous EGCT in our study had an inferior survival rate compared to malignant EGCT, but without statistical significance. However, other factors, such as treatment abandonment or a patient's preexisting conditions, might have affected the treatment outcome. Among the 3 teratomatous EGCT patients who died in this study, only 1 patient died of a refractory disease, while another patient died of disease progression due to treatment refusal and the other patient with DS died of infection not related to cancer treatment several months after completing therapy.

The 5-year OS rate of 81.1% in this cohort was comparatively favorable to 70.6% of the previous Thai study.[6] However, the aforementioned study included both IGCT and EGCT; the interpretation should be cautious. Improvements in supportive care may account for the better outcome in our study, given the fact that the chemotherapy protocol has not drastically changed. The outcome of present study was inferior to that of developed countries[5]; this may be due to the higher proportion of teratomatous EGCT in that study compared to our study, 78.7% versus 38.6%.

The survival rate of advanced-stage disease was still inferior to early-stage disease[5], including the results of our study. Although several treatment approaches, such as an intensive dose of PEB[21] and high dose chemotherapy with autologous stem cell rescue[22] were initiated in patients with advanced disease, they failed to demonstrate any survival benefit. In addition, disease progression was the major cause of death in our study especially in patients with advanced stage. More effective treatment approaches may be required for such patients. Younger age at diagnosis i.e. less than 11 years old and gonadal tumor in origin were also reported to be a good predictor for survival.[23] Both groups also provided the better survival in our study but without statistical significance, a larger sample size might be needed to better determine the prognostic factors.

A few patients with relapse can be salvaged by surgery. The Cox regression analysis in our study also demonstrated that surgery significantly improved the survival rate. Therefore, for patients whose tumor cannot be completely removed, repeated surgery may be warranted.

There were limitations in this study that need to be mentioned. First, as is common with retrospective studies, some data might be missing or incomplete. Secondly, the sample size in this cohort appears to be small; some significant prognostic factors might be not salient. Thirdly, our center often receives complicated cases, possibly limiting the generalizability of our data and findings.

CONCLUSION

The outcome of EGCT in this study seemed to be favorable but still inferior to that of developed countries, possibly due to the higher proportion of nonteratomatous EGCT in our study. The adequacy of surgery appeared to be factor-associated with better clinical outcomes, whereas novel therapy may be warranted for those patients who are unresponsive to the current treatment.

Conflict of interest: The authors have no conflicts of interest to declare.

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Renal Outcomes of Childhood IgA Nephropathy and Henoch Schönlein Purpura Nephritis

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ABSTRACT

Objective: Henoch-Schönlein purpura nephritis (HSPN) is considered the systemic form of IgA nephropathy (IgAN). However, differing clinicopathological features and renal outcomes of children with IgAN and HSPN have been reported in some studies.

Materials and Methods: This study retrospectively reviewed children with IgAN and HSPN younger than 18 years, between January 2004 and December 2015. The clinicopathological characteristics at diagnosis and the renal outcomes after at least 1 year of follow-up were compared between the two groups.

Results: A total of 54 children, comprising 21 with IgAN and 33 with HSPN, were recruited. The children with HSPN were younger than the children with IgAN. Gross hematuria and nephritic syndrome at the initial presentation were more common in children with IgAN. Regarding the pathological findings, IgAN had greater chronicity than HSPN. After a median follow-up period from first presentation to renal outcomes measurement of 4.0 years (1.3-12.2) in children with IgAN and 4.2 years (1.1-11.4) in children with HSPN, the renal outcomes were better in the latter group. The incidence of chronic kidney disease (CKD) was 28.6% in children with IgAN and 6.1% in children with HSPN ($p = 0.02$). Complete recovery was observed more frequently in children with HSPN than in children with IgAN (57.1% in IgAN vs. 87.9% in HSPN, $p = 0.01$).

Conclusion: Childhood IgAN has greater chronicity and worse renal outcomes than childhood HSPN, with a lower rate of complete recovery and a higher frequency of CKD. We recommend long-term follow-up for CKD in children with IgAN.

Keywords: Chronic kidney disease; Chronic renal disease; End-stage renal disease; Henoch-Schönlein purpura nephritis; IgA nephropathy (Siriraj Med J 2021; 73: 687-694)

INTRODUCTION

IgA nephropathy (IgAN) and Henoch-Schönlein purpura (HSP) are common causes of glomerulonephritis in children.[1] IgAN is a type of primary glomerulonephritis.[2,3] HSP is a clinical syndrome that affects many organs, including the kidneys (HSP nephritis, HSPN), and is classified as a type of systemic vasculitis.[1,4] HSP was redesignated IgA vasculitis in the second International Chapel Hill Consensus Conference (CHCC 2012),[5] but this term has not yet come into widespread use. A multivariate analysis showed that age of onset > 4 years, severe abdominal pain, and persistent purpura were significantly associated with the development of HSPN.[6]

HSP is thought to be a systemic form of IgAN because these two conditions share several clinical, histological, and immunological features.[7,8] The renal

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http://dx.doi.org/10.33192/Smj.2021.88

pathological features of HSPN are identical to those in IgAN, which is associated with the deposition of IgA in the mesangium. HSP mainly affects children,[9] whereas IgAN occurs more frequently in adults.[2] Recently, Kamei et al[10] posited that the two disorders were variants of a single disease because 6 children with IgAN developed HSPN 5 months to 14 years later. Few clinical studies have compared IgAN and HSPN in adults.[11,12] A study of adults by Calvo-Rio et al.[11] observed more severe renal outcomes in patients with IgAN than in patients with HSPN (not limited to biopsy-proven HSPN). Another matched cohort in Korea demonstrated that there were no significant differences in renal outcomes between these two conditions.[12] To date, the only one clinical study comparing IgAN and HSPN in children has been published; that study was conducted in 1987[13] and showed that children with HSPN had a higher incidence of chronic kidney disease (CKD) than children with IgAN (16% in HSPN vs. 5% in IgAN), in contrast to comparative studies conducted in adults. However, limited data were available on children receiving immunosuppressive drugs in that study. Additionally, that report included the time period before the routine use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs). The results of previous studies[14,15] revealed an association between treatment with ACEIs and/or ARBs and reduced proteinuria in children with IgAN and HSPN. The reduction of proteinuria over time can slow progression to end-stage renal disease (ESRD) in patients with IgAN and HSPN.[14,16] Therefore, the differences in clinicopathological characteristics and renal outcomes between childhood IgAN and HSPN have not yet been determined.

The aim of this study was to compare the clinical characteristics, renal pathology, and renal outcomes of children with IgAN and HSPN during the period when ACEIs and/or ARBs were routinely used at a single tertiary care hospital.

MATERIALS AND METHODS

Study population

The study population included all children aged less than 18 years who were diagnosed with IgAN or HSPN at Siriraj Hospital between January 2004 and December 2015. The exclusion criteria were (i) a renal biopsy performed at another institution, (ii) less than 1 year of follow-up, and (iii) missing data. All children with IgAN underwent renal biopsy and were diagnosed according to the Oxford classification[17] which is based on the presence of dominant or codominant IgA staining in glomeruli without systemic disease.

HSP was diagnosed according to the European League Against Rheumatism (EULAR)/Paediatric Rheumatology European Society (PreS)-endorsed consensus criteria for the classification of childhood vasculitides.[18] The diagnostic criteria included palpable purpura in the presence of at least one of the following four features: (i) diffuse abdominal pain, (ii) any biopsy showing predominant IgA deposition, (iii) arthritis or arthralgia, and (iv) renal involvement. HSPN was defined as HSP accompanied by renal involvement including at least one of the following: (i) proteinuria, (ii) hematuria, (iii) acute kidney injury or rapidly progressive glomerulonephritis (RPGN), or (iv) renal biopsy showing predominant IgA deposition. Renal biopsy was performed in patients with nephrotic syndrome, decreased renal function, or substantial proteinuria that persisted for more than 1 month.

Clinical definitions

Proteinuria was defined as a urine protein-to-creatinine ratio (UPCR) greater than 0.2 mg/mg and categorized as absent, mild or severe proteinuria. Mild and severe proteinuria were defined as UPCR 0.2-1 and > 1 mg/mg, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula with an enzymatic method.[19] Nephritic syndrome was defined as hematuria with either hypertension or eGFR < 90 ml/min/1.73 m^2 at presentation. Nephrotic syndrome was diagnosed if nephrotic-range proteinuria (UPCR > 2 mg/mg) and hypoalbuminemia (serum albumin < 2.5 g/dL) were present. Hypertension was diagnosed if blood pressure was greater than the 95th percentile for age, gender, and height or greater than 130/90 mmHg in adolescent participants. RPGN was a clinical syndrome diagnosed if children manifested features of nephritis syndrome and had progressive loss of renal function over a short period of time.

Renal outcomes were classified into 3 categories according to renal manifestations observed at the last follow-up visit: (i) remission, (ii) isolated microscopic hematuria, or (iii) CKD. Remission was defined as normal renal function with no proteinuria or microscopic hematuria. Hematuria was defined as > 5 red blood cells per high-power field in a centrifuged urine specimen. Isolated microscopic hematuria was diagnosed if children had microscopic hematuria with normal renal function and no proteinuria. We defined CKD as a persistent eGFR < 60 ml/min/1.73 m^2 for at least 3 months or persistent proteinuria > 3 months. ESRD was defined as eGFR < 15 ml/min/1.73 m^2.

Treatment

All patients received supportive treatment according to their individual needs, including fluid and electrolyte control, blood pressure control, correction of acidosis, and renal replacement therapy. Furthermore, the children received immunosuppressive drugs, such as pulse methylprednisolone, glucocorticoids, cyclophosphamide, or azathioprine, depending on the disease severity. Some children with HSPN received glucocorticoids due to extrarenal symptoms such as severe abdominal pain. The children received ACEIs and/or ARBs to reduce proteinuria and treat hypertension.

Statistical analysis

Descriptive statistics were calculated for the baseline demographic and clinical characteristics. Continuous data were presented as the mean (± standard deviation) for variables with a normal distribution or as the median and range for variables that were not normally distributed. Categorical data were expressed as absolute numbers and percentages. Statistical significance was determined using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or the Mann-Whitney *U* test for continuous variables, as appropriate. A *P* value < 0.05 was considered statistically significant. All statistical calculations were performed using PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA).

Data were obtained from electronic patient records. This study was approved by the Siriraj Hospital Ethics Board.

RESULTS

Clinical and pathological features

Seventy children were diagnosed with either IgAN or HSPN from January 2004 to December 2015 at Siriraj Hospital. Of these children, 16 were followed up for less than 1 year, thus meeting the exclusion criteria. Fifty-four children were included in the final study population, with 21 (38.9%) in the IgAN group and 33 (61.1%) in the HSPN group. The median follow-up durations in the IgAN and HSPN groups were 4.0 years (1.3-12.2) and 4.2 years (1.1-11.4), respectively, and there was no statistically significant difference between them (p = 0.97). Baseline demographic and clinical characteristics are summarized in Table 1. Children with IgAN were significantly older. The mean age of onset was 11.2±3.0 years and 9.0±3.3 years (p = 0.02) for children with IgAN and HSPN, respectively. The two groups were similar in sex distribution and severity of renal involvement (proteinuria, initial eGFR, and nephrotic syndrome) at presentation. However, children with IgAN were more likely than those with HSPN to present with gross hematuria (61.9% in IgAN vs. 30.3% in HSPN, p = 0.03) and nephritic syndrome (81.0% in IgAN vs. 39.4% in HSPN, p = 0.01). Baseline eGFR was comparable between the two groups (87.5 (9.2-253.2) ml/min/1.73 m^2 in IgAN vs. 104.5 (9.5-261.4) ml/min/1.73 m^2 in HSPN, p= 0.13).

Renal biopsy was performed in all children with IgAN and 20 (60.6%) children with HSPN. The median (min-max) time from first presentation to renal biopsy were similar between groups: 10 days (0-359) in the IgAN group and 7 days (0-271) in HSPN group (p = 0.71). Table 2 shows the frequency of renal pathological features at the time of diagnosis. The most common pathological finding was mesangial proliferation in both groups (76.2% in IgAN vs. 70.0% in HSPN, p = 0.73). Crescents (57.1% in IgAN vs. 55.0% in HSPN, p = 1.00) and endocapillary proliferation (23.8% in IgAN vs. 40.0% in HSPN, p = 0.33) were similar in both groups. Children with IgAN were more likely than those with HSPN to show chronicity on renal biopsy, including tubular atrophy and interstitial fibrosis (76.2% in IgAN vs. 25.0% in HSPN, p = 0.002). Additionally, children with IgAN had a higher percentage of global sclerosis than those with HSPN, but the difference was not statistically significant (42.9% in IgAN vs. 15.0% in HSPN, p = 0.09).

Treatment

The immunosuppressive medications used within the 1st year after diagnosis are summarized in Table 3. Due to the retrospective nature of the study, treatment showed some variation among physicians. Pulse methylprednisolone 30 mg/kg (maximum 1 g) for 3-5 consecutive days was initially prescribed to 19.0% of children with IgAN and 12.1% of children with HSPN due to RPGN (p=0.70). Most children with HSPN received prednisolone (90.9%), whereas only 57.1% of children with IgAN received prednisolone (p = 0.006). One possible reason is that prednisolone was generally prescribed in many children with HSP because of extrarenal symptoms such as severe abdominal pain. In contrast, all children with IgAN received prednisolone due to renal indications. However, the prescription frequency of other immunosuppressive drugs, such as cyclophosphamide and azathioprine, did not differ between the groups. These drugs were used in a small number of children who did not respond to corticosteroids. None of the children in this study received mycophenolate mofetil. ACEIs were prescribed to 42.9% (9/21) and 36.4% (12/33) of children with IgAN and HSPN (p = 0.64), respectively.

TABLE 1. Baseline demographic and clinical characteristics of children with HSPN and IgAN.

Characteristics	HSPN (n=33)	IgAN (n=21)	*P*
Sex, n (%)			
Male	18 (54.5)	16 (76.2)	0.15
Age, years (mean±SD)	9.0±3.3	11.2±3.0	0.02
Gross hematuria, n (%)	10 (30.3)	13 (61.9)	0.03
Proteinuria[a], n (%)			
No proteinuria	5 (15.2)	8 (38.1)	0.15
Mild proteinuria	14 (42.4)	5 (23.8)	
Heavy proteinuria	14 (42.4)	8 (38.1)	
eGFR, ml/min/ 1.73m^2 (median, max-min)	104.5 (9.5-261.4)	87.5 (9.2-253.2)	0.13
Nephritic syndrome[b], n (%)	13 (39.4)	17 (81.0)	0.01
Nephrotic syndrome[c], n (%)	2 (14.3)	3 (23.1)	0.65

HSPN, Henoch Schönlein Purpura Nephritis; IgAN, IgA nephropathy; UPCR, urine protein to creatinine ratio; eGFR, estimated glomerular filtration rate

[a] No, UPCR < 0.2; mild, UPCR 0.2-1; heavy proteinuria, UPCR > 1 mg/mg

[b] Nephritic syndrome includes hematuria with either hypertension or eGFR < 90 ml/min/ 1.73m^2

[c] Nephrotic syndrome includes hypoalbuminemia (serum albumin < 2.5 g/dL) and nephrotic range proteinuria (UPCR > 2 mg/mg)

TABLE 2. Frequency of renal pathologic features at time of diagnosis.

Renal pathology	HSPN (n=20)	IgAN (n=21)	*P*
Mesangial proloferation, n (%)	14 (70.0)	16 (76.2)	0.73
Endocapillary proliferation, n (%)	8 (40.0)	5 (23.8)	0.33
Crescents[a], n (%)	11 (55.0)	12 (57.1)	1.00
Global sclerosis, n (%)	3 (15.0)	9 (42.9)	0.09
Tubular atrophy and interstitial fibrosis, n (%)	5 (25.0)	16 (76.2)	0.002

[a]Any crescents

TABLE 3. Immunosuppressive medications within the 1st year after diagnosis.

Medication	HSPN (n=33)	IgAN (n=21)	*P*
Pulse methylprednisolone, n (%)	4 (12.1)	4 (19.0)	0.70
Prednisolone, n (%)	30 (90.9)	12 (57.1)	0.006
Cyclophosphamide, n (%)	9 (27.3)	4 (19.0)	0.54
Azathioprine, n (%)	2 (6.1)	2 (9.5)	0.64

Renal outcomes

The renal outcomes at the last follow-up visit in 21 children with IgAN and 33 children with HSPN are summarized in Table 4. The median (min-max) length of follow-up from first presentation to renal outcomes measurement was similar between groups: 4.0 years (1.3-12.2) in the IgAN group and 4.2 years (1.1-11.4) in the HSPN group (p = 0.97). The renal outcomes were better in children with HSPN than with IgAN. Complete recovery was more frequent in children with HSPN than with IgAN (87.9% in HSPN vs. 57.1% in IgAN, p = 0.01). Persistent isolated microscopic hematuria was observed more frequently in children with IgAN than with HSPN (14.3% in IgAN vs. 6.1% in HSPN, p = 0.32).

The incidence of CKD was 28.6% in children with IgAN and 6.1% in those with HSPN (p = 0.02). There was no significant difference in ESRD in either group (14.3% in IgAN vs 6.1% in HSPN, p = 0.37). Three children with IgAN (14.3%) required renal replacement therapy. Two children with HSPN (6.1%) progressed to ESRD and required renal replacement therapy. All children with ESRD exhibited significant crescentic involvement greater than 50% and tubular atrophy and interstitial fibrosis greater than 25% on their first renal biopsy. They received immunosuppressive drugs, including pulse methylprednisolone, prednisolone, and pulse cyclophosphamide, but did not respond.

None of the children in this study died.

DISCUSSION

IgAN and HSPN are common glomerular disorders in pediatric patients with the potential to progress to CKD.[1,2,7] The pathogenesis of these two conditions is similar, being associated with galactose-deficient IgA1 and increased formation of IgA1 immune complexes in circulation; these complexes are ultimately deposited in glomeruli.[20,21] This study demonstrated that childhood IgAN has greater chronicity and worse renal outcomes than childhood HSPN. The incidence of CKD was 28.6% in children with IgAN and 6.1% in children with HSPN (p= 0.02). Complete recovery was observed more frequently in children with HSPN than in children with IgAN.

Demographic data demonstrated a predominance of males in both diseases (76.2% in IgAN vs. 54.5% in HSPN), and children with HSPN were significantly younger than children with IgAN (11.2±3.0 years in IgAN vs. 9.0±3.3 years in HSPN, p = 0.02), as in previous pediatric studies.[8,9,13,22-25] Both groups included in this study exhibited similar characteristics of initial renal involvement, including proteinuria, nephrotic syndrome and initial eGFR, except that children with IgAN were more likely to present with gross hematuria (61.9% in IgAN vs. 30.3% in HSPN, p =0.03) and nephritic syndrome (81.0% in IgAN vs. 39.4% in HSPN, p = 0.01). In this regard, no major differences were observed when our results were compared with those from other pediatric series.[9,14,23,24,26]

Although IgAN is the most common glomerular disease during the second and third decades of life, the mean age of children with IgAN in previous studies was approximately 10-15 years old.[8,15,23,25] In support of this notion, the mean age of children with IgAN in this study was 11.2±3.0 years. Gross hematuria is commonly present in children with IgAN (71.0%).[23] As expected, our results showed that 13 of 21 (61.9%) children with IgAN had gross hematuria at initial presentation. The presence of nephrotic syndrome in previous pediatric series was 1.1-14%,[8,26] which was lower than the rate observed in this study (23.1%).

The mean age of HSP in children is approximately 6-8 years old.[1,8,14] However, the mean age of children with HSPN in pediatric series is higher, at approximately 8-14 years old.[8,9,14,24,27,2] Likewise, the mean age at presentation in children with HSPN in this study was 9.0 ± 3.3 years. Gross hematuria is uncommon in children with HSPN, occurring in approximately 10-14% of cases.[24,27] In this

TABLE 4. Renal outcome at last follow up.

Renal outcome	HSPN (n=33)	IgAN (n=21)	*P*
Complete recovery, n (%)	29 (87.9)	12 (57.1)	0.01
Isolated microscopic hematuria, n (%)	2 (6.1)	3 (14.3)	0.32
Chronic kidney disease, n (%)	2 (6.1)	6 (28.6)	0.02

study, however, a larger proportion of children with HSPN (30.3%) had gross hematuria at presentation. Previous series demonstrated that the rate of nephrotic syndrome in childhood HSPN was 5-45%.[8,9,14,24,27,28] This range was supported by this study, in which 14.3% of children with HSPN had nephrotic syndrome at the initial presentation.

Pathological findings in children with IgAN and HSPN have been shown to depend on the timing of renal biopsy.[9,29] Children in the early stages of both disorders generally have mesangial and endocapillary proliferation, while those with late-stage disease generally have segmental or global sclerosis and tubular atrophy interstitial fibrosis.[9,22] Consistent with a previous study,[8] considerable mesangial proliferation was the most common renal pathological feature observed in patients with both disorders in this study (76.2% in patients with IgAN vs 70.0% in patients with HSPN). Tubular atrophy and interstitial fibrosis are pathological features that are independently associated with unfavorable renal outcomes.[9,23,30] Our results would appear to confirm a higher rate of tubular atrophy and interstitial fibrosis in children with IgAN than in children with HSPN (76.2% in IgAN vs 25% in HSPN, p=0.002), which led us to hypothesize that renal biopsy in children with HSPN was performed earlier.

Corticosteroids decrease the intensity and duration of abdominal pain and the severity of arthritis in children with HSP.[4,31] However, the use of corticosteroids in children with HSP does not effectively prevent the development of nephritis.[31,32] The use of corticosteroids was more common in children with HSPN than with IgAN in this study (57.1% in IgAN vs 90.9% in HSPN, p=0.006), probably due to the frequent extrarenal manifestations presented in children with HSPN. In contrast, corticosteroids were generally given to children with IgAN only if there were renal indications. To date, there is little evidence to support the additional use of adjunctive therapy with immunosuppression, such as mycophenolate mofetil or azathioprine, as a standard regimen in either children with IgAN or children with HSPN.[33,34]

Data on renal outcomes in children with IgAN and HSPN varied from complete recovery to ESRD. In a series of pediatric patients, 5-43% of children with IgAN[13,23] and 4-13% of children with HSPN[13,14,24,35] developed CKD, including ESRD. However, these results should be interpreted with caution because discrepancies could be related to several factors, such as differences in patient selection, treatment strategies, duration of follow-up, and outcome measurement. Patient selection bias existed, particularly for HSPN, can make renal outcomes highly variable. In this regard, some centers included only biopsy-proven HSPN,[9,14,27,28] while others analyzed data regardless of whether a biopsy was performed.[13,24,36] Additionally, some countries have active urine screening programs, which increase the likelihood that children with IgAN will be diagnosed and treated in the early stages of disease; this may affect renal outcomes. Moreover, immunosuppressive medications differed depending on the preferences of individual centers, and different treatment strategies may also affect renal outcomes. Furthermore, the discrepancy between renal outcome measurements among centers made these variables difficult to compare.

A study comparing childhood IgAN and HSPN in a single center[13] found that HSPN could be more aggressive than IgAN, since higher incidence of CKD was observed in children with HSPN (5.0% in IgAN vs. 16.0% in HSPN). In contrast, this study reported better renal outcomes in children with HSPN than with IgAN, since children with HSPN achieved a higher rate of complete recovery (57.1% in IgAN vs 87.9% in HSPN, p=0.01) and a lower incidence of CKD than children with IgAN (28.6% in IgAN vs. 6.1% in HSPN, p=0.02). The median time from first presentation to renal outcomes measurement was similar between groups in this study. One possible explanation is that children with IgAN had a longer course of disease before being diagnosed and this was supported by the findings that IFTA was more common in children with IgAN than in children with HSPN in this study. Although the median time from first presentation to renal biopsy were similar between groups in this study, the diagnosis of IgAN depended on a renal biopsy, and thus children with early-stage IgAN and subtle clinical symptoms might be missed initially and present later with full-blown disease and had chronicity on the renal pathology. In addition, our country has no routine screening urinalysis in children; therefore, mild cases of IgAN are probably missed. In contrast, the diagnosis of HSP was based on clinical symptoms; almost all children with HSP presented with obvious, palpable purpura that led them to seek medical attention. Routine urinalysis was required in all children with HSP; therefore, renal involvement may be identified and treated in the early stages of disease. This finding might explain why children with IgAN had worse renal outcomes than children with HSPN in this study.

Long-term follow-up studies revealed that the urinalysis of 29-43% of pediatric patients with IgAN returned to normal.[13,23,34] This was supported by this study, in which more than half of children with IgAN (57.1%) completely recovered. The incidence of CKD in this study was 28.6% which was close to the overall

incidence of childhood IgAN in previous pediatric studies (5-43%).[13,23] Three (14.3%) of the 21 children with IgAN in our study developed ESRD, similar to the long-term ESRD rate (11%) reported by a Finnish study.[23] All patients with ESRD in this study experienced significant tubular atrophy and interstitial fibrosis.

The course of HSPN is usually favorable. Most children with HSPN (87.9%) achieved complete recovery after a median follow-up period of 3.5 years (1.1-11.4) in this study. These results are consistent with previously reported rates (66-85%).[24,28,35] However, approximately 4-13% of children with HSPN develop CKD.[14,24,35] Similar to the previous study, the incidence of CKD in this study was 6.1%. Two (6.1%) of the 33 children with HSPN in this study developed ESRD, which was similar to the rates reported in other pediatric studies (0-7%).[24,27,34,36]

This study has several strengths. First, this report is the first to compare renal outcomes between children with HSPN and IgAN in the era of ACEIs and/or ARBs, revealing superior renal outcomes in childhood IgAN. Second, this study is homogenous in terms of the analysis of renal outcomes because the same diagnostic criteria were used for both IgAN and HSPN. Third, the children received similar immunosuppressive treatment according to disease severity, despite the absence of standardized management for both diseases. Our study also has several limitations. First, this study employed a retrospective design. Second, the renal outcome data for childhood IgAN and HSPN in this study were obtained from a tertiary center in Thailand; therefore, these data may be difficult to generalize to the whole population. For example, many children with HSPN were referred when they had severe renal involvement at onset. Patients with mild cases of HSPN, might not be referred and might instead be followed at primary and secondary hospitals. Third, our country does not perform school urinalysis screening programs; therefore, children with early-stage IgAN are not detected and were not included. Overall, children with IgAN in this study are not representative of the whole childhood IgA population, especially mild cases. Fourth, relatively fewer patients were analyzed in this study. Further prospective cohort multicenter studies and studies comparing the renal outcomes between 2 groups with similar renal pathologies are required to clarify these limitations.

CONCLUSION

In conclusion, differences were observed between childhood IgAN and HSPN. Children with HSPN were younger than children with IgAN. Gross hematuria and nephritis syndrome occurred more frequently in children with IgAN than in those with HSPN, and the chronicity of renal pathology was also higher in children with IgAN. Additionally, the renal outcomes of children with IgAN were worse than children with HSPN. We recommend long-term follow-up for CKD in children with IgAN.

ACKNOWLEDGEMENTS

The authors are grateful to all of the participants and attending physicians for their contributions.

Funding Sources: This study was supported by the Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Conflicts of interest: The authors declare that there are no conflicts of interest in this study.

Statement of Ethics: This study was approved by the Siriraj Hospital Ethics Board (Si 380/2016).

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Effects of Physical Exercise Program on Physical Mobility of Patients with Cranial Surgery

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ABSTRACT

Objective: This research aimed to study the effects of a physical exercise program on physical mobility in cranial surgery patients.

Materials and Methods: The researcher used a quasi-experimental method of surveying 58 patients who had cranial surgery at Siriraj Hospital. The research group was divided into two groups: an experimental group (28 patients) participating in a physical exercise program of patients after cranial surgery, and a control group (30 patients) receiving routine nursing care only. The evaluation of the patients' physical mobility was performed three days after the surgery.

Results: Most patients in the research group had an intracranial tumor (86.2%). One day after the surgery, the experimental group had minor pain at the wound site while the control group had moderate pain. Both groups felt discomfort (64.2%) or had muscle stiffness in the neck and shoulder areas (63.3%). Three days after the surgery, at the end of the program, the body movement function of both groups was reduced compared with the preoperative data. However, the experimental group showed better body movement function scores than the control one as the scores of the former were reduced less than those of the latter at $p < 0.05$.

Conclusion: Nurses who provide health care services to patients after cranial surgery should apply the physical exercise program to promote the recovery of the patients' physical mobility.

Keywords: Physical exercise; physical mobility; cranial surgery (Siriraj Med J 2021; 73: 695-701)

INTRODUCTION

Cranial surgery can be applied to treat different intracranial diseases[1] such as tumors, blood clots, brain abscesses, repair broken cranial bones or clip blood vessels in patients with cerebrovascular aneurysms.[2] However, the surgery affects the brain and blood vessels. The brain tissues are damaged, leading to limited activity, decreased mobility[3] and different neurological deficits: gait (76.3%) and balance (48.3%).[4] Hence, the patients face the inability to self-care.[3] Moreover, the patients need to be positioned correctly to facilitate the surgery. This includes forcing the head to be raised up and stay in an appropriate angle while being pressed by a Mayfield[5] for 4-6 hours.[6] The patients' neck and shoulder muscles take the weight, creating taut bands[7,8] and aches in the muscles. They have difficulties lowering, raising and turning their heads. The pressure on the blood vessels reduces blood and oxygen circulation to the muscles[7,9],

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http://dx.doi.org/10.33192/Smj.2021.89

so the patients feel dizzy when changing the position. Moreover, the postoperative pain complicates early ambulation and delays early recovery.[10-12]

Most patients who have had cranial surgery face limitations in performing daily activities, and only 18% of these patients can resume working normally following surgery.[13] Fostering early recovery is very important. In general, 59% of patients who have normal preoperative body movement and receive postoperative recovery promotion show a better body movement function at an 81.5% rate.[14] The recovery promotion should start from the patients' admission.[15] Physicians or nurses should provide them with general preoperative knowledge and teach physical exercise, step by step, to prepare the muscles while the patients stay in bed until they can walk.[16,17] This is considered nursing therapeutics capable of fostering cranial surgery patients, who are in health and illness transition of Meleis' transition theory, achieve complete this transition[18,19], which contributes in turn to postoperative recovery, improves physical mobility, reduces complications from bed bounding[20] and admission days.[12] Before starting exercise, the patients will be evaluated in terms of dizziness and wound pain and will be eased of muscle pain in the neck and shoulder areas. Many studies have shown that massaging can reduce pain[21] and stress to blood vessels in the muscles, while increasing blood and oxygen circulation to the brain and eliminating dizziness.[22] Thus, massage is an appropriate and effective treatment for relieving neck and shoulder muscle stress and promoting early ambulation in patients who have had surgery.

Most of the previous studies were rehabilitation programs for patients who had chronic neurological symptoms and long-term impaired body functions.[23-25] In the area of patients who had cranial surgery, a previous study concerning early recovery after surgery (ERAS) programs was found to have encouraged patients to have early mobility from the first 24 hours after surgery. Furthermore, patients who received the ERAS program had early recovery with reduced LOS in hospital.[12,17,20,26] However, rehabilitation and ERAS programs in the past did not study massage for relief of muscle pain, massaging to ease muscle pain was done with patients who had a thyroidectomy[27], and nurses did not begin exercise from the first 24 hours after surgery when patients were in the ICU. Therefore, to prepare muscles for ambulation with exercise and to prepare patients for transfer from the ICU to the ward on the second day after surgery, patients received massage to relax the neck and shoulder muscles. This role was performed by nurses for comfort, relieve muscle pain and increase blood circulation to the brain tissues of patients, as a consequence, patients were more likely to have improved physical mobility. Thus, the researcher developed a physical exercise program for patients who had a cranial surgery. The first phase of the exercise started 24 hours after the surgery. Once the patients' conditions were stable[16,26], they were massaged to relieve muscle stress in the neck and shoulder areas before starting active ROM exercise, strengthen the thigh muscles and quadriceps extension until they could get up from the bed and walk. The goal was to promote physical mobility to recover quickly.

MATERIALS AND METHODS

This quasi-experimental research was certified by the Human Research Ethics Committee, Faculty of Medicine, Siriraj Hospital, Mahidol University (Si 065/2020). The research groups were calculated using influence size determination from mean difference of body functions in similar research studies.[25] The results were 26 patients for a group. Additional patients were included at a 15% rate in case some dropped out.[24] The power of test was 0.80, and confidence in the test (α) was 0.05. The final research groups had 30 patients each.

Population and samples

The population was patients who had cranial surgery at a super tertiary hospital. The samples had the same characteristics as the population. The selection criteria were 1) undergoing cranial surgery; 2) age ≥ 18 years old; 3) Glasgow Coma Scale = 15; 4) Thai Mental State Examination scores > 23; 5) ability to move the body or no limitations in terms of body movement; and 6) understanding and being able to communicate in Thai. The exclusion criteria were 1) having a mental disease history; 2) wearing ventriculostomy drain when starting active exercise; and 3) having a congenital disease which prevents exercising and massaging. The criteria to consider termination from the research were 1) severe postoperative complications; 2) consciousness level decreasing by 2 points in 24 hours; and 3) failing the readiness assessment before starting physical exercise.

Data collection method

The research group received a physical exercise program of patients after cranial surgery (CVI 0.9) from the researcher, who is a nurse. The duration of the exercise was approximately 30 - 45 minutes each time. The program included sharing of knowledge from manuals of physical exercise for patients with cranial surgery (CVI 0.8) one day before the operation. Next, one day after the operation in the ICU, the researcher stimulated

the patients via a breathing exercise and passive ROM exercises for both upper and lower extremities (totality 11 positions, 10 times per position, for two sessions) while staying in bed. Two to three days after, the patients could partially move their bodies. The researcher massaged the patients' upper trapezius and splenius capitis areas to relax muscles by using vibration, stroking, petrissage and friction along with encouraging patients to perform active ROM exercises for both the upper and lower extremities (totality 11 positions, 10 times per position, for 2 sessions). Next, the patients performed an exercise to strengthen the thigh muscles for five times and did quadriceps extensions for five minutes. The researcher then helped the patients step down from the bed to sit by the bedside and stimulated them to stand beside the bed before leading the patients to tread for five minutes, take a break for 2-3 minutes, continue treading for five minutes, then walk around the bed. The exercises depended on the ability of each patient. The researcher assessed the physical readiness and treated wound pain for the patients before starting the program every time. During the exercises, the researcher monitored any changes and pain levels for safety. For the control group, the patients received routine nursing care.

Data collection

Data collection was conducted by a research assistant, starting from the control group and then the experimental group. First data collection: one day before the operation. This data was used as baseline data. Physical mobility data were collected by the Clinical Outcome Variables Scale (COVS). Three points were related: 1) gross motor and gait; 2) mobility; and 3) arm function. The higher the COVS, the better the physical mobility. The COVS assessment revealed inter-rater reliability at 0.97[28] and internal consistency at 0.93.[23] ROM of the neck and shoulders was measured by a goniometer. The confidence value of goniometer use between the expert and research assistant was 0.97. Second data collection: three days after the operation. Physical mobility was assessed by COVS, and ROM of the neck and shoulder was measured by a goniometer. Third data collection: one day before leaving the hospital physical mobility was assessed by COVS.

Statistical analysis

All of the data were analyzed using SPSS (version 25). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and were compared using independent t-test or Mann-Whitney U test. Categorical data were expressed as number (percentage), and were compared using the Pearson chi-square test or Fisher's exact test. A *p-value* < 0.05 was considered statistically significant.

RESULTS

The experimental group consisted of 22 female and 6 male patients for a total of 28. The average age was 53.86. The control group consisted of 20 female and 10 male patients for a total of 30. The average age was 50.67. Personal data of the patients are shown in Table 1. There were no differences between both groups. Two patients in the experimental group dropped out as arrhythmia and high blood pressure were identified at the beginning.

One day after the surgery, before starting the program, both the experimental and control groups felt discomfort and muscle stiffness ($p = 1.0$). There were no differences in the wound pain of both groups ($p = 0.074$) (Table 1). Three days after the surgery, the discomfort and muscle stiffness of the experimental group was better at a 63.3% rate. Also, easing the wound pain every time before starting the program differentiated the pain of both groups significantly ($p = 0.003$) (Table 2).

The results of the physical exercise program of patients after cranial surgery and muscle relief massage differentiated COVS scores of both groups. Three days after the operation, the reduction of COVS scores of the experimental group was significantly less than those of the control group ($p = 0.03$). This meant the physical mobility of the former was better. The patients resumed walking faster, both three days after and one day before discharge, with statistical significance ($p = 0.01$, 0.004, respectively) (Fig 1). Furthermore, ROM of the neck and shoulder was significantly better than that of the control group ($p = 0.001$, 0.001, respectively) (Table 2).

DISCUSSION

Due to cranial surgery, both groups' physical mobility scores of three days after the operation decreased more than preoperative scores. These findings were in line with many other studies that found issues of reduced postoperative body movement[3,4], resulting from the operation, wound pain and muscle overuse at the upper trapezius and splenius capitis areas. The latter led to leakage to Ca^{2+} from sarcoplasmic reticulum to sarcolemma, combination of Ca^{2+} and adenosine triphosphate, and attachment of actin to myosin, which created a taut band.[9] Pressure to blood vessels and circulation under the muscles produced local hypoxia and anaerobic metabolism. Lactic acid was built up in the muscles and stimulated the nerve endings to feel pain, so the patients felt acute muscle aches and pains. The symptoms could last days or weeks, but no

TABLE 1. Personal data and treatment.

	Experimental group (*n* = 28)	Control group (*n* = 30)	*p*-value
Age: year	53.86 ± 12.55	50.67 ± 14.84	0.382
Female	22 (78.6)	20 (66.7)	0.385
BMI	25.33 ± 4.42	25.31 ± 5.31	0.988
Hypertension	9 (32.1)	13 (43.3)	0.427
Diabetes	5 (17.9)	3 (10.0)	0.464
Hyperlipidemia	9 (32.1)	9 (30.0)	1.00
Diagnosis			
Intracranial tumor	24 (85.7)	26 (86.7)	0.626
Cerebrovascular	2 (7.1)	1 (3.3)	
Cranial trauma	0	2 (6.7)	
Functional	2 (7.1)	1 (3.3)	
Lesion location: lobe			
Frontal lobe	4 (14.3)	5 (16.7)	0.547
Temporal lobe	2 (7.1)	5 (16.7)	
Parietal lobe	7 (25)	3 (10)	
Occipital lobe	7 (25)	9 (30)	
Multiple lobes	8 (28.6)	8 (26.7)	
Operation: craniotomy with			
Tumor removal	24 (85.7)	26 (86.7)	0.922
Clipping aneurysm	2 (7.1)	1 (3.3)	
Temporal lobectomy	1 (3.6)	1 (3.3)	
Other	1 (3.6)	2 (6.7)	
Duration of surgery: hours			
≤ 4	13 (46.4)	13 (43.3)	1.00
> 4	15 (53.6)	17 (56.7)	
Discomfort or stiffness of muscle			
Yes	18 (64.2)	19 (63.3)	1.00
Area of muscle			
Upper trapezius	6 (21.4)	7 (23.3)	0.565
Neck (splenius capitis)	4 (14.3)	4 (13.3)	
Shoulder	1 (3.6)	2 (6.7)	
Neck and upper trapezius	1 (3.6)	2 (6.7)	
Upper trapezius and shoulder	2 (7.1)	0 (0)	
Neck, upper trapezius and shoulder	0 (0)	2 (6.7)	
Arms and legs	2[1] (7.1)	11 (3.3)	
Back	2[2] (7.1)	1 (3.3)	
Surgery position in patients with discomfort or stiffness of muscle			
Supine	10 (55.6)	9 (47.4)	1.00
Lateral	1 (5.6)	2 (10.5)	
Park – bench	5 (27.8)	5 (26.3)	
Prone	2 (11.1)	3 (15.8)	
Pain on POD1 (NRS)			
Mild	14 (50.0)	6 (20.0)	0.074
Moderate	9 (32.1)	14 (46.7)	
Severe	4 (14.3)	9 (30.0)	

[1] In conjunction with neck or upper trapezius, [2] combined with upper trapezius or shoulder
Values are expressed as number (percentage), mean ± standard deviation

TABLE 2. COVS and ROM scores before and after surgery.

	Experimental group (*n* = 28)	Control group (*n* = 30)	*p*-value
COVS (pre-operation)#	80 (7)	80 (8)	0.453
COVS (POD3)#	68 (9)	62 (27)	
Difference COVS scores (posttest – pretest)#	-10.5 (8.5)	-16.5 (18.25)	0.03*
POD3			
ROM of neck#	190 (59)	127.50 (84)	0.001*
ROM of shoulder#	1244.50 (203)	1085 (298)	0.001*
Pain (NRS)†	0.25 ± 0.64	1.60 ± 1.97	0.003*
LOS#	7 (3)	10 (4)	0.001*

*p-value < 0.05
†Value is expressed as mean ± standard deviation, #Values are expressed median (interquartile range)

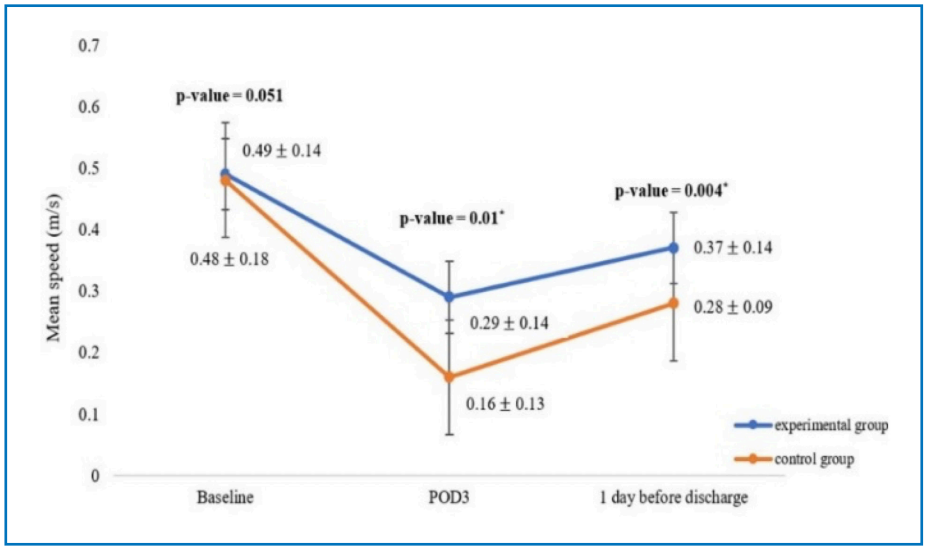

Fig 1. Comparison of speed between experimental and control groups.

more than two months.[8,27] The motion range of the neck and shoulders was reduced, which slowed the patients' movement and affected postoperative recovery.

This study showed that the physical exercise program of patients after cranial surgery including preoperative exercise knowledge sharing, early body movement stimulation and muscle preparation within the first 24 hours after the operation such as passive and active ROM exercises of both the upper and lower extremities, strengthen the thigh muscles and quadriceps extension, caused striated a skeletal muscle to contract harder. Consequently, the muscles used more energy, converting chemical energy into kinetic energy and increasing the cross-sectional area of Type 2 muscle fibers and resulting in muscle hypertrophy. With full growth of muscle fibers, the muscles became stronger, enabling patients to exercise more and move better, respectively.[29] This also prepared the patients' muscles before they could step down from the bed until walk around. Overall recovery was faster. More than three-quarters of the patients were able to walk by the bedside three days after surgery at a rate of 86.7%. The physical mobility of the experimental group decreased less than the physical mobility of those without the support program. Therefore, the patients in

the experimental group had complete health and illness transition.[18] The study of Wang et al. (2018) found that the elective craniotomy patients who received the ERAS program could do early off-bed activities and ambulation by the third day after the surgery. The success rate was 95%, which was significantly more than another group that did not have the program ($p < 0.0001$).[12]

In terms of the assessment of body readiness and management of localized wound pain from injuries at brain tissues, cortex nerves and blood vessels, which could be relieved pain by medication[30], both study groups had similar levels of wound pain before they were forced to step down from the bed, and they received similar amounts of painkiller. However, the experimental group had lower wound pain scores in POD3 than the control group (Table 2). The results were similar to those of the study of Qu et al. (2020) who found that pain management after cranial surgery in the patients receiving ERAS programs generated significantly lower wound pain scores in POD3 than the other group ($p < 0.001$).[26] Moreover, massaging was an alternative medicine that had a mechanism to send nerve currents along a beta or alpha nerve fiber to signal and stimulate S.G. cells to inhibit the function of transmission cells. The mechanism controlling the gate at the spinal cord level was thus closed. No nerval signal was sent to the brain, so the patients felt no pain.[31] Also, there was endorphins and enkephalins secretion to defy Substance P. This caused the gate to close and inhibited the transmission of nerve pain from the brain. The perception of pain was reduced. The patients felt relaxed, which enhanced pain relief.

The patients' ameliorated body movement was partially from discomfort management and massaging to relax the muscles. After receiving massages, two-thirds of the patients felt more comfort and less muscle stress. Furthermore, ROM of the neck and shoulders was better than the control group, and the experimental group could recover close to the normal state. Thus, they could exercise and move their bodies actively. The results were similar to those of Gemmell et al. (2008) who used post-isometric relaxation, which is similar to massage. The study found that the pain decreased immediately, and ROM was increased significantly ($p < 0.05$).[21] Increased ROM is related to decreased pain[32], the results after massaging by Doppler ultrasound showed increased blood and lymph circulation.[22] This circulation led to nutrient and oxygen supplies to the muscles, waste removal from the tissue cells and signal stimulation of focal adhesion kinase enzyme and extracellular signal-regulated kinase enzyme to reduce the contracture of sarcomere. The trigger points were relaxed with less cytokine and more mitochondria synthesis.[33] The muscles were stimulated to recover from fatigue more quickly.[34] Moreover, massaging relaxed the upper trapezius muscle, loosened the pressure of the vertebral artery under the muscle and increased blood circulation to the cerebral and basilar arteries. The brain tissues gained more oxygen so the patients' headache and dizziness were eased.[35,22] The experimental group could move their bodies more comfortably than the other group.

The physical exercise program of patients after cranial surgery was important in terms of promoting body movements such as sitting and standing, stepping down to sit beside the bed, performing various activities to help the patients resume walking faster (Fig 1) and leaving the hospital earlier than the other group (Table 2). The nursing method helped enhance recovery after surgery.

CONCLUSION

The physical exercise program of patients after cranial surgery including body exercise, muscle relaxing massage, knowledge sharing and management of symptoms affecting postoperative recovery improved the patients' physical mobility. As a result, nurses who take care of cranial surgery patients should use this program as a guideline to promote early movement of patients after surgery.

ACKNOWLEDGEMENTS

I would like to thank the Division of Neurosurgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, for supporting the neurosurgery research funding from the Siriraj Foundation, and Associate Professor Doctor Wattana Jalayondeja, specialist from the Faculty of Physical Therapy, Mahidol University, who taught muscle relaxing massage techniques and how to use a goniometer. I also would like to thank the head of the patient ward, staffs and research participants who cooperated and helped with data collection.

Abbreviations: ERAS = enhance recovery after surgery, LOS = length of stay, ICU = Intensive Care Unit, CVI = content validity index, ROM = range of motion, COVS = Clinical Outcome Variable Scale, BMI = body mass index, NRS = numeric rating scale, POD = postoperative day, S.G. cell = Substantia gelatinosa cell,

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Leak-Testing of an Endoscopic Aerosol Box for Preventing SARS-CoV-2 Infection during Upper Gastrointestinal Endoscopy

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ABSTRACT

Objective: The SARS-CoV-2 virus has infected many healthcare professionals. Endoscopy is an aerosol-generating procedure and the endoscopy team is at risk of exposure and infection. We describe the leak-testing of an aerosol box that uses a glove-covering for the endoscope.

Materials and Methods: An endoscopic aerosol box with a glove-covering over the endoscope was made for gastroscopy, EUS and ERCP procedures and was tested for leakage of aerosol/airborne particles. Fine particulate matter (PM) from burnt incense sticks was used as a model for viral aerosol. The leakage from the box was measured by comparing readings from 2 PM light-scattering sensors, one placed inside the box and the other just outside the glove opening in a sealed container. Negative pressure conditions were also used to see if this had any effect on the leakage.

Results: The concentration levels of the particulate matter differed with different negative pressure conditions and movement of the endoscope through the glove. Very little leakage was seen with the endoscope stationary even with no negative pressure, at 2.4%, 0.17% and 0.07% for PM1, PM2.5 and PM10, respectively. The maximum leakage was 14% for PM1, 8.7% for PM2.5 and 2.6% for PM10 in the moving-endoscope condition and no negative pressure. This reduced to 6.2%, 1.3% and 0.37% respectively when suction was applied at full strength (negative pressure of -0.05 bar).

Conclusion: The glove covering significantly reduced the passage of particles. The particulate leak was seen most with the smallest particles and reached 14% for PM1 without negative pressure. This reduced to 6.2% with maximum negative pressure using the wall suction.

Keywords: SARS-CoV-2, Endoscopy; aerosol; barrier; aerosol generating procedure (Siriraj Med J 2021; 73: 702-709)

INTRODUCTION

The current SARS-CoV-2 pandemic has caused worldwide social and economic disruption and death. The SARS-CoV-2 virus causes gastrointestinal symptoms[1] and has been found in the gastrointestinal tract[2-4] and oral mucosa.[5] There is a risk that the virus may aerosolize during upper GI endoscopy[6], putting the endoscopy staff at risk of infection. International guidelines have recommended, amongst other things, postponing routine procedure, screening patients and wearing appropriate

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http://dx.doi.org/10.33192/Smj.2021.90

personal protective equipment (PPE) during the endoscopic procedure.[7,8] However, guidelines have not recommended the use of any additional barrier methods other than PPE in preventing aerosolized droplet spreading to the endoscopist.

A similar concern for the infection risk from aerosolized droplets has arisen during intubation and extubation of endotracheal tubes for COVID-19 positive patients and a report has suggested that an "aerosol box" can limit the aerosol exposure of the anesthetist during endotracheal tube manipulation.[9] A similar aerosol box has recently been proposed for use in upper GI endoscopy to prevent aerosol exposure of the endoscopist.[10] More recently another report has described an adaptation of the aerosol box by using a glove covering for the endoscope as it enters the box.[11]

Our upper GI endoscopy aerosol box is an adaptation of the aerosol box described above, made specifically for upper GI endoscopy. Although the core concept of our aerosol box is similar in the use of a glove-covering for the endoscope, we had designed it prior to seeing the report above and have some differences to the design. In this report we describe our design of the endoscopic aerosol box and the results of leak testing from the box using fine particulate matter (PM1, PM2.5, PM10) as a model for viral aerosol particles.

METHODS AND MATERIALS

The aerosol endoscopic box used in this study was designed, tested and produced using transparent acrylic plastic material (Fig 1) prior to seeing the reports from Japan.[10,11] The essential component of the adapted aerosol box in this study is the opening through which the scope is passed. The opening uses a rubber glove to cover the endoscope to prevent viral aerosol and droplets from reaching the endoscopist. The adapted aerosol box has a round opening with raised rounded edges with a diameter of 9 cm specifically made so that the rubber glove may be stretched over and attached to it (Fig 1). This opening is on a separate acrylic plate that can be slid into a slot on the main aerosol box (Figs 1 & 2). Three plates, each with the opening at a different position on the plate, are available for use with each endoscopic aerosol box, so that the position of the opening can be adjusted to be opposite the mouth of each patient.

To use the rubber glove as a covering for the endoscope, a small cut is made in one of the finger-ends of the glove, through which the endoscope could be passed (Figs 3 & 4). The size of the glove can be varied depending the diameter of the scope. During the procedure, the scope has room to maneuver as the opening of the box where the glove is attached to is 9 cm in diameter. As the scope is removed at the end of the procedure, the glove finger can be pinched to prevent leakage and another glove can be placed over the opening to seal off any possible aerosol leak once the endoscope is completely removed. The glove(s) can then be removed and disposed appropriately at the end of the procedure. The other sides of the box have openings which can be opened and closed, to be used for reaching into the box as necessary, while the pedal side of the box (where the patient's body extends) can be covered with a waterproof material that is attached to the box and sealed around the patient (see example in Fig 2 below).

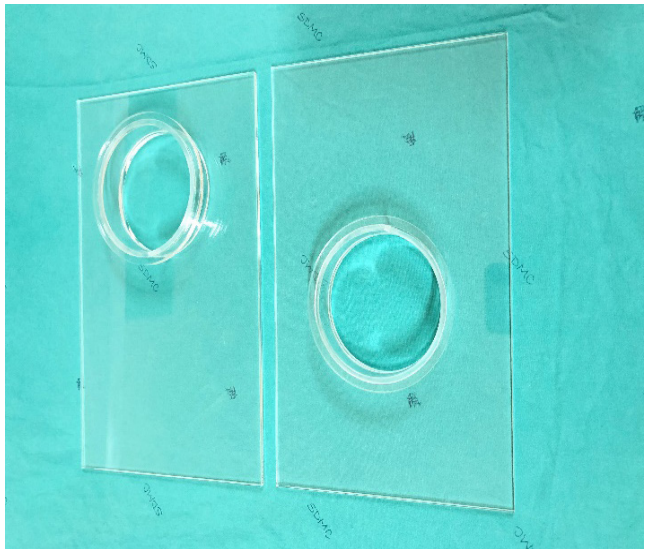

Fig 1. Acrylic plates with the opening for the glove cover at different positions.

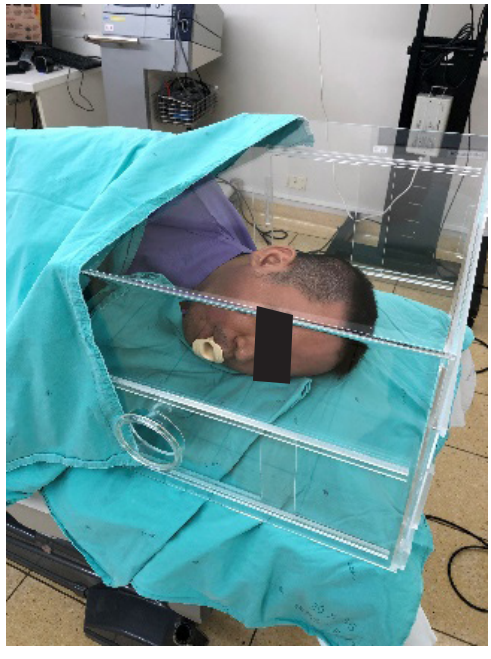

Fig 2. The transparent endoscopic aerosol box, showing the opening for the scope (An endoscopy unit staff is modeling as the patient).

Fig 3. The endoscope passing through the cut end of the finger of the glove.

Fig 4. The insertion of the endoscope through the glove when attached to the opening of the endoscopic aerosol box. (An endoscopy unit staff is modeling as a patient).

The adapted aerosol box also has other smaller openings to allow various tubes to pass through (but can be closed if not used). It has a separate smaller hole through which a rubber tube can be inserted and negative pressure applied using an additional wall suction. In our experiment, two modes were used, regular and high suction modes, producing pressures of -190 mmHg and -280 mmHg respectively. This tube, which could be attached to a ventilator HEPA filter, is used to suck out the air inside the box and remove both the carbon dioxide and viral aerosol from the box. There is also another opening through which the ventilator's corrugated tube can pass in cases where the patient is intubated.

The design of the box is shown in the supplemental materials.

The endoscopic aerosol box was tested for leakage of fine particulate matters (PM1, PM2.5, PM10) produced from burning a commercially available incense stick inside the endoscopy aerosol box. This was used as a model for viral particles. In order to monitor the leakage characteristics of the box, the testing method similar to that done by Ng et al.[12] was adapted. The leaked fine particulate matter was measured with an optical sensor (PMS7003 G7 sensor Module Air Particle dust laser sensor) capable of scattering and absorbance measurements of light to target in situ sensing of fine particulate matter. The sensing system had the capability to measure the averaged concentration of particulate matter sized 1.0 mm, 2.5 mm and 10 mm. One sensor was placed in the endoscopic aerosol box with the burning incensing stick and another was placed in a sealed container attached to the endoscope-glove-opening of the box to measure the percentage leakage of the particulate matter through the opening. The sealed container prevented entry of fine particulate matter from the ambient environment which would distort the readings of the leaked PM from the box. The concentration of the particulate matter was measured simultaneously and at the steady state, defined as no progressive increase or decrease in concentration over 2 mins of observation.

The light scattering sensor was also able to measure the ambient pressure and this was used to measure the level of negative pressure achieved in the box at different levels of wall suction (no suction, regular suction, high suction). An Arduino UNO was used as an interface between a computer and the sensing system. The data acquisition was performed through a serial communication application that was developed within the Arduino platform. Due to the sealed container holding the PM sensor, an actual endoscope could not be passed through the glove and a large pen with a similar diameter to a gastroscope was used in its stead. The attached glove was cut at the fingertip and the pen was passed through the cut opening connecting the inside of the aerosol box to the sealed container holding the sensor. The PM leakage was measured when the pen in a stationary position, and also when the pen was moved vigorously (to mimic movement of the endoscope), and at different levels of suction/negative pressure within the box. The ambient leakage of the particulate matter was also measured near the other openings on the side of the box closest to the patient's vertex, through which the corrugated tubes leading to the ventilator would pass. The PM sensors would measure the three PM levels every second and record these in the computer.

The set up for the PM leakage test is shown in Fig 5.

The study was approved by the local ethics committee of the hospital (COA. MURA2020/799) on the 14th May 2020

Fig 5. The set up for testing PM leakage from the opening with glove attached. The burning incense stick can be seen in the endoscopic aerosol box and the two PM sensors are placed inside the aerosol box and the sealed compartment attached to the endoscope-glove opening respectively.

Statistical analysis

Statistical analysis was performed using SPSS Statistics by IBM version 25. Continuous variables with normal distribution were expressed as mean (standard deviation) and analyzed with student T-test. Paired t-tests and Pearson correlation were performed to compare the leakage rates using different suction pressures within the endoscopic aerosol box.

RESULTS

The overall averaged concentrations of PM 1.0, 2.5 and 10 inside the chamber (n=14, $p<0.05$) were found to be 140 μg/m^3, 2,134 μg/m^3 and 6,089 μg/m^3 respectively.

Tests were conducted at different pressure conditions to identify the role of pressure/suction on the concentration of particulate matter in the chamber and the effects in controlling the leakage. The results are shown in Table 1. As can be seen from the table, negative pressures produced by wall suction reduced the PM concentration in the chamber, particularly PM1 and PM10.

To determine the rate of leakage from the chamber, paired t-test was conducted on the set of raw data measured from the chamber and the target location corresponding to the different testing scenario. The results are tabulated below in Table 2. Thus the leakage was calculated as a percentage of the averaged concentration in the endoscopic aerosol box.

Very little leakage occurred when the pen was stationary, with PM1 leak of 2.4%, PM2.5 0.17% and PM10 leak of 0.07%. There was no detectable leakage when the pen was stationary and the suction was on. The highest leakage of 14% was recorded the pen was moved vigorously in the glove without any suction pressure. But the averaged concentration of leaked PM1 decreased subsequently to 8.9% and 6.2% when negative suction pressure was increased from zero to -0.01 and -0.05 bar respectively. A similar trend was observed in the ambient leakage test. Another trend was evident regarding the size of the particles; the leakage was higher for smaller particle size.

The effect of pressure on leakage can also be comprehended from a Pearson-correlation test which correlated between the pressure and PM concentration levels as shown in Table 3 below.

TABLE 1. Concentration of particulate matter for each pressure condition at stable state.

Pressure (bar)	Concentration of Particulate Matter inside Chamber at Stable condition(μg/m^3)		
	PM1.0	PM2.5	PM10
0	210.53 (SD=12.46 CV=0.059)	2531.7 (SD=85.5 CV=0.03)	10792.8 (SD=408.5 CV=0.03)
-0.01	148.5 (SD=12.44 CV=0.08)	2312.01 (SD=213.1 CV=0.09)	6662.2 (SD=562.6 CV=0.08)
-0.05	96.3 (SD=8.67 CV=0.09)	2298.4 (SD=155.99 CV=0.067)	3831.817 (SD=491.9 CV=0.12)

Abbreviations: SD= standard deviation, CV= Coefficient of Variation.

TABLE 2. The percentage of particulate matter leak from the averaged PM level in the endoscopic aerosol box for each pressure level

		Leakage %		
	Chamber Gauge Pressure(bar)	PM1	PM2.5	PM10
Without Moving pen	0	2.4	0.17	0.07
	-0.01	0	0	0
	-0.05	0	0	0
Moving pen	0	14	8.7	2.6
	-0.01	8.9	1.5	0.75
	-0.05	6.2	1.3	0.37
Ambient Leakage	0	9.6	7.6	3.7
	-0.01	3.2	0.6	0.4
	-0.05	2.4	0.4	0.2

TABLE 3. The effect of pressure on PM leakage

	Pressure	Pm1.0	PM2.5	PM10	
Pressure	Pearson Correlation	1	.434	.481	.501
	Sig. (2-tailed)		.243	.190	.170
	N	9	9	9	9

When the incense stick was removed from the box, the rate of reduction of the fine particulate matter inside the box, with the wall suction at -0.05 bar, is shown in Fig 7. As can be seen from the graph, it took approximately 2 mins, using the high suction mode, for the PM10 concentration to decrease by 50%.

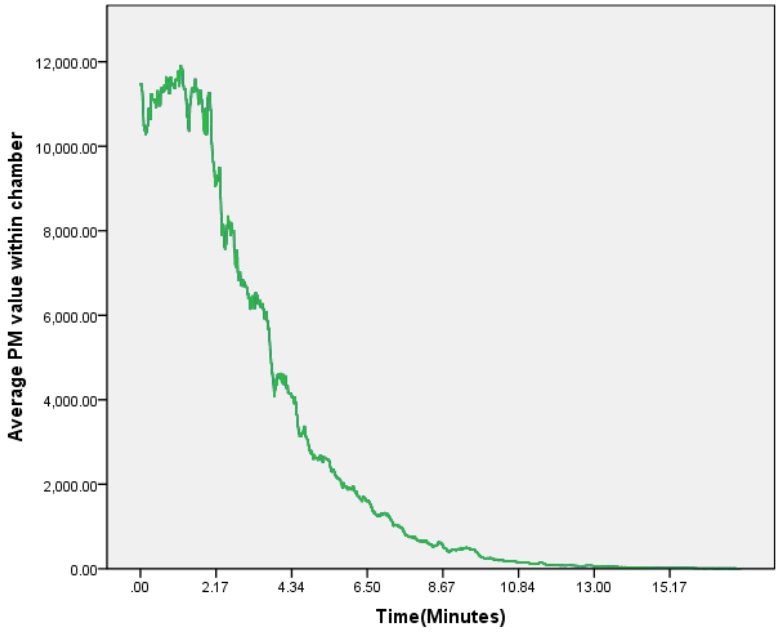

Fig 7. The rate of reduction of PM10 within the box with aspiration of the air inside using full strength wall suction.

DISCUSSION

The SARS-CoV-2 virus has infected many healthcare workers[13,14] and is transmitted by aerosols and droplets.[15] It has also been found in the buccal mucosa and the gastrointestinal tract.[2,4,5] Gastroscopy and EUS/ERCP are thought to be at-risk procedures because of aerosol generation from the patient.[6] For protection various endoscopic societies have recommended endoscopists wear PPE for protection.[7,8] Here we report the evaluation of an endoscopic aerosol box using a glove-cover opening, which was designed to decrease aerosol exposure to the endoscopist.

Previously an aerosol box for endoscopy has been reported, similar in design to that suggested for intubation by anaesthetists, with just a hole for the endoscope to pass through. However, there is a concern that the virus may be airborne and much smaller particles are produced by the patient[16] and therefore the risk of exposure may not be solely from the spray of large particles. Another recent report in fact raised the concern that these 'open' aerosol boxes may actually increase the exposure for medical personnel to the virus.[17] An endoscopic aerosol box barrier with a glove-covering for the endoscope may thus be a solution to reduce the exposure of viruses to the endoscopist, both from direct spray of large particles and leakage of smaller particles from the box.

Although there has been an earlier publication describing an aerosol endoscopy box using a glove-covering for the endoscope[11], our aerosol box was designed independently and our study was performed before seeing the publication. Our aerosol box design also varied in some ways from the prior published design. Our aerosol box used a different method to attach the glove, had sliding doors/ openings which could be used to pass tubes or for assistants to insert their hands to help the patient if necessary, and our aerosol box was also smaller in design so that it would be easier to close off the open side where the patient's body protruded, to prevent small particulate matter/aerosol leak, rather than just preventing direct spray from the patient's mouth.

We tested the passage of fine particulate matter of different sizes leaking through the glove-covering of our aerosol box. Although previous articles have demonstrated visually that such a design may decrease the amount of sprayed droplets from patients[10,11], we quantified the amount of leakage of small particles of different sizes. The different sizes of the particulate matter used in our experiment was used to demonstrate the different levels of leakage of SARS-CoV-2 virus particles depending on their size, as there is a concern that viral particles are produced from infected patients in a variety of sizes.[16] This leakage is likely to be more pronounced in 'open' aerosol boxes.

Our results demonstrated that there was very little leakage of PM of all sizes when the glove covering was used and pen/endoscope model was stationary (2.4%, 0.7% and 0.17% for PM1, PM2, PM10 in the no suction group respectively, and no leakage when suction was switched on), but this increased when the pen was moved vigorously. The results also demonstrated that smaller particles leaked more than larger particles. The percent leakage was 14%, 8.7% and 2.6% for PM1, PM2.5 and PM10 respectively, when measured in the worst condition, namely vigorous movement of the pen with no suction applied. The leakage was reduced when the suction was turned on and negative pressure was applied through a rubber tube inserted into the box. The leakage dropped to 6.2%, 1.3% and 0.37% for PM1, PM2.5 and PM10, respectively. We suspect that this situation would be closest to clinical practice, and this would therefore mean than the glove-covering, along with wall suction, would help reduce the exposure of approximately 93.8%, 98.7% and 99.6% of exhaled aerosol with approximate sizes of PM1, PM2, PM10, respectively, for the endoscopist during the procedure. We also demonstrated that the wall suction, commonly used for aspirating saliva during an endoscopic procedure, when used to suck out the air in the endoscopic aerosol box, was able to reduce the PM level by 50% over an interval of approximately 2 minutes. The use of the pen as a model for the endoscopy was necessary to keep the particulate matter inside the container for analysis. However, during the testing of our model, we wiggled the pen very vigorously, much more than an endoscope would normally be moved in a procedure done by an expert. Consequently, we think that our results cover the range of leakage that would be seen in a normal gastroscopy. In a separate on-going study, the use of the box (in non-COVID-19 patients) was not difficult for expert endoscopists, and the movement of scope was not thought to be limited nor need to be specifically adapted for the glove covering. The normal endoscopic movements in and out of the glove in a straight path would minimize the aerosol leakage from the covering.

The glove covering set-up for our aerosol box could be used repeatedly with cheap and commonly available materials. It also allowed flexibility of movement of the scope during the procedure whilst also preventing viral aerosol directly reaching the endoscopist. A report has suggested that uncovered openings of the aerosol/intubation boxes actually increase the risk of airborne exposure from the patient.[17] Although we did not directly compare with

other aerosol box models, our glove-covering model for the endoscopy should decrease exposure from both the direct spray of large particle aerosols, and the leakage of smaller airborne particles from the patient in comparison to uncovered intubation boxes. Although in our model we used the rubber gloves available in our endoscopic unit as it was cheap and easily available, other gloves, such as latex-allergy gloves could be used. Theoretically other elastic materials could also be used as the endoscope cover, but we thought that general availability and cost of the material would be important in the situation of the pandemic, so we did not try to test other materials in our model.

We also note that another group has suggested using an anesthetic mask to prevent aerosol droplet spread during the endoscopic procedure.[18] We think that our endoscopic aerosol box allows more flexibility for the endoscopist in two ways. Firstly, larger endoscopes, such as those used for endoscopic ultrasound or ERCP with stent removal, may be more easily manipulated using our endoscopic aerosol box, as the opening size can be varied as needed. Secondly, the box can easily be used for the intubated patient, in comparison to the anesthetic mask which would impede the endotracheal tube. This may be particularly pertinent for the patient with COVID-19 who may have problems with oxygenation or in cases with variceal bleeding who require intubation.

In comparison to a box with a single uncovered hole for the scope, as suggested by Sagami et al[10], we think that our design is also more flexible. The positioning of the opening hole and scope can be adjusted to different patient size and anatomy, as well as the opening can be adapted for endoscopes of differing sizes. As mentioned previously, Kagami et al. reported the use of the glove-covering for an endoscopic aerosol box.[11] Their design appears to be slightly different to ours, and as their design has only been reported briefly, so we are unable to see if there is any practical difference compared with our design.

We have used the endoscopic aerosol box in our unit on patients for EGD, ERCP and EUS without any complications. However, because Thailand had managed to control the initial spread in the country well, and testing was limited to symptomatic or high-risk patients, we did not have any confirmed COVID-19 infected patients to use the aerosol endoscopic box on. Nevertheless, we feel that the box is a useful equipment to improve the safety of the endoscopy team, and we wanted to report and share the design of the endoscopic aerosol box for other endoscopists to use in view of the ongoing infection from SARS-CoV-2 virus in many countries. The design can be seen in the supplementary data, and can be copied and used without asking for further permission. Some adaptation and change in size of the box may be required for the larger Caucasian and African population. In the future the glove-covered aerosol box may be useful for endoscopy of patients with risk of other infections such as patients with active tuberculosis.

The main limitation of this study was that the use of fine particulate matter from burning an incense stick, as a model for viral aerosol, may not have been identical to real-life conditions as the concentration from the incense stick did not fluctuate with respiration or coughing. Further testing with models that are closer to human respiration/coughing would be useful to confirm the benefit of the box and the level of particle leakage from the box. Also, we could not measure the leakage of particles at the time of removal of the box for cleaning. We do not know if endoscopy assistants would be at increased risk during the removal of the box and during cleaning or not. However, the endoscopic aerosol box is easily cleaned by wiping with 75-90% alcohol solution and washing with liquid soap.

CONCLUSION

An endoscopic aerosol box using a glove-cover for the endoscope decreased the leakage of fine particles of various sizes substantially. The addition of negative pressure to remove the air inside the box using standard wall suction decreases this leak even further. The combination of the endoscopic aerosol box with a glove cover and in-box suction would decrease the risk of infection from COVID-19 infected patients for the endoscopist and other team members. The box may be replicated and used in areas with high COVID-19 prevalence to reduce the transmission to healthcare staff during endoscopy.

ACKNOWLEDGMENTS

We are grateful for Mr. Bibhu Sharma from the BART lab, Faculty of Engineering, Mahidol University for helping with the PM measurement and analysis. We also thank Mr. Noppon Chuklin and Retail Business Solutions Co Ltd for the production and design art of the aerosol endoscopy box.

Supplemental material: Design specifications of the endoscopic aerosol box.

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Operating Room and Flight Deck: What Do These Places Have in Common?

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ABSTRACT

This review article grounds itself into the advent of aviation safety concepts that share some aspects into healthcare industry, practically and theoretically. These concepts are originally invented for aviation-related operation to ensure safety in flight but there are some aspects that can be related to healthcare context especially in surgery. Because aviation and healthcare are high reliability industries and neither patients nor passenger safety are compromised, safety concepts from aviation may prove useful for healthcare. The objective of this review was to scrutinize the concepts of aviation safety that may be applicable to healthcare. Data collection was based upon a review of literatures. This review article contributes to a broader knowledge from both fields of work regarding operational safety. The review shows that there are several practical concepts including Crew Resource Management, checklists and readbacks, sterile cockpit, and human factors of fatigue and stress that healthcare professionals can adopt and adapt them into their daily operation. Moreover, theoretical concepts such as Swiss cheese model and Threat and Error Management can be applied into healthcare context. This review invokes scenarios of each concept from both industries. The results show that communication is the key to promote safer operation and those concepts can be adopted to promote better safety at work. Future studies should extend the concepts of this review into an experimental research to analyze the effect of concepts on actual healthcare settings or utilize qualitative study to investigate the application of concepts in healthcare environment.

Keywords: Aviation; patient safety; pilot; safety; surgeon; surgery (Siriraj Med J 2021; 73: 710-720)

INTRODUCTION

Safety is essential and considered an utmost goal in aviation. The problem is that aviation accidents always result in enormous loss of life and assets, attracting worldwide attention as well as huge financial costs for all stakeholders. Therefore, the aviation industry is rigorously determined to learn from past lessons from incidents and accidents to prompt better safety procedures and practices. In terms of the rules in pilots' standard operating procedures, there is always someone who has paid for it with their life. In an honest, sincere and truthful way, pilots' standard operating procedures are written in blood. Thereby, pilots have an interest in conforming to the rigorous safety policies and procedures they must follow as the probability exists that they would pay for any shortcomings of the safety procedures with their own lives as well. These are the reasons why the aviation industry has instigated a dominant

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http://dx.doi.org/10.33192/Smj.2021.91

safety culture. However, pilot error seems to remain the primary cause of aviation accidents.[1] On the other hand, medical errors in the healthcare industry provide a serious threat to patient safety as they are estimated to be accountable for 3% of all hospital admissions.[2] Toward the goal of reducing the risk of patient harm, the notion of aviation safety policies and practices may be adopted for the medical field, especially for surgeons. Both the operating room in a hospital and the cockpit in an aircraft, surgeons and flight crews, share a lot of things in common in terms of rigorous training, in-depth technical knowledge, keen eye-hand coordination, and responsibility for operational safety. Moreover, these intangible components of professionalism in both professions are commodified and considered valuable capital for an organization.[3,4]

The objective of this review article is to scrutinize the advent concepts of aviation safety that may be applicable to the healthcare industry. Data collection was based upon a systematic review of related literature including texts, research papers, practitioner papers, academic manuscripts, and other relevant online resources from both academic and practitioner perspectives. This review article contributes to a broader knowledge from both fields of work regarding operational safety.

Described below are reviews of several aviation safety concepts, practically and theoretically, that have been introduced and could possibly be adapted into medical practices. This review article also aims to incorporate existing safety-related literature, pointing towards reported aviation safety philosophy and providing examples related to daily surgical practices.

Practical Concepts

Crew Resource Management (CRM)

Hazard industries, namely healthcare and aviation, rely mostly on effective teamwork exercise owing to the complicate, dynamic and critical safety nature context of their industries. It is inadequate that these teams are built upon individual experts, but the team itself must be high expertise team in order to practice high level of technical performance and team attitudes and behaviors to function safely and adaptively to achieve goals. An expert team is defined as a set of interdependent team members, each of whom possesses unique and expert-level knowledge, skills and experience related to task performance, and who adapt, coordinate and cooperate as a team, thereby producing sustainable and repeatable team functioning at superior or at least near optimal level of performance.[5] Team working on surgical operation share similar characteristic to those in aviation in that they operate in high-risk environments where situation between life and death of patient involves. Moreover, team members always change and surgical operation team are built upon skillful individuals such as surgeons, anesthesiologists, anesthetists, nurses and medical technicians who might or might not know each other and might not have been working together before. Members need assurance that their teammates know and understand their duties and can use their abilities and knowledge collaboratively to intervene or recover operation. This can be built over time as members feel familiar with each other and improve personal working relationships. When there is the possibility for things to go wrong or rapidly deteriorate at work such as midflight engine failure in aviation or a patient blood pressure rapidly drop during operation, there is even more reliance on the teamwork capability to respond quickly to manage the unforeseen situations.[6]

Apart from those CRM factors aforementioned, there are several crucial elements regarding CRM practices that describe safer operation among aviation and medical practitioners alike. These are situation awareness, decision making and SHELL Model.

Situation awareness comprises three stages which are, the perception of the elements in the environment in a matter of current time and space orientation, the comprehension of their meaning and the projection of their status in the near future and thus, proper decision making is made to mitigate risks.[7] With these three components combined, situation awareness may support better choice of action as this involves cognition and short-term memory or working memory. Moreover, situation awareness is relevant to dynamic working environment such as flight deck and operating room and hence is not the same as the still knowledge of long-term memory under static working 1condition.[8] Flight crew and surgeons, who are always situationally aware, have an ability to access to a precise mental representation of the dynamic environment that is broader than that which can be upheld in the restricted capacity of working memory. For instance, in aviation 1context, during final approach stage, there is a sudden conflict of aircraft traffic during final approach path, but if the good situation-aware pilot can call on suddenly to respond accordingly to this situation, the pilot will decide accordingly to maneuver aircraft so rapidly and accurately that the flight path is safe from air traffic collision during final approach due to the ability to rapidly access the information from working memory.[9] In healthcare context, during perfusion and cardioplegia management, after an administration of a bolus of cardioplegia solution, the surge11on notifies

that the heart is filling up with blood or full heart. The good situation-aware surgeo1n can recall to root cause suddenly to respond to this situation that there might be an improper operation of heart-lung bypass circuits. The surgeon suddenly makes a decision to fully isolate the heart's profusion circuit by adjusting the aortic cross-clamp and bolus of cardioplegia will later on be re-administrated.[10] Situation awareness helps support the response to the unexpected events that may arise anytime during their flight mission or operating procedure.[11]

According to SHELL model in Fig 1, this model can help understand human factor element in CRM concept. The SHELL model is a conceptual model of human factors that helps clarify the human factor relationships between resource, system, environment and human.[12] The model represents several wavy squares to illustrate different elements of imperfect interacting components which are Software (policies, procedures, practices), Hardware (machines, aircraft), Environment (working context) and Liveware (man). The core component of this model is the man (Liveware), flight crew or operating room crew in this case, and this is considered as the most sensitive system component as human is subject to great variation in performance and limitation and all other components ought to be adapted to fit with this centered Liveware such as Liveware-Hardware (man and machine), Liveware-Software (man and procedure), Liveware-Environment (man and working environment). According to CRM concept, Liveware-Liveware (man and man) is the most essential interaction term as this interface is about interpersonal interaction; moreover, the human is the weakest point in safety operation and considered as the major cause of an accident.[13,14] Liveware-Liveware (L-L) interaction encompasses the interrelationships among the individuals within operator groups. In aviation context, pilots are the centered liveware that interacts with engineers, ground crew, cabin crew, air traffic controller and passengers. In healthcare context, surgeons are the centered liveware that interacts with anesthesiologists, anesthetists, perfusionist, medical interns and patients. Human interaction can influence work behavior and performance. Thereby, the L-L interface is mostly concerned with interpersonal relationship, crew cooperation, communication and leadership. Poor L-L interface can be result in a risky working situation. For example, bad interpersonal relationship between captain and first officer can lead to an undesirable cockpit environment and this can also lead to an accident as seen in Korean Air Flight 801. First officer and flight engineer failed to challenge captain for the wrong ground base radio navigation aid approach and captain did not listen to his subordinates then the aircraft crashed into the hill about 3 nautical miles short of the runway.[15] To mitigate L-L interface risk, appropriate CRM training can be applied to those flight crew and operating room crew that always assigned to work together as a team.[16]

Fig 1. SHELL Model Adapted from ICAO

Both healthcare and aviation are high reliable industries and specific training is necessary. Crew Resource Management (CRM) concept is introduced to support and enhance teamwork exercise and team performance. CRM is the effective use of all available resources for flight crew personnel to assure a safe and efficient operation, reducing error, avoiding stress and increasing efficiency.[17] This type of training incorporates simulator-based scenarios and on the job training (OJT) to allow team members to practice both technical skill and soft skill and attain feedback on their performance from instructors. CRM ensures that team members responsibilities are clearly defined and properly delegated when a sudden change in workload occurs. In summary, it helps team members to solve unforeseen problem.[18] In aviation, problem solving is more efficient when the immediate corrective actions of designated crew members are clearly defined. In operating room, the need for close cooperation and intensive communication between members may be slightly deviant from aviation as many surgeons, anesthesiologists, technicians and nurses tend to focus on their own work and only consult with each other whenever they need.[19,20] However, cardiac surgeons represents a close CRM practice to pilots seeing that they are accustomed to frequently communicate with perfusion technicians, anesthetist and anesthesiologist at their mission.[21] Less cooperation between medical staff in operating room tends to rise due to distinct and delimit competencies and responsibilities of surgeons and anesthesiologist compared to flight crews. Disagreement

between surgeons and anesthesiologist needs to be resolved by absolute consensus as these two professions share the same level of responsibility. While in aviation, captain or Pilot-in-Command (PIC) always has ultimate decision.[22] In practice, active communication between operating team members is the key and can help improve a smoother operating process and yield a better result. For example, if anesthetists were briefed in advance regarding patient condition, they would cope with hemodynamic and metabolic changes confidently and then they can mitigate the risk of detrimental impact from aorta-cross clamping.[23]

Checklists and readbacks

In aviation context, checklists have been developed for each phase of the flight mission including taxi, takeoff, climb, level flight, descend, approach and landing as well as for emergency situations that may arise during mission. Pilots are strongly encouraged and committed to abide by these checklists and any deviation from checklists is considered a flight regulation violation. Moreover, checklists are specifically designed to the specific type of aircraft to assure that all safety-related elements are included. In healthcare, back in 2008, the World Health Organization (WHO) released surgical safety checklists to embrace patient safety. WHO surgical safety checklist tries to imitate each phase of the flight mission by dividing each phase of surgical operation including anesthesia, incision and wound closure.[24] Even though WHO did not force medical practitioners to adhere to this checklist but WHO strongly encourages them to edit the proposed checklist to their own operation. In fact, by customizing checklist for their own interests of interventions like aviation checklist that is tailored made for specific type of aircraft, may seem logical.[25] For instance, vascular surgery operation might need different safety checks for endovascular procedures than for orthopaedical surgery. For the most complicated or infrequent performed procedures, even more intervention-specific checklist may be necessary.[26]

Effective, yet efficient communication is determined as a very basic human necessity which is particularly essential to assure safety in high-reliability industries, healthcare and aviation alike. In spite of minor error in communication during operation, damage and loss can be anticipated.[27] A readback, in aviation, is defined as a procedure whereby the receiving station repeats a received transmitted message or an appropriate part thereof back to the transmitting station in order to obtain confirmation of correct reception.[28] In short, the process of readback involves the person receiving information repeating it back verbally to the sender and this will let the sender know the message has been received and provides a chance to correct any discrepancies. Some past air accidents involving poor communication between pilots and air traffic controller and this emphasizes that human errors in communication still occur even in advances technology in aviation. On the contrary, it is essential to develop communication phraseology or standard protocols in high-reliability industries like, marine, aviation and surgery.[29] Past study revealed that a significant source of surgical errors can be contributed to a poor communication before, during and after surgery. Poor verbal communication accounted for approximately 85% of undesired event related to verbal communication but poor written communication only accounted for approximately 4%.[30] According to this result, the patient safety needs formal readback. Readback, in this medical-related case, can be ranging from readbacking orders among team members operating on patient so as to reduce incidence of perioperative complications to readbacking medication orders over the phone when verbal transmission of critical information is inevitable.[31,32] Past study quantified the impact of readback as a communication technique for improving transmission of clinically relevant information during a critical phrase of work. It found that when anesthetists mentioned items of information to anesthesiologists in a simulated emergency situation, the anesthesiologists were much more likely to correctly answer a question about the information after the scenario if they had repeated it back at the time it was mentioned to them and this could promote a better level of patient safety during operation.[33] Moreover, psychology study also suggested that repeating back important information is likely to help improve memory. This is determined as 'production effect', the phenomenon where speaking words improve memory of those spoken words.[34] While aviation checklists is mandatory to mitigate human error risk that might lead to an unsafe situation, in operating room setting, surgeons and team members should consider which scenarios are critical and design their own specific checklist as per scenarios, especially in the critical phrase of the procedure that requires immediate action.

Sterile cockpit

Even though an operating room is literally sterile for sanitary purpose, sterile cockpit, in aviation context, does not mean that the flight deck is sanitized by any disinfection agents. It means that the flight crews in the cockpit keep the environment of a cockpit safe from all

non-pertinent conversation and non-essential activities are disregarded during critical phases of flight especially takeoff and landing. This concept of sterile cockpit has stemmed from the notion that distracting activities cause pilot errors and reduce pilot flight performance.[35] Nonetheless, the working environment of an operating theater is less structured than a cockpit with much more distractions including noisy sound from outside operating room, ringing phone, non-relevant conversation about next patients among members, inquiries from medical students and nurses, and many more.[36] These are sources of distraction and might contribute to a lower levels of dexterity and concentration of surgeon at procedure.[37] For instance, a cardiovascular surgeon is going to start a complex endovascular procedure that two catheter introducers have to be placed. While attempting to bilateral femoral access, surgeon is distracted by an incoming phone call consulting about previously operated patient and the assisting medical student needing to discuss his report log. In the same time, anesthetist has left the operating room to fetch a stent graft and the anesthesiologist also left the room for a coffee break. Later on, surgeon finds out that heparin was administrated twice from new coming anesthetist and anesthesiologist. Countermeasures to mitigate the distraction risk could be simple such as reducing background noise by using sound proof material wall or prohibition of phone call might help create more peaceful environment. Lead surgeon can encourage team members to regain a focus by telling them that a critical phase of procedure is about to commence and all team members need to focus on the work at present before everything else. As the concept of sterile cockpit is to remain focus and concentrate on the current critical situation, surgeons ought to perform leadership and professional demeanor at work and they must take the current job at hand seriously.[38]

Human factors: fatigue and stress

Fatigue is one of the most common physiological problems for flight crews and will adversely affect individuals who are otherwise in good health condition. It has frequently been considered as the causal factor in aviation incidents and accidents as fatigue degrades performance and tired flight crews cannot carry out flying tasks as reliably and accurately as they should normally perform. Moreover, They are irritable and less alert, willing to accept lower standards of accuracy and performance.[39] Fatigue begins when the pilot commences a flight continuously and increases with each hour in the air. As a result, at the time of landing when reflexes and judgement should be at high, the pilot is most affected by the cumulative effects of fatigue. In addition, the major danger of fatigue is that it is cumulative and the pilot might not recognize its effect. Fatigue can be caused by many factors such as lack of sleep, poor food, long-haul flight, heavy workloads, frustration from work and uncomfortable working condition.[40] In this matter, pilots share the same occupational fatigue with surgeons. Many surgeons also face long working hours, night shift duties and several pressures at work. The effect of fatigue from various factor such as long working hour and work challenges on the quality of work of surgeons has been studied and it effect the same way as found in pilots.[41] Acute fatigue is easily treated by good nutrition and sufficient rest. A sound physical condition and a healthy psychological attitude combining with good diet and adequate sleep are pilots and surgeons best super weapons in fighting fatigue.[42] For the long working hours in surgeons' duty, hospital managements and surgeons need to work together and discuss the proper working hours. If surgeon and anesthesiologist decide to adjourn a procedure in case of fatigue and weariness, it may turn out to be better off for patient safety and hospital management should consider this as a proper decision.[43,44]

Stress indeed is generated by the task itself and it is not always negative as the sympathetic nervous system responds to stress and supplies the resources to deal with the upcoming demands. Factors contributing to stress are generally classified into three categories which are physical, physiological and psychological stressors. Physical stressors include extreme temperature, noise, vibration, lack of oxygen, etc. Physiological stressors include fatigue, hunger, disease, etc. Psychological stressors relate to emotional factors such as worries, poor personal relationship, financial problem, etc.[45] It is quintessential that both pilot and surgeon are able to recognize when stress levels are getting too high. If they are suffering from domestic stress, divorce, bereavement or even moody sensation, the cockpit or operating room might not be suitable places for them. Besides, the stress of flying or operating also consume energy. This energy is derived from oxygen and blood sugar. Pilots who fly for too long without eating or surgeons who operate procedures for too long and skip meal will face low blood sugar or hypo glycaemia; that is to say, their energy reserve will be low and cause reactions to be sluggish and effect their work performance drastically.[46] Due to high-reliability work context in aviation, every pilot needs to pass physical and mental fitness checkup annually to be qualified for flight duty

and medical fitness. This ensures adequate operational safety in every flight. Sign of chronic stress are varied such as forgetfulness, repeated mistakes, tense stomach and it may erode individuals' self-image. Challenges at work can also lead to burnout.[47] However, stress is manageable. There are several ways that pilots and surgeons can deal with stress. The physiological stressors can be controlled by maintaining sound physical fitness or getting adequate sleep. The physical stressors can be reduced by making the cockpit or operating room environment as relax as possible. A conscious effort to avoid stressful situation and support from family, friends and colleagues can minimize psychological stressors. If needed, professional mental counseling help restore psychological equanimity.[48-50]

Theoretical concepts

Swiss cheese model

Swiss cheese model, portrayed in Fig 2, was hypothesized that most accidents or incidents could be traced to one or more of four level of failure that had been placed in order consecutively.[51] These four levels of failure include organizational influences (organization-level), unsafe supervision (supervision controls), preconditions for unsafe acts (work-related processes) and the unsafe acts themselves (people). The cheese layers can be portrayed as layers of defenses and the holes are considered as lapses in defensive layers. Whether or not latent or manifested failures, it can be seen that over time, the holes in the cheese will line up straights and threats will find a way to get through all cheese layers and cause an incidents or accidents. This event is considered as a trajectory of accident opportunities. The underpinned concepts proposed by Swiss cheese model is a proper view on human factors in term of error, that is to say, human error is a general symptom of system failures that demands explanation.[52]

In aviation context, for instance, even when many things can go wrong such as an aircraft traffic separation infringement in case that the traffic conflict is not regarded or resolved by air traffic controller, pilots or traffic collision avoidance system (TCAS) in the aircraft will still get the job done and cause a very small chance that aircraft may collide each other midair. Air traffic controller inability to resolve conflict traffic is considers and a threat that pass through a hole of one cheese but pilot and TCAS ability to detect conflict traffic is another cheese that block this threat to pass through. However, if threat can pass through all the layers of cheese, accident or incident can be anticipated. In aviation scenarios, flight crew working for an airline that has poor safety procedure (organization influence) with poor pilot training record and supervision (unsafe supervision) are operating a commercial flight, when there is an air traffic conflict during critical final approach (precondition of unsafe acts), pilots ignore cautions from both TCAS and air traffic controller (unsafe acts). In this case all holes in the cheese will line up straights and threats will get through all cheese layers and cause a serious accident. In operating room context, a vascular surgeon working for a hospital that has marginal standard operating procedure (organization influence) with poorly-trained operating room crew (unsafe supervision) is operating an axillofemoral by pass, the procedure is uneventful until the anesthesiologist notices a sharp drop in blood pressure causing a demand in blood transfusion (precondition of unsafe acts). Anesthesiologist suggests that excessive blood loss is the cause but it is disregarded by surgeon (unsafe acts). Later on, it is found that the cause is stemmed from a disagreement between the

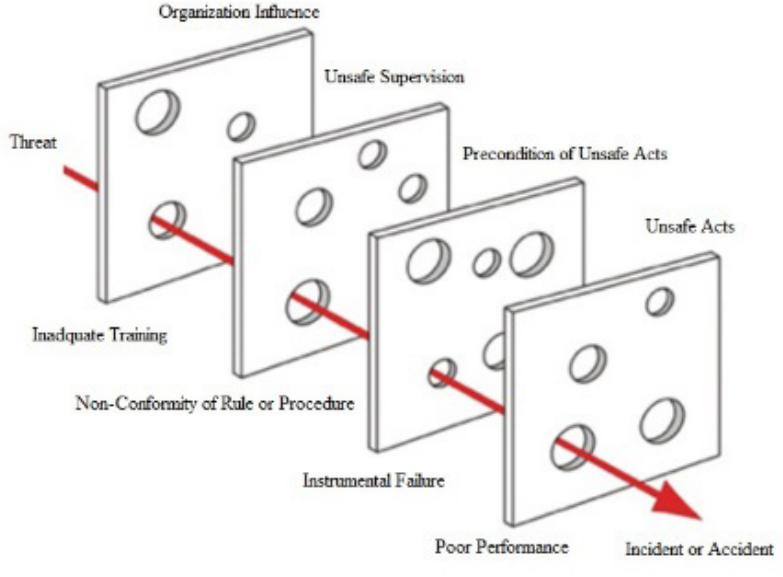

Fig 2. Swiss Cheese Model Adapted from James Reason

forceful femoral pulses and the perceived hypotension. It is also recognized that cross-clamping of the axillary artery has also intervened blood flow towards the radial artery where invasive pressure measurement occurs. In this case, the threat can pass through all defensive line and causing incident.[53,54]

Threat and error management

Originally, threat and error management model may be developed for flight deck operation; nevertheless, this can be used at healthcare or other industries as well. Threat and Error Management (TEM) is a conceptualized framework that helps in understanding, from an operational perspective, the intra-relationship between operational safety and human performance in dynamic and challenging operational context.[55] This model is descriptive and diagnostic of both human and system performance and the main objective of this model is to understand error management namely error detection and error response rather than only focusing on error causality. There are three main components in TEM, from aviation perspective: threats, errors and undesired aircraft states (UAS).

Threats are defined as events or errors that occur beyond the influence of the flight crew, increase operational complexity and which must be managed to maintain the margins of safety.[56] During operation, flight crews need to manage various external complexities. such as adverse meteorological condition, air traffic congestion and aircraft technical malfunction. Some threats can be anticipated as they are expected to flight crews such as adverse meteorological condition and air traffic. These can be found in notice to airman (NOTAM) and weather forecast information. However, some threats cannot be anticipated such as in-flight technical malfunction occurring without any warning. In this case aircrews need to apply skills and knowledge to cope with this threat. To simplify, threats are something bad that arise from outside the cockpit. However, there are some internal threats relating to human factor and limitations such as inappropriate crew scheduling event. When current flight crew are unexpectedly assigned to fly an extra flight due to an absence of other crew calling in sick, this can possibly deteriorate their flight performance and affect human factor limitation, which is fatigue.[57] Another example for internal threat ascribed to human factors is an instant diarrhea attack in flight crew during flight due to unclean food intake or norovirus transmission on an airplane. In this case, good situation awareness needs to be exercised to correct and properly manage the situation. Pilot needs to detect the symptom early and instantly pass aircraft flight control to co-pilot to avoid unusual aircraft flight attitudes.

Error are defined as actions or inactions by the flight crews that lead to deviations from flight crews intentions or expectations.[58] Unmanaged or mismanaged errors mostly lead to undesired aircraft stated and error in the operational context hence leads to reduce the margins of safety and increase the possibility of adverse events to occur. Despite the modern aircraft computer technology, erroneous pilot can input incorrect flight parameter into flight computer and this will lead to future adverse event. Regardless of the error types, errors effect on safety depends upon whether the flight crews detect and responds to the error before it may lead to an adverse event or potential unsafe outcome. From the safety aspects, operational errors that are timely detected and promptly responded to will not reduce margins of safety; besides, proper error management represents an example of successful human performance.[59,60] To simplify, errors are something bad that arise from the pilots.

Undesired Aircraft States (UAS) are defined as flight crew-induced aircraft position or speed deviations, misapplication of flight controls, or incorrect automation system configuration, associated with a reduction in margins of safety.[61] UAS resulting from ineffective threat and error management may lead to adverse situation and reduce margins of safety in flight mission as UAS is the last chance for pilots to act accordingly so as to prevent upcoming incident or accident. Examples of UAS include exceeding speed restriction during an approach, landing short of runway or lining up for the incorrect runway for takeoff. To simplify, Undesired Aircraft States (UAS) are the result from threats and errors.

In healthcare context, disturbing sound made by an overly excited orthopedic surgeon in the operating room nearby or inexperience crewmates performing incorrect procedure may contribute to reduced levels of concentration of a surgeon and these can be considered as threats. Moreover, overwork that causing fatigue and stress and surgeon's poor health condition can be considered as internal threats that affect human factor and limitations. Mismanaged operating treatment or failure to following standard operating procedure due to various factors that are stemmed from surgeon can be regarded as error. A sign of sudden drop in blood pressure and patient arrest are, in this case, considered as undesired aircraft states.

According to Fig 3, at the top of the inverted triangle is considered as safe operations. That is where the operation always strives to be; nonetheless, pilots and

surgeons experience several threats during their mission. Therefore, they should constantly be prepared for those threats to maintain a safe operation. In addition, apart from threat, several errors stemmed from pilots and surgeons can be anticipated. They need to instantly act accordingly to prevent further adverse event that will lead to undesired aircraft states and eventually accident.[62] Proper communication also plays an important role in TEM. It was regarded as Concerned, Uncomfortable and Safety (CUS) words. If surgeons hear another teammate says "I am concerned.", "I feel uncomfortable about this.", or "Patient safety is currently being compromised.", they should stop what they are doing and listen to address those concerns accordingly.

Fig 3. Threat and Error Management Model Adapted from United Airlines

All in all, both practical and theoretical concepts regarding safety can be summarized as shown in Table 1.

DISCUSSION

According to the four operational concepts and two theoretical concepts of aviation safety mentioned previously, it can be seen that there is one element that the concepts have in common, which is "communication". This finding shares the same insight corresponding with past research concerning the impact of communication in healthcare.[63-66] Therefore, even these aviation-related safety concepts might not be entirely applied to healthcare industry. Rest assured; effective communication is still be the key to promote better patient safety in healthcare environment. In regard to effective communication within team members, lead surgeons should lower their ego at work and listen to their team members even more. Even seasoned or highly-experienced surgeons can still be questioned regarding the operating problem at present and their resolution or problem-solving procedure should be explained to their teammates to ensure that the team is on the same page. Surgeons should not take team communication as the challenge to their authority but they should consider the effective communication as a better way to promote teamwork to ensure better patient safety. Another aspect relating to effective communication is briefings, pre-operative briefing is also important to promote patient safety. In aviation, pre-flight briefing is mandatory and this process is written in every company standard operating procedures (SOPs) as pre-flight briefing allows a clear understanding and awareness among flight crew about weather condition, planned flight route, passenger and cargo status and aircraft condition. Healthcare alike, pre-operative briefing regarding patient's status and planned operation procedures could allow a better understanding and awareness among team members at their mission. After finishing flight mission or operating procedure, post-flight debrief or post-operative debrief can be done to summarize overall mission scenarios. By debriefing, team members can be readily prepared for the next mission and apply experience from the past job to the next assignments.

As mentioned earlier, both aviation and health care are high-reliability fields; passenger safety must never be compromised, just as patient safety must never be compromised. That is to say, the margin of safety must never be diminished. Both pilots and surgeons must adopt these safety concepts together with effective communication skills and bring these important assets with them to the cockpit or operating room to ensure more reliability in their day-to-day operations to promote the utmost goal, which is safety at work.

CONCLUSION

This review article aims to portray aviation-related concepts that apply to surgical safety strategies. However, these concepts remain only partially applicable to healthcare. Even though a few of these operationalized concepts have been applied to surgical practice, none have been properly verified or validated. Past studies have claimed that these concepts could improve patient safety and operating outcomes, but there have also been various arguments that these concepts may not be totally compatible with healthcare.[67,68] At the very least, effective communication plays an important role to promote safety at work for both professions. Indeed, despite

TABLE 1. Summary of Practical Concepts and Theoretical Concepts in Safety.

Safety Concepts	Aviation Context	Healthcare Context	Similarities	Differences
Crew Resource Management (CRM)	- Two pilots, which are Captain and First Officer, work with Cabin Crew, Engineer and Air Traffic Controller within the flight mission.	- Surgeon works with Anesthesiologist, Anesthetist, Medical Technician within the operating room.	- Team working operates in high-risk environments. - Team members are skillful and professional and always change in difference tasks.	- Pilot-in-Command or Captain is responsible for absolute decision. - Disagreement needs to be solved by consensus from both surgeon and anesthesiologist.
Checklists	- Checklists are mandatory and any deviation from checklists is considered as a violation. - Checklists have been developed for each phase of the flight.	- Checklists are optional. - Surgical Checklists proposed by WHO can be edited to suite different interests of interventions.	- Checklists have been designed to suite different phrase or different progress of work.	- In aviation, checklists are mandatory. - In healthcare checklists are optional.
Readbacks	- A procedure whereby the receiving station repeats a received transmitted message or an appropriate part thereof back to the transmitting station to attain confirmation of correct reception.	- The person receiving information repeats it back verbally to the sender and the sender will know whether the message has been received correctly.	- The concept of “reading-it-back” to confirm the correctness and completeness of communication.	- In flight, readbacks are required as a transmission over radio frequency might not be clear due to radio noise and frequency interruption. - In healthcare, readbacks are encouraged in the critical phase of clinical communication to promote more patient safety.
Sterile Cockpit	- Flight crews keep the environment of a cockpit free from all non-relevant conversation during critical phases of flight.	- Operating crews encourage each other to regain a focus in a critical phase of procedure.	- The notion of “staying focus” on the critical phase of work.	- Flight deck is isolated and well-structured. - Operating room is less-structured than a cockpit with more distractions from both inside and outside
Human Factor: Fatigue	- Fatigue begins after a long flight hour.	- Fatigue begins after a long hour of clinical work.	- Fatigue degrades work performance.	- Flight duty time is regulated by law. - Management and surgeons need to set a middle ground on working hour.
Human Factor: Stress	- Stress is generated by continuous challenges at flight mission.	- Stress is generated by the operating task itself.	- Mind stress is acceptable but intensive stress will deteriorate work performance.	- Annually, every pilot needs to pass both physical and mental fitness examination before flight. - Physical and mental fitness examination is not required to perform duty in healthcare.
Swiss Cheese Model	- Four levels of failure can be poor SOPs, inadequate training, instrument failure and poor piloting technique	- Four levels of failure can be poor SOPs, insufficient training, poor operating tools technique, and improper operating skill	- Four levels of failure include organizational influence, unsafe supervision, preconditions for unsafe acts and unsafe acts.	- Aviation accident result in enormous loss of lives and assets and pilots pay it with their own life. - Failure in operating room cause a single loss of life.
Threat and Error Management (TEM)	- Threat: Bad weather, congested air traffic, technical failure. - Error: Poor piloting technique, cockpit mismanagement. - UAS: Improper airspeed, Failure to maintain glide path during approach.	- Threat: Improper procedure performed by inexperience teammate. - Error: Mismanaged operating treatment by surgeon. - UAS: A sign of sudden drop in blood pressure, patient arrest.	- Threat is considered as an external factor. - Error is regarded as an internal factor. - Undesired Aircraft States (UAS) is a result from threat and error and this considered as a last chance to correct to prevent future adverse event.	- In aviation, in spite of advance technology of aircraft computer, aircraft automation can be overridden by erroneous pilot. - In operating theater, error can be prevented by suitable communication between crews.

obvious similarities between these two professions, there are a number of differences as well. Besides, the implementation of aviation safety practices and concepts in the surgical context may be less than optimal. For example, pilots are required to conform to flight duty time strictly as this is regulated by law. Nonconformity to this rule and overworking as a pilot can be considered a serious safety violation; both the pilots and their airlines will be penalized accordingly. However, long working hours contributing to fatigue among healthcare professionals are not formally regulated by law. In this matter, hospital management and surgeons need to have a mutual agreement regarding the limits of working hours. Notwithstanding, the sound and solid safety record of aviation has been indisputable and proven itself for decades. These aviation safety concepts will continue to be a useful source of inspiration for any healthcare professional striving to achieve superior patient safety standards.

Limitations

Even though this review article shed light on novel aspects of aviation safety concepts into patient safety in healthcare context, there were some limitations. Because this article is a review article, future study should probably extend the concepts of this review into an experimental research to analyze the effect of those concepts on actual healthcare settings. Additionally, qualitative research may prove useful to investigate the real application of these concepts in actual healthcare context as qualitative study can delve deep down into richer results that quantitative research cannot find.

ACKNOWLEDGEMENTS

The lead author would like to thank my co-authors for great support on this work. This review was funded by Graduate School Scholarship, Prince of Songkla University. Scholarship Contract Number PSU_PHD2562-001

Conflict of interest: There is no conflict of interest.

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Access to Healthcare as a Fundamental Right or Privilege?

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ABSTRACT

Right to health is a government obligation to provide its citizens with necessary medical services regardless of their ability to pay. The right to health requires the state to develop policies and action plans to achieve accessible health care. Ensuring access to healthcare services is an important social responsibility; because of its socio-economic nature, demand for it often carries not only individual but also social aspects that need to be considered and requires the consolidation of consumer funds. Peculiarities of the medical market such as health risk and uncertainty, incomplete information, limited competition, external effects, production of public goods, lead to special forms of economic relations in the medical market, which requires the development of appropriate regulatory mechanisms. In countries, where an individual's financial contribution to health care does not depend on his or her health risk, there is a principle of universal health care, which covers the entire population. Human is a higher social capital for whom health care is considered a right and not a privilege not only for humanistic and moral reasons, but also for rational, utilitarian approaches, as universal access benefits both the individual and society as it increases labor productivity.

Keywords: Healthcare; human rights; healthcare rights; universal healthcare (Siriraj Med J 2021; 73: 721-726)

The scope of the right to healthcare

Human rights are universal legal guarantees protecting individuals and groups against actions and omissions that interfere with fundamental freedoms, entitlements and human dignity. The international community must treat human rights on a global, equitable and equal basis. The state is responsible for protecting human rights, regardless of national identity.

After World War II, the international community adopted the Universal Declaration of Human Rights (1948). The International Covenant on Economic, Social and Cultural Rights and the International Covenant on Civil and Political Rights were adopted by the United Nations General Assembly in 1966. Rights fall into two categories: individual freedoms and population-based entitlements. Population-based entitlements require that the government allocate adequate funds for services, or mandate organizations to pay for services, for example, the right to education or to healthcare.

We must distinguish between the right to health and the right to health care. The right to health includes many determinants of health, such as income and social status, social support networks, education, working conditions, social and physical environments, individual health practices and coping skills, healthy child development, biology and genetic endowment, gender and culture. Thus,

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http://dx.doi.org/10.33192/Smj.2021.92

the right to health requires a much broader guarantee than the right to health care.

According to the Constitution of the World Health Organization, health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity; enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.[5] In many countries of the world, according to the national constitution, the population has the right to guaranteed health care.[6] Pope John XXIII in his encyclical, Pacem in Terris (Peace on Earth), explicitly stated that healthcare is a right rather than a privilege.

The right to health does not mean the right to be healthy, and that the governments of poor countries are obliged to create high-tech expensive medical services for which they do not have adequate resources. However, the right to health care requires the state to develop policies and action plans to achieve accessible health care.[7] Health care, as a right, does not mean the provision of services by medical organizations in the form of charity, or the provision of absolutely all services by the state. The right to health care means that the state is obliged to do everything possible to provide the population with the necessary medical services, regardless of their solvency.

The right to health is assessed according to four criteria: 1) Existence. Public health and medical organizations, goods and services should be in sufficient quantity; 2) Accessibility: Medical organizations and health services should be accessible to all without any discrimination. Accessibility is assessed by 4 criteria: non-discrimination, physical accessibility, economic accessibility, access to information; 3) Acceptability: All medical organizations, goods and services must comply with the principles of medical ethics, take into account cultural characteristics, gender and age requirements, confidentiality. 4) Quality: Medical organizations, goods and services must be of adequate quality.

There are two approaches to the right to health care. One part advocates health care as a human right because healthcare is a human necessity. The second part opposes and believes that healthcare is one of the types of commodity and it can be supplied by the market.

A market can only be effective when the distribution of resources is based on solvency and not on the principle of equity. Health is not a marketable product. The law of supply and demand do not work in the medical market as health commodities has specific characteristics that make it different from marketable goods. These specific peculiarities are asymmetric information, uncertainty, limited competition, production of public good and the externalities.[8] Such a difference between the medical market and the normal market is due to the socio-economic nature of medical services. Such situations where the market is unable to allocate resources efficiently are called market failures. This specificity of the health sector leads to special forms of economic relations in the medical market, which requires the development of appropriate regulatory mechanisms. To achieve equal access to medical services, the government will develop a health policy based on the principle of equitable funding.

In European countries and Canada, health care is considered as a public service, the provision of which is the responsibility of the public sector and does not depend on individual income. The principle of universal healthcare operates in these countries. Universal coverage means not only protecting the population from financial risks, but also guaranteeing the provision of high quality medical services and ensuring a fair and equal right to health for all people. The right of access to health services for all promotes solidarity among them and is considered an important cornerstone of statehood. Healthcare funding is not based on actuarial principles, accordingly, person's financial contributions to health care do not depend on his or her health status or risk.

Health care is considered a fundamental human right not only for humanistic and moral reasons, but also because of rational, utilitarian approaches.[9] Universal access benefits both the individual and the community as it provides an increase in workforce productivity.

Unlike many developed countries, health care in the USA is not considered a right or a constitutional principle. There is no legislative framework in the U.S. that provides for the right to health. There is a selective social protection system in the United States. It is based on population needs assessment procedures and involves the state covering only that part of the population who are socially vulnerable or need services more because of high risk.

The U.S. healthcare system reflects the peculiarities of the American socio-economic model, ideology, and traditions. In the first half of the nineteenth century, the French political scientist and historian Alexis de Tocqueville was the first to emphasize American exclusivity and uniqueness. "The condition of Americans is quite special, and it can be said that no other democratic people can ever achieve something like this". The principles of individualism and anti-statism have been firmly entrenched in American public consciousness. Recognition of individual rights hindered the development of social rights, as state interventions were often perceived as an obstacle to

the right to liberty. If the principles of equality, social protection and public solidarity have always prevailed in the development of social policy in European countries, in the US such a thing proved unacceptable for a certain part of the citizens. From their point of view, a person is responsible for his/her own destiny and actions, while the idea of transferring responsibility to the state does not enjoy much support. In the US, healthcare is not considered as the most important social function of the state, but as a service that, like other services, is sold in the medical market. However, according to polls, 65–86% of respondents in the US support access to health care should be a right.

Despite the annual increase in health care spending, there is still a problem with access to healthcare in the United States.[1] Even the state program such as Medicare, which covers high risk people of retirement age and with disabilities, requires patients to share significant costs, so-called Co-payments. Because of this, about half of healthcare costs are borne by the insured themselves, which places a heavy burden on them. As of 2018, the number of uninsured in the US is 11% (30 million people). In addition, there are so-called insufficiently insured people who have health insurance but spend 10% or more of their income out of pocket out of medical expenses. The number of people with insufficient insurance is 29 million. In contrast to the US, other developed countries have universal medical coverage which covers medical services for the population at much lower costs. Child mortality and life expectancy in the US lag significantly behind those of other developed countries.[2]

Nevertheless, the right to health care in the USA is not a radical concept. This is evidenced by the state programs "medicare" and "medicaid", as well as the program of medical care for war veterans, which treats health care as a right. However, in the US, the state is not obliged to provide healthcare to all its citizens.

Ensuring the right to health care requires large investment resources. Various funding mechanisms are used to achieve universal health care goals, namely the social security model (Bismarck model) and the tax-based model (Beveridge model). Social insurance was first introduced in Germany in 1883. Employees and employers are required to pay social security contributions at hospital box offices. Bismarck's model of social insurance is based on the principles of federalism and decentralization of powers. Federal governing bodies define the institutional model and guidelines, the parties have residual legislative powers, and the regional institutions exercise legal oversight over local health structures. Despite universal health care, there is no state monopoly on funding, in particular, hospital cash registers (Kranken Kassen) and regional disease funds are public rather than governmental institutions. The state establishes a basic package of medical services. Social insurance funds have different insurance premiums, which are calculated on the basis of income and are co-financed by employers and employees. Despite this, the role of the private sector in the delivery of medical services is important. Social security systems have been introduced in many Western European countries. In addition to social security contributions,

Philosophical aspects of access to health care

It is interesting to discuss the issue - access to healthcare is a human right or a privilege - from a philosophical point of view. According to the Greek philosopher Aristotle (384-322 BC), everything that is alive has a soul. The soul is the life-giving force and is responsible for the development of all living things. The soul cannot grow by itself, by its own forces. Its development requires the efforts of both the individual and society as a whole. Aristotle believed that humanity could not be better if man existed only by himself, on his own, and was not cared for by social mechanisms. The same can be said of human health, which cannot be achieved by itself, on its own. Public efforts are essential for human health.

Thomas Hobbes (1588-1679) in his work - "Leviathan" presents "right by nature" (jus naturales) and "law by nature" (lex naturalis). "The natural right is the freedom of man to use his power as he wishes, to sustain his life, and therefore to do whatever he thinks is the best way to achieve this goal". Unlike "right by nature", the "law of nature," or the mind, allows a person to figure out what must be done to sustain life. When people have the freedom to "do what they want, everyone is at war with each other". The law of nature requires each of us to relinquish our right to renounce freedom and thus give more freedom to other people. With this concession people think that others will have the same kindness towards them and they will also give up their freedom. When a person relinquishes freedom or transfers any right to another, "he does so because he himself receives equal rights. The motive and purpose of the waiver or transfer of the right is nothing but the personal security of the person in terms of being able to protect his life".

"Obligation" is created by "denial of a natural right". "Natural right" does not require obligations from a person. In the natural state, everyone is self-reliant and a person can do everything that suits his interests. By denying the "natural right", all members of society pledge to each other to coexist peacefully and thus ensure each other's security. When people renounce a "natural right"

or transfer it to another, a contract or agreement arises. The transition from "natural right" to "natural law" takes the form of a public contract: people agree to obey the law, because the alternative is a state of total war. If we consider the Hobbes concept in relation to health, for a safe life, people transfer the "right" to access medical care to a society in which all members pledge to cooperate. That is, society agrees that healthcare is a right and it should be accessible to all.

The American publicist Thomas Paine (1737-1809) distinguishes natural rights and civil rights. Natural rights belong to man by the force of his existence (freedom of belief, right to expression, striving for happiness ...), while civil rights belong to man as long as he is a member of society. Civil rights are guaranteed by society. They cannot be fully implemented without the help of the community.

Civil rights arose from natural rights. Man alone cannot ensure security. Ensuring collective security is handed over to the state. Civil power should not be used to suppress the natural rights of individuals. Human rights include the rights of other human beings, the protection of which is incumbent on this person.

Thus, access to health is considered a matter of both personal and national security. In modern society, all people transfer their natural rights to the state, thus creating a capital of collective security. Every person has a safety and benefit from common well-being, as well as the right to access health.

According to Hannah Arendt (1906-1975), and her work "The Human Condition" (1958), people reached an agreement on common welfare and handed over their natural rights to the state for their collective security. People, in addition to being equal, are different from each other. People differ from each other in word (what they say) and action (what initiative they take). Some people become better known for their words, while others become richer by their actions. Such diversity between people creates "difference", but it does not change equality. People differ in height, weight, ethnicity, income, gender, age, or religion. They have distinctive features and individual places in the world, but they are all equal. People make their own contribution to the development of society. In this public space where the rule of law prevails, people coexist, they interact with each other through words and actions, thus wanting to register themselves in society. Different segments of the population have different needs for medical care. The poor and the elderly tend to need medical care more. The united efforts of the people, solidarity, are needed to eliminate the problem of access to medical services arising from this difference. "For man, the reality of the world is guaranteed by the existence of others."

John Rawls (1921-2002) paid special attention to access to health for all in his book "Theory of Justice" (1971). According to Rawls's social justice argument, health care is a right because, (1) it promotes equality of opportunity and benefits the least well-off members of society; And (2) from a utilitarian point of view, guaranteed medical care increases the well-being of more people.

Norman Daniels, based on the principle of John Rawls, gave us the rationale for universal health care. John Rawls believes that every person has the right to inviolability (protection of physical and mental condition, right to life, right to privacy ...), which is based on justice. Therefore, the rights secured by the judiciary in a just society are not subject to political bargaining.

CONCLUSION

People are socially valuable entities that, through the power of morality, have made implicit agreements with each other as well as with the state. Through natural rights, we protect our own individuality, and also those to whom we collectively transmit common good. Under natural laws and natural rights, access to health for human beings is a right and not a privilege. The health status of the population depends on the social structure of a particular country, state policy and national culture. In rich countries, the average life expectancy of people is high. However, the health of the population depends not only on the country's economy, but also on the distribution of wealth. The more the state invests in healthcare, the higher the health rates. The problem of health inequality in different groups of the population must be addressed by correcting economic inequality. Health care reform should focus not only on the provision of medical services, but also on access to health care for the entire population. Thus, state policy plays a major role in improving the health of the population. The health care system should be arranged in such a way that the welfare of the patient is paramount for him. Every health care system must guarantee accessibility to healthcare for the entire population and must protect it from catastrophic health care costs. Every citizen should have access to high quality medical services. Good health benefits all: the individual and the community, and the well-being of the country in general. Health is a determinant of human productivity. The healthier a person is, the more able-bodied he is. Improving health promotes the acquisition of knowledge, the development of learning skills and creativity. Healthy and educated workers respond more

easily to technological and innovative processes, which is the determining factor for the successful implementation of reforms. Thus, human health contributes to the growth of the economy as it increases the able-bodied population.

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