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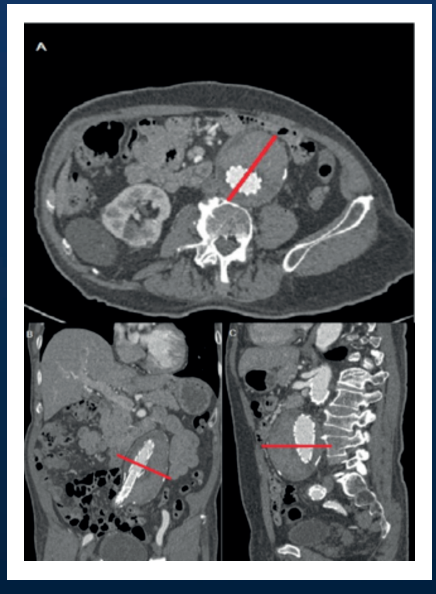

By Karnkawin Patharateeranart, et al.

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Achievement of Metabolic Goals among Different Health Insurance Schemes in Thai Patients with Type 2 Diabetes Mellitus: a Nationwide Study

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ABSTRACT

Objective: Thailand has three healthcare insurance schemes, including: Universal Health Coverage (UHC), Social Health Insurance (SHI), and Civil Servant Medical Benefit (CSMB). UHC has the narrowest drug coverage, SHI uses its own list, and CSMB offers the greatest drug coverage. The aim of this study was to investigate metabolic goal achievement in patients with type 2 diabetes mellitus (T2DM) compared among the three healthcare schemes in Thailand.

Methods: Data were obtained from a nationwide survey administered by MedResNet during 2011 to 2012. A cross-sectional survey was conducted in patients with T2DM aged >35 years who were treated for at least 12 months. The data were retrospectively collected from medical records.

Results: Of 49,303 T2DM patients that were recruited, 69.8% were female. CSMB patients were the oldest and had the longest diabetes duration. Achievement of BP, HbA1c, and LDL goals was 32.8%, 33.3%, and 42.5%, respectively. UHC patients had the highest percentage of BP control achievement (<130/80 mmHg; 33.1%), while CSMB patients had the highest percentage of HbA_{1c} (<7%; 40.4%) and LDL (<100 mg/dL; 49%) achievement. CSMB patients had the highest prevalence of 2-goal (16.8% for T2DM without HT) and 3-goal achievement (8.2% for T2DM with HT). Multivariate analysis revealed the CSMB scheme to be significantly associated with 3-goal achievement compared to the UHC scheme (odds ratio: 1.48, 95% confidence interval: 1.30-1.67; $p<0.01$).

Conclusion: The prevalence of metabolic goal achievement in patients with T2DM in Thailand is low. CSMB patients have the highest prevalence of 2-goal and 3-goal achievement.

Keywords: Blood pressure; glycemic level; health insurance; lipid level; type 2 diabetes mellitus (Siriraj Med J 2020; 72: 1-9)

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant non-communicable disease. It can cause micro- and macro-vascular complications that lead to disability and mortality.[1] In addition to glycemic control, blood pressure and lipid control are also very important for reducing these vascular complications. Previous study demonstrated that intensified multifactorial intervention aimed at multiple risk factors reduced the risk of microvascular complications, cardiovascular events, and cardiovascular death.[2,3]

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Mortality and morbidity rates in patients with T2DM have fallen considerably over recent decades.[4-6] These improvements in diabetes care may be attributed to improvements in several factors, including level of patient (e.g., literacy, patient education, motivation), level of healthcare professional (e.g., knowledge, awareness), and level of healthcare system (e.g., broader list of drugs, increased budgets). For the healthcare professional, the Thai Clinical Practice Guideline for Diabetes was developed and it is revised approximately every 3 years. This guideline provides basic knowledge about diabetes, treatment goals, medication adjustment, and complication management. It is distributed to primary and secondary care physicians located in all regions of Thailand. Regarding the healthcare system, access to medical care and essential medicine are very important for optimizing outcomes. The cost of medicine consumed approximately 40% of the total direct medical cost in a developed country[7], and approximately 25-65% of total spending on health in developing countries.[8]

Thailand implemented universal health coverage in 2002. There are three main health insurance schemes, including: 1) the Civil Servant Medical Benefit (CSMB) scheme for government employees and their dependents, 2) the Social Health Insurance (SHI) scheme for private sector employees, and 3) the Universal Health Coverage (UHC) scheme for the rest of Thai population. In 2017, CSMB, SHI, and UHC covered approximately 4.4, 10.6, and 48.0 million Thai people, respectively.[9] The expansion of health insurance coverage increased access to medicines in primary care, especially for chronic diseases, such as diabetes and hypertension.[8] However, the drug lists, budgets, and payment methods all differ among the three health coverage schemes in Thailand. UHC has the narrowest drug coverage, as dictated by the Thailand National List of Essential Medicines (NLEM), with a closed-end budget system; SHI uses its own drug list with a closed-end budget system; and, CSMB offers the greatest drug coverage with an open-end budget system.[9] UHC and CSMB beneficiaries can receive medical service without any copayment while SHI beneficiaries have to pay a monthly deductible around 25 US dollars. Thus, the aim of this study was to investigate metabolic goal achievement in patients with T2DM compared among the three healthcare schemes in Thailand.

MATERIALS AND METHODS

Study design

The data evaluated in this study were obtained from a nationwide survey, entitled "An Assessment on Quality of Care among Patients Diagnosed with Type 2 Diabetes and Hypertension Visiting Ministry of Public Health and Bangkok Metropolitan Administration Hospitals in Thailand (Thailand DM/HT)". This survey was administered by the Medical Research Foundation Thailand (MedResNet). This survey was a cross-sectional study conducted in patients with T2DM and/or hypertension who were aged >35 years and treated for more than 12 months in hospitals across Thailand during 2011 to 2012. A two-stage stratified cluster proportional to the size sampling technique was used to select a representative sample of patients with T2DM and/or hypertension in Thailand. The first stage of sample collection was from the 77 provinces in Thailand that comprised 77 strata. The second stage of sample collection was from hospitals and clinics, which were stratified into five strata according to their size, in each province. University hospitals were excluded from this survey. At each hospital or clinic, health care personnel, usually a registered nurse would invite patients to participate into the study by signing a consent form for providing permission to review and abstract his or her medical records. The most recent data within 12 months, including general information, the status of diabetes complications, and laboratory results, were retrospectively collected from medical records by trained health care professionals. This national survey was approved by the Institutional Ethical Review Committee for Research in Human Subjects, Thailand Ministry of Public Health, and by the Royal Thai Army Medical Department Ethical Review Board. The authors of this study received approval to use the MedResNet database. The protocol for this study was approved by the Siriraj Institutional Review Board [SIRB] (Si 376/2014).

Study population

This study included patients with T2DM who were enrolled in the UHC, CSMB, and SHI public health insurance schemes in Thailand. Baseline characteristics and metabolic goal achievement were compared among health insurance schemes.

Goals of treatment

At the time of data collection, the targets of metabolic control were BP <130/80 mmHg, HbA_{1c} <7%, and LDL <100 mg/dL, as recommended by the American Diabetes Association (ADA) in 2011.[10] The BP and HbA_{1c} targets were the same targets as the current recommendations by the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension[11] and a consensus report by the ADA and the European Association for the Study of Diabetes.[12] However, the current recommendation for treatment of hypercholesterolemia recommends

using moderate- or high-intensity statin in people with diabetes.[13] There were 2 goals set for patients in the T2DM without HT group (HbA_{1c} and LDL), and there were 3 goals set for patients in the T2DM with HT group (BP, HbA_{1c}, and LDL).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Continuous data are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical data are reported as number and percentage. One-way analysis of variance (ANOVA) or Kruskal-Wallis test was used to analyze continuous data, and chi-square test was used to evaluate categorical data. Univariate logistic regression analysis was used to identify factors significantly associated with 3-goal achievement. Multiple logistic regression analysis was employed to adjust factors associated with 3-goal achievement. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Of the 49,303 T2DM patients recruited, 76.3% had UHC coverage, 19.5% had CSMB coverage, and 4.2% had SHI coverage. Around 69% (n=33,887) of patients had hypertension (DM with HT group). The mean ± standard deviation age of patients was 59±10.7 years, and 70% of patients were female. There were significant differences in baseline characteristics among the 3 healthcare schemes, as shown in Table 1. CSMB patients were the oldest and had the longest duration of diabetes, whereas SHI patients were the youngest and had the shortest duration of diabetes. The majority of UHC patients were followed-up at community hospitals. In contrast, CSMB and SHI patients were followed-up in relatively equal proportions at all 3 levels of hospitals. UHC patients had the lowest mean BP (131.5±16/75±10 mmHg), and CSMB patients had the lowest mean HbA_{1c} (7.7±1.8%) and LDL (106.0±37.0 mg/dL) levels.

Metabolic goal achievement

The overall achievement of BP, HbA_{1c}, and LDL goals was 32.8%, 33.3%, and 42.5%, respectively. Among the evaluated schemes, UHC patients had the highest percentage of overall BP control achievement (33.1%). CSMB patients had the highest percentage of overall glycemic (40.4%) and LDL control (49.0%) as shown in Fig 1. The achievement of HbA_{1c} and LDL goals was not different between UHC and SHI patients. CSMB patients had the highest prevalence of 2-goal and 3-goal achievement as shown in Fig 2A & B. Specific to 1-goal achievement, the percentage of LDL achievement was greater than that of HbA_{1c} and BP achievement. The overall percentage of 1-goal achievement was not different among the schemes. Regarding 2-goal achievement, the percentage of HbA_{1c} and LDL achievement was the greatest compared to other combinations. Metabolic goal achievement among DM with hypertension and without hypertension is shown in Table 2.

Univariate logistic regression analysis showed scheme, gender, age, duration of diabetes, and BMI to be associated with 3-goal achievement. Multiple logistic regression analysis revealed CSMB scheme (compared with UHC scheme), older age, shorter duration of diabetes, and lower BMI to be associated with 3-goal achievement (Table 3).

DISCUSSION

All Thai citizens have been covered by public universal health coverage since 2002. All three Thailand insurance schemes provide essential laboratory investigations and medications for blood pressure, glycemic, and lipid control. However, in the present study, the prevalence of each metabolic goal achievement in patients with T2DM was approximately 30-40% and 3-goal achievement was only 6.1%, which were close to the rates reported from developing countries[14,15] but lower than the rates reported from developed countries.[16,17] The 3-goal achievement percentage of study from India[14] and Ethiopia[15] was 9% and 8.5%, respectively. However, the BP goal of those studies was < 140/90 mmHg which was higher than BP goal of the present study. In the US during 2007-2010, the percentage of BP, HbA_{1c}, and LDL achievement was 51.3%, 52.2%, and 56.8%, respectively, while the rate of 3-goal achievement plus non-smoking status was 14.3%. The prevalence of metabolic goal achievement in the US increased markedly during 1999-2010.[16] In Thailand, the percentage of glycemic goal achievement increased from 26.3% in 2003 (data from Thailand Diabetes Registry (TDR) Project)[18] to 33.3% in the present study (2011-2012). However, the data in the TDR project came from university hospitals, which may treat cases of T2DM that are more complicated than those included in our study. In this study, the prevalence of LDL goal achievement was the highest, which is similar to the findings of a US study[16], followed by HbA_{1c} and BP goal achievement. However, there was no conclusion which risk factor had the greatest influence to morbidities and mortality in patients with T2DM. Lizheng Shi, *et al* suggested LDL level to be the strongest risk factor for diabetes complications and mortality in veterans with T2DM.[19] Soffia Gudbjörnsdottir,

TABLE 1. Baseline characteristics compared among different Thailand health schemes.

Characteristics	Total (N=49,303)	Universal Health Coverage Scheme (n=37,633)	Civil Servant Medical Benefit Scheme (n=9,641)	Social Health Insurance Scheme (n=2,029)	*P*-value
Hospital size, %					
Regional hospital (>500 beds)	15.6%	12.8%	23.0%	31.6%	
General hospital (200-500 beds)	22.9%	19.5%	33.7%	35.4%	***<0.01***
Community hospital (<120 beds)	61.5%	67.7%	43.4%	33.0%	
Female gender, %	69.8%	72.9%	61.4%	51.5%	***<0.01***
Age (years)	59±10.7	58.3±10.4	64.3±9.8*	49.4±8.8†‡	***<0.01***
<40 years, %	3.2%	3.3%	0.7%	13.8%	***<0.01***
40-49 years, %	14.9%	16.3%	5.4%	34.1%	
50-59 years, %	34.4%	36.2%	26.3%	40.2%	
60-69 years, %	29.7%	29.3%	35.4%	10.6%	
≥70 years, %	17.7%	14.9%	32.1%	1.4%	
BMI (kg/m^2), %	25.7±4.4	25.7±4.4	25.7±4.3	26.6±4.5†‡	***<0.01***
Duration of diabetes (years), median (IQR)	6 (3, 9)	6 (3, 9)	6 (4, 10)*	4 (3, 7)†‡	***<0.01***
<5 years, %	37.4%	38.3%	31.1%	51.0%	***<0.01***
5-9 years, %	41.4%	41.6%	41.6%	36.4%	
10-14 years, %	15.2%	14.6%	18.6%	9.9%	
≥15 years, %	6.0%	5.5%	8.7%	2.8%	
Blood pressure (mmHg)					
Hypertension group (n=33,887)					
Systolic	132.0±16	131.5±16.0	132.0±16.0*	133.0±16.0†‡	***<0.01***
Diastolic	75.0±11	75.0±10.0	74.0±11.0*	79.0±11.0†‡	***<0.01***
HbA_{1c}, %	8.1±2.0	8.2±2.0	7.7±1.8*	8.0±1.9‡	***<0.01***
LDL (mg/dL)	110±37	112±37	106±37*	111±37‡	***<0.01***
Triglyceride (mg/dL), median (IQR)	157 (113, 221)	155 (111, 128)	138 (100,192)*	143 (103, 199)†‡	***<0.01***
GFR (ml/min/1.73 m^2)	68±26	68±26	65±24*	84±24†‡	***<0.01***
Hypoglycemia, %	4.4%	4.6%	3.9%*	2.9%†‡	***<0.01***

Data presented as percentage (%) or mean ± standard deviation

* indicates $p<0.05$ between UHC and CSMB, † indicates $p<0.05$ between UHC and SHI, ‡ indicates $p<0.05$ between CSMB and SHI

Abbreviations: BMI = body mass index; IQR = interquartile range; HbA_{1c} = glycated hemoglobin; LDL = low-density lipoprotein cholesterol; GFR = glomerular filtration rate; UHC = Universal Health Coverage; CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance

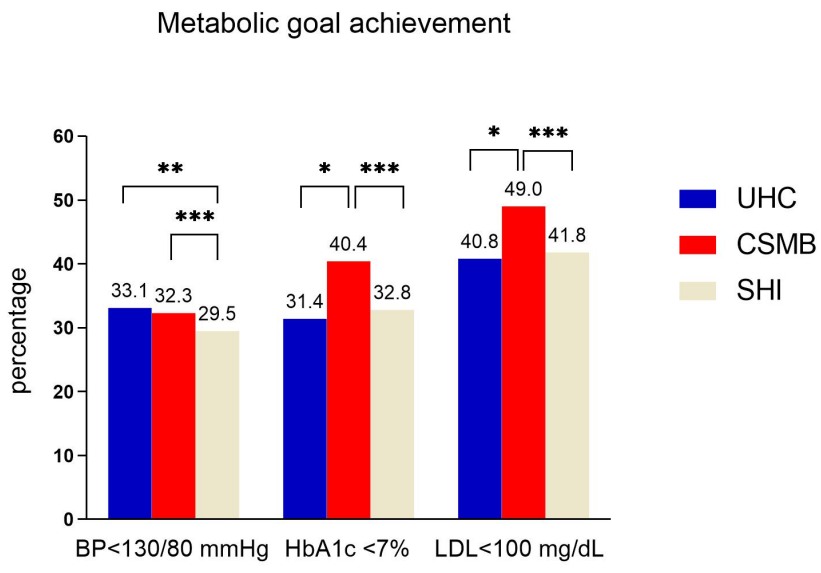

Fig 1. Metabolic goal achievement compared among different health schemes.
*indicates $p<0.05$ between UHC and CSMB ,
**indicates $p<0.05$ between UHC and SHI ,
***indicates $p<0.05$ between CSMB and SHI
Abbreviations: CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance; UHC = Universal Health Coverage

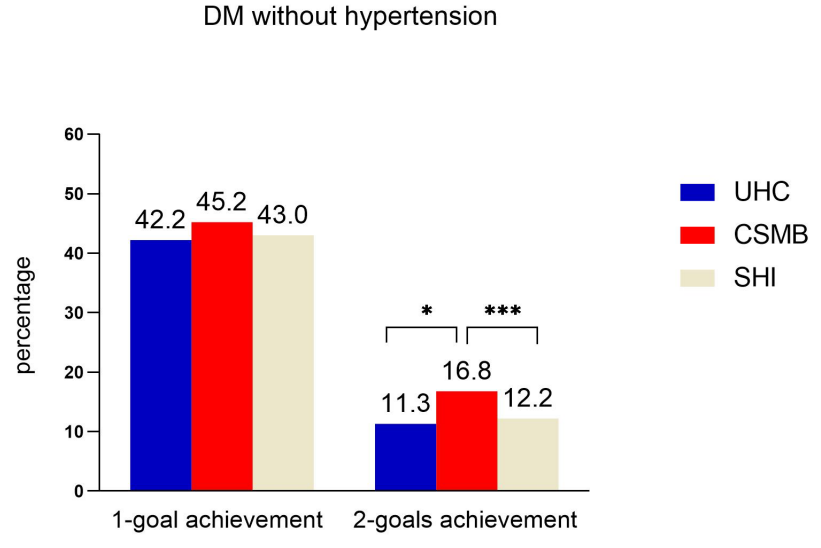

Fig 2A. Number of goal achievement of DM without hypertension group compared among different health schemes.
*indicates $p<0.05$ between UHC and CSMB ,
***indicates $p<0.05$ between CSMB and SHI
Abbreviations: CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance; UHC = Universal Health Coverage

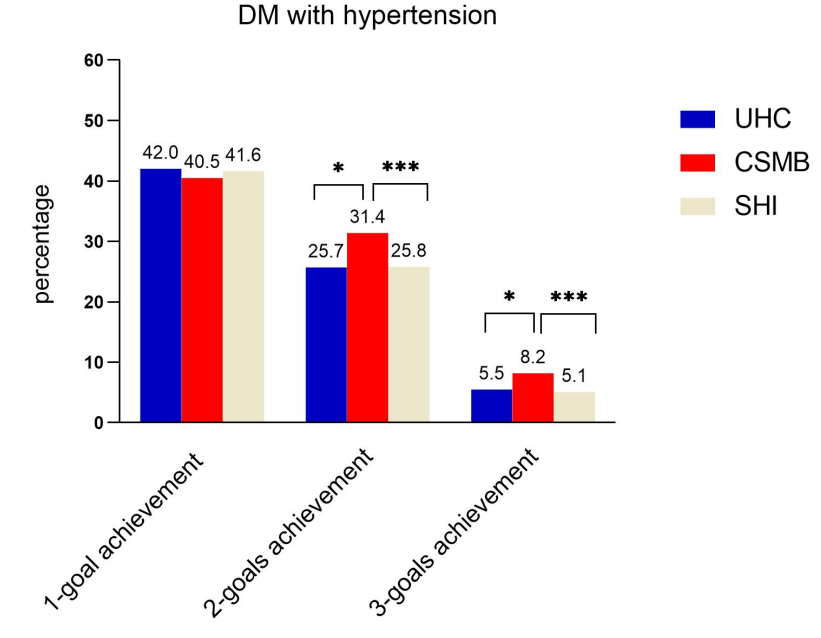

Fig 2B. Number of goal achievement of DM with hypertension group compared among different health schemes.
*indicates $p<0.05$ between UHC and CSMB ,
***indicates $p<0.05$ between CSMB and SHI
Abbreviations: CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance; UHC = Universal Health Coverage

TABLE 2. Metabolic goal achievement among DM with hypertension and without hypertension.

Metabolic goals	Total (n=49,303)	Universal Health Coverage Scheme (n=37,633)	Civil Servant Medical Benefit Scheme (n=9,641)	Social Health Insurance Scheme (n=2,029)	*P*-value
DM without hypertension	(n=15,416)	(n=12,383)	(n=2,319)	(n=714)	
1 goal achieved, %					
HbA_{1c} <7%	15.1%	14.6%	17.7%*	16.5%	***0.03***
LDL <100 mg/dL	27.6%	27.7%	27.5%	26.4%	0.84
2 goals achieved, %					
HbA_{1c} and LDL	12.3%	11.3%	16.8%*	12.2%‡	***<0.01***
DM with hypertension	(n=33,887)	(n=25,250)	(n=7,322)	(n=1,315)	
1 goal achieved, %					
HbA_{1c} <7%	12.3%	12.1%	13.1%	12.6%	0.12
LDL <100 mg/dL	17.4%	17.0%	18.5%	17.3%	0.06
BP <130/80 mmHg	11.9%	12.9%	8.9%*	11.7%‡	***<0.01***
2 goals achieved, %					
HbA_{1c} and LDL	11.5%	10.3%	15.0%*	12.7%†‡	***<0.01***
LDL and BP	9.7%	9.5%	10.3%	9.1%	0.19
HbA_{1c} and BP	5.8%	5.9%	6.0%	4.1%	0.052
3 goals achieved, %					
HbA_{1c} LDL and BP	6.1%	5.5%	8.2%*	5.1%‡	***<0.01***

*indicates $p<0.05$ between UHC and CSMB, †indicates $p<0.05$ between UHC and SHI, ‡indicates $p<0.05$ between CSMB and SHI
Abbreviations: BP = blood pressure; HT = hypertension; HbA_{1c} = glycated hemoglobin; LDL = low-density lipoprotein cholesterol; DM = diabetes mellitus; GFR = glomerular filtration rate; UHC = Universal Health Coverage; CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance

et al reported HbA_{1c} level to be the strongest predictor of stroke and acute myocardial infarction.[20] However, both of those studies confirmed that the higher the number of goals achieved to reduce cardiovascular risk factors, the lower the rate of morbidities and mortality.[19,20] This supports the importance of metabolic goal achievement in this patient population.

After adjusting for gender, age, duration of diabetes, and BMI, the CSMB scheme was still found to be associated with 3-goal achievement. This difference in metabolic control among schemes might be explained by one or more of the following factors: 1) differences in the lists of available medicine, 2) opportunity or not to consult a specialist, and/or 3) socioeconomic and/or geographic barrier.

First, UHC patients have to use the medicines listed in the Thailand NLEM (supplementary data), and most of these medicines are lower-cost alternatives. The drug list for SHI patients differs among hospitals, but it should be at least comparable to the NLEM. In contrast, the use of non-essential medicines is permitted for CSMB patients if physicians confirm them to be clinically indicated.[21]

TABLE 3. Multiple logistic regression analysis of 3-goal achievement.

Factors	Odds ratio	95% CI	*P*-value
UHC scheme	1.00		
CSMB scheme	1.48	1.30-1.69	***<0.01***
SHI scheme	0.99	0.71-1.41	0.99
Female	1.00		
Male	1.097	0.97-1.24	0.14
Age <40 years	1.00		
Age 40-49 years	2.55	1.11-5.88	***0.03***
Age 50-59 years	2.87	1.27-6.50	***0.01***
Age 60-69 years	3.34	3.34-1.48	***<0.01***
Age ≥70 years	4.29	4.29-1.89	***<0.01***
DM duration <5 years	1.00		
DM duration 5-9.9 years	0.95	0.83-1.08	0.44
DM duration 10-14.9 years	0.82	0.68-0.97	***0.02***
DM duration ≥15 years	0.64	0.49-0.83	***<0.01***
BMI ≥30 kg/m²	1.00		
BMI 25-29.9 kg/m²	1.21	0.99-1.48	0.55
BMI 23-24.9 kg/m²	1.43	1.15-1.77	***<0.01***
BMI <23 kg/m²	1.84	1.51-2.25	***<0.01***

A *p*-value<0.05 indicates statistical significance

Abbreviations: CI = confidence interval; UC = Universal Health Coverage; CSMB = Civil Servant Medical Benefit; SHI = Social Health Insurance; DM = diabetes mellitus; BMI = body mass index

For BP achievement, although only generic drugs are available in the NLEM, all antihypertensive drug classes are included. Contrarily, only moderate-intensity statin (NLEM 2008-2012) and low-cost anti-hyperglycemic agents are available in the NLEM for lipid and glycemic control. This might causes differences in lipid and glycemic control among schemes, but similar for BP control between UHC and CSMB. Second, UHC and SHI use a primary healthcare gatekeeping system. This means that patients can only access hospitals where they are registered, while CSMB allows patients to access specialists directly.[21] It should be mentioned that care given by specialists does not always ensure better metabolic control than care given by general practitioners.[22,23] Third, most CSMB patients live in urban settings and have higher socioeconomic status, whereas most UHC patients live in rural areas and have lower socioeconomic status.[21] Therefore, CSMB patients might have higher health awareness and health literacy. Although health centers and district hospitals are distributed across Thailand, geographic barriers remain a problem in some rural areas. However, data about the specialty of doctor, residency and socioeconomic status among health scheme were not collected in this study.

To reduce the disparities among health insurance schemes, the inclusion of some new anti-hyperglycemic agents and high potency statin with lowest acquisition cost to the NELM might improve glycemic and lipid control in UHC and SHI patients. There should also be strict indications and verification for the use of high-cost medicines to control the budget in all 3 schemes.

Otherwise, the expansion of the drug list will cause rapid cost escalation, as observed in the CSMB scheme. In 2014, expenditure per CSMB member was 4 times higher than that per UHC member.[21] Furthermore, appropriate referral to specialists might optimize metabolic goal achievement.

The strength of this study is a large number study population that represents all 5 regions of Thailand and different sized hospitals except university hospitals. Moreover, data were abstracted from medical records by trained healthcare professionals. Thus, the data used in this study should be considered more accurate than self-reported data. Although this study represents the context in 2011-2012, the trend of metabolic goal achievement among the 3 Thailand healthcare schemes may currently be the same. This hypothesis is based on the fact that the drug classes for BP, cholesterol and, glycemic control for type 2 diabetes in the NELM 2018 are similar to those listed in the NELM 2008-2012, except for the addition of a high-intensity statin for hypercholesterolemia treatment.

There are some limitations in this study. First, there might be some selection bias because of a nature of cross sectional study. Therefore, it can only demonstrate the association not cause and effect. Second, there were no data about other factors that might influence the metabolic goal achievements such as educational level, health literacy, income or residency. Therefore, we did not adjust those factors in the multiple logistic regression analysis. Finally, there were unequal sample sizes in each scheme since majority of Thai population use UHC scheme.

CONCLUSION

The prevalence of blood pressure, glycemic, and lipid control achievement in patients with T2DM in Thailand is low. CSMB patients have the highest prevalence of HbA_{1c}, LDL, 2-goal, and 3-goal achievement. Exploring the factors that contribute to differences among healthcare schemes may improve diabetes care in Thailand.

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This manuscript was not prepared in collaboration with Investigators of the Thailand DM/HT study and does not necessarily reflect the opinions or views of the Thailand DM/HT study, the Thailand NHSO or the Thailand MedResNet.

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Breastmilk Macronutrient Levels and Infant Growth During the First Three Months: a Cohort Study

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ABSTRACT

Objective: The first three months after birth is a critical time interval for growth and development. Breastmilk is a natural nutrition source for infants. However, studies on the practice of exclusive breastfeeding and infant growth tend to result in contradictions. The objective of this study was to investigate the correlation between breastmilk macronutrient levels and infant growth during the first three months.

Methods: We conducted an observational cohort study at Universitas Airlangga Hospital from June-October 2018. Subjects were enrolled using total sampling. Infant anthropometry, as defined by body weight, body length, and head circumference, were measured. Breastmilk specimens were collected using a breast pump and then sent directly for analysis. Lactose, protein, fat, and total calorie levels were obtained using a human milk analyzer. Procedures were repeated three times, once per month. The Pearson correlation coefficient was used for statistical analysis.

Results: Forty participants were enrolled in this study. There was a positive correlation between breastmilk total calories and head circumference growth during the first ($p = 0.039$), second ($p = 0.020$), and third month ($p = 0.020$). Breastmilk protein level was positively correlated with body length ($p < 0.05$) and head circumference ($p < 0.05$) during the first month. There was no correlation between body weight and breastmilk macronutrients or total calories ($p > 0.05$).

Conclusion: Breastmilk macronutrient levels correlate to infant growth in a unique pattern. Total calories and first month protein correlated positively with infant head circumference. However, calorie source, e.g., lactose or fat, did not correlate with infant body weight and length.

Keywords: Breastmilk; nutrition; growth; infant; macronutrient (Siriraj Med J 2020; 72: 10-17)

INTRODUCTION

Growth and development are the main features that distinguish between children and adults. The first three months after birth is a critical time interval for growth and development. The brain volume increases quickest during this time, at roughly 1% per day after birth; the rate slows to 0.4% per day by the end of third month.[1] Child growth itself is commonly associated with nutrition intake. Abnormal nutrition intake will result in aberrant growth. In return, deviation from normal growth may indicate serious health problems.[2] Hence, nutrition is an important aspect to be observed during childhood.

Breastmilk is a natural nutrition source for infants. Human breastmilk contains specific components that avert malnutrition and offer optimal growth for infants.[3,4]

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Lactose, a main breastmilk component, is positively correlated to infant weight, adiposity, and body mass index in the 3-month-old infant.[5]

Although various proteins in breastmilk are lower than in formulated milk,[6] breastmilk contains specific free amino acids (such as glutamine) that are positively correlated with length gain.[7,8] Another study showed that a higher n-3/n-6 ratio in breastmilk positively correlates with infant length.[9] However, no matter how good breastmilk may appear to be for the infant, studies on the practice of exclusive breastfeeding and infant growth tend to result in contradictions. According to an Indonesian Health Department report, although exclusive breastfeeding increased from 15.3% to 30.2% between 2010-2013, stunting and malnutrition remain serious problems. One study showed that exclusive 6-month breastfeeding leads to underweight infants.[10] However, other studies instead reported overweightness in exclusively breastfed infants.[9,11] These differences do not apparently correlate with the breastfeeding itself, but rather are more correlated with breastmilk macronutrient content.[11,12] Hence, in this study we aimed to investigate the correlation between breastmilk macronutrients and infant growth during the first three months.

MATERIALS AND METHODS

Study design

This study was an observational cohort deign that aimed to explain the correlation between breastmilk macronutrients, defined by carbohydrates (in the form of lactose), protein, and fat, and infant anthropometry, defined by body weight, body length, and head circumference. This study was conducted at the Universitas Airlangga Hospital from June to October 2018. Ethical clearance was issued by the Ethics Committee at the Universitas Airlangga Hospital, Surabaya, Indonesia, with clearance number 108/KEH/2018.

Study subjects

Subjects were enrolled using total sampling methods, where all candidates who met inclusion criteria were recruited during the study period. Inclusion criteria were term neonates with a birthweight > 2,500 g. The infant's mother must exclusively breastfeed without any additional nutritional intake for at least three months. Exclusive breastfeeding was not defined by a daily measurable dose, but rather as natural as possible where the infant was satiated. The mothers also had to have their Mother and Child Health Handbook still available for data tracking and cross-checking. The Mother and Child Health Handbook is a book officially given by the Indonesian government to each pregnant mother in order to help keep track of her and her baby's health status. Informed consent signed by the mother was required to participate in this study. Preterm infants, infants with congenital disease, and mothers with HIV infection who were unable to breastfeed were excluded from this study. Participants were considered dropped-out when the mother did not exclusively breastfeed, the Mother and Child Health Handbook was missing, the mother or infant did not survive during our observation, or she decided to withdraw from the study.

Study questionnaire

A questionnaire was provided to obtain characteristics about the mothers and infants, as well as a tool for monitoring inclusion criteria. We sought data about the mother's age, parity, education, and employment, while for the child we confirmed sex and method of birth. The monitoring questions were assessed each month and consisted of infant general condition and breastfeeding status. To obtain body mass index data for mothers during pregnancy, data from the Mother and Child Health Handbook were used. Questionnaires were completed by the investigator after participants provided written informed consent.

Anthropometrical measurements

We measured the infant's body weight, length, and head circumference as anthropometric indicators. All measurements used metric scales and were performed at the Universitas Airlangga Hospital directly by investigator. The measurement was repeated once per month for three months. Measurement of body weight used an analogue infant scale with an accuracy of ± 0.1 kg. The infant scale was placed on a flat table that was not easy to sway. Before body weight was measured, the needle was set to zero. Babies were weighed naked without clothing and accessories. Body weight was recorded as the point where needle was most stable. Body length measurement was performed using an infantometer. The infants were first positioned lying on a flat bed. The infant's head was attached to the numerical barrier while the examiner's left hand pressed the knee straight and the right hand pressed the toe to the foot. Length was measured based on the pointed number on the outer edge of the gauge. Head circumference was measured with metered tape. The tape was looped over the forehead, between eyebrows, above the two ears, and passing the occiput. The metered tape was then pulled slightly tighter, and the value that crossed the zero point was read.

Breastmilk specimen collection

Breastmilk specimens were collected individually by each mother using a breast pump at random times. Full breastmilk expression, including foremilk and hindmilk, was used as a sample. To collect the sample, pumped breastmilk was first collected in a 50 mL sterile bottle. The minimum analyzable amount for each specimen was 3 mL, which was collected using sterile plastic tube. Collected breastmilk was then sent directly to the laboratory for analysis. We did not store any samples because they were all directly analyzed after collection. This procedure was repeated once a month for three months.

Breastmilk macronutrient analysis

Laboratory analysis was conducted at the Universitas Airlangga Hospital. Macronutrient analysis was performed using the Miris Human Milk Analysis instrument set (Miris, Sweden). Samples were first reheated to the optimal temperature and then homogenized with a 20 J/mL ultrasonic wave. Homogenized samples were analyzed under mid-infrared (mid-IR) transmission spectroscopy. Results are presented for lactose (g/100 mL), protein (g/100 mL), soluble fat (g/100 mL), and total calories (kcal/100 mL). The Pearson correlation coefficient was used to analyze the data using SPSS version 22.0. Results are presented in tables.

RESULTS

Subject characteristics

We enrolled 40 subjects for this study. A total of 10 participants were excluded, all due to non-exclusive breastfeeding. The remaining subjects finished all the observations and were included in the study. The mothers average age was 29.5 years old. Most of them were on their second parity (43%). The majority of the mothers were high school graduates (60%), followed by middle school graduates (17%). Most of the mothers (60%) were unemployed and taking a role as a housewife. With regards to the children, the number of male and female subjects was approximately the same (binomial non-parametric test, $p > 0.05$). Caesarean section occurrence was relatively high (47%) and served as the only assisted method of delivery in our study. Detailed information about subject characteristics is provided in Table 1, while the anthropometry summary is presented in Table 2.

Breastmilk macronutrient profile

We measured the breastmilk lactose, protein, fat, and total calories profile. We found that lactose was the most abundant breastmilk macronutrient (compared to protein and fat). The highest lactose concentration was detected in the third month of observations, with 4.17 ± 0.81 g/100 mL breastmilk. In our population, protein was the smallest component found in breastmilk. Its concentration peaked at the first month of observation at 1.89 ± 0.38 g/100 mL. We observed a slow but gradual decrease in the protein concentration each month. Fat was the second most abundant macronutrient; its concentration was the highest in the second month at 3.56 ± 0.96 g/100 mL, but dropped rapidly to 2.80 ± 1.16 g/100 mL (unlike the other macronutrients that did not exhibit such sharp temporal changes). Total breastmilk calories changed each month; it generally followed the same pattern as protein. The peak was 56.73 ± 9.77 kcal/100 mL in the first month, followed by a gradual decrease over the time. The complete breastmilk macronutrient profile is provided in Table 3.

Correlation between breastmilk macronutrients and infant anthropometry

Prior to performing the correlation tests, the Kolmogorov-Smirnov test was used to test the data distribution for all variables. All anthropometric measurements as well as breastmilk carbohydrates, protein, fat, and total calories were normally distributed ($p > 0.05$). Hence, the Pearson correlation coefficient was calculated for all variables. A detailed summary of the p-values, Pearson r correlation strength value, and the respective time of measurement is presented in Table 4.

We did not find any correlation between body weight and breastmilk macronutrients (carbohydrates, protein, or fat $p > 0.05$). We also did not find any correlation between breastmilk total calories and infant body weight ($p > 0.05$). These results were consistently found for all monthly observations.

Protein was related to infant growth, especially during the first month; protein was positively correlated with body length ($p < 0.05$) and head circumference ($p < 0.05$) for first month. However, there were no correlations between these measures and protein levels during the second and third months ($p > 0.05$).

There was also a positive correlation between breast milk total calories and infant head circumference for all three months of observations; ($p < 0.05$; Table 4).

DISCUSSION

During their first three months of life, infants grow faster than at older ages due to the larger body volume-to-surface ratio. Hence, young infants have an average higher average metabolic rate per kg body weight and require greater nutrient intake for body temperature regulation at this time.[12] This pattern of metabolism

TABLE 1. Participant characteristics.

Characteristic	Total (n = 30)
Mothers	
Age (years; mean ± SD)	29.5 ± 7.19
Parity	
First birth	7 (23%)
Second birth	13 (43%)
Third birth	5 (17%)
Fourth birth	3 (10%)
Fifth birth	2 (7%)
Highest Education	
Elementary school	3 (10%)
Middle school	5 (17%)
High school	18 (60%)
Vocational	3 (10%)
Bachelor's	1 (3%)
Mother's employment	
Housewife	18 (60%)
Employee	6 (20%)
Self-employed	6 (20%)
Infants	
Sex	
Male	17 (57%)
Female	13 (43%)
Mode of delivery	
Normal	16 (53%)
Caesarean section	14 (47%)
Birth weight (g; mean ± SD)	3123 ± 47.5
Birth length (cm; mean ± SD)	48.7 ± 0.50

TABLE 2. Infant anthropometric characteristics.

Components	Mean ± SD		
	1st month	2nd month	3rd month
Weight (kg)	3.46 ± 0.54 (normal[1])	4.51 ± 0.83 (normal[1])	5.60 ± 0.59 (normal[1])
Length (cm)	51.95 ± 2.40 (normal[1])	55.40 ± 2.11 (normal[1])	59.60 ± 2.14 (normal[1])
Head circumference (cm)	34.73 ± 1.16 (normal[1])	36.90 ± 1.11 (normal[1])	38.84 ± 1.10 (normal[1])

[1]Normal range is based on World Health Organization Z-score chart of body weight-for-age, length-for-age, and head circumference-for-age for children aged 0-2 years.

TABLE 3. Breastmilk macronutrients and total calories profile.

Components	Mean ± SD 1st month	2nd month	3rd month
Lactose (g/100 mL)	3.77 ± 0.72	3.72 ± 0.79	4.17 ± 0.81
Protein (g/100 mL)	1.89 ± 0.38	1.83 ± 0.43	1.72 ± 0.37
Fat (g/ 100 mL)	3.41 ± 0.97	3.56 ± 0.96	2.80 ± 1.16
Total calories (kcal/100 mL)	56.73 ± 9.77	55.50 ± 9.62	53.37 ± 10.72

TABLE 4. BCorrelations between breastmilk macronutrients and infant growth.

		Lactose		Protein		Fat		Total calories	
		r	*p*	r	*p*	r	*p*	r	*p*
Weight	1st month	0.051	0.79	-0.264	0.158	0.141	0.457	0.276	0.139
	2nd month	0.247	0.189	-0.037	0.847	0.152	0.423	0.269	0.151
	3rd month	0.488	0.189	-0.002	0.847	-0.023	0.423	-0.006	0.151
Length	1st month	0.291	0.118	0.501	0.005*	0.024	0.898	0.109	0.566
	2nd month	0.193	0.308	-0.044	0.817	0.101	0.597	0.283	0.129
	3rd month	0.577	0.308	-0.226	0.817	-0.177	0.597	-0.181	0.129
Head Circumference	1st month	0.222	0.238	0.468	0.009*	0.047	0.804	0.379	0.039*
	2nd month	0.278	0.136	-0.08	0.673	0.276	0.14	0.423	0.020*
	3rd month	0.445	0.136	-0.015	0.673	0.189	0.14	0.264	0.020*

Notes: r, Pearson's correlation coefficient; *statistically significant correlation ($p < 0.05$).

requires higher caloric input, and this need is met by macronutrients. Breastmilk is a natural source of such nutrition, and its content is critical for infant nutrition.

Weight and length are important anthropometric values in growing infants. We observed normal weight and length increases of exclusively breastfed infants during the study time interval. Our results differ from previous studies. One study showed 3.1% of infants were underweight in a cohort of exclusively breastfed infants at their third month of age[10], while another reported excessive overweightness in an exclusively breastfed cohort.[9,11] Our disparate results might be due to differences in subject characteristics, research methodology, and/or breastmilk quality. Hence, assessing breastmilk macronutrient levels is crucially important.

Head circumference has a relationship with brain volume, and it is often used to assess brain growth after a baby is born.[13,14] Evidence shows that total energy in breastmilk supports the energy requirements for brain growth,[15] which we will discuss later. However, the growth trajectory of the exclusively-breastfed infant brain is still poorly studied. Further studies are needed to assess how a specific breastmilk component could affect infant brain growth.

Compared to several previous studies in developed and developing countries, breastmilk in this study had lower lactose levels. Research in South Korea showed that breastmilk lactose levels in the third month averaged 7.1 ± 0.5 g/100 ml.[16] Similarly, research in the Philippines showed a higher mean lactose level, 7.3 ± 0.58 g/100 ml.[17] Lactose levels in breast milk are known to be higher in mothers who have more breast milk.[7] A study showed that formula feeding can increase the quantity of breast milk a breastfeeding mother produces.[18] This observation further reinforces the importance of maternal formula feeding during pregnancy.

In this study, the first month breastmilk fat content was lower compared to other reports. Of the analyzed macronutrients, our measured third-month fat level was the lowest when compared with other studies.[17,19] Fat content is the most variable macronutrient in breastmilk.[20] An Indonesian study of breastmilk fat levels reported an average of 5.94 ± 15.9 g/100 ml,[21] which is similar with studies conducted in South Korea (3.2 ± 1.0 g/100 ml)[16] and China (3.11 ± 1.13) g/100 ml).[22] These fat level differences are linked to variations in the maternal diet, age, type of analyzed samples (hindmilk or foremilk), breastfeeding time, and breastmilk storage conditions post-pumping.[16,22-25] Unfortunately, daily diet data and cohort data of maternal body mass index were not available in our study, and thus we could not confirm whether fat content variability in our samples was due to that factor.

In our study, breastmilk fat level was not directly correlated toward any child growth anthropometric measures. However, total calories were positively correlated to head circumference growth. Hence, we emphasize that both lactose and fat are important calorie sources used for brain development. There is limited evidence on how total caloric intake affects brain volume, which can be represented as head circumference. However, in the 1970s, a study showed that caloric intake is very important to achieve normal head circumference. The study showed that exposure to subnormal temperature (< 35°C) and failure to achieve a caloric intake of 120 cal/kg/day leads to abnormal head circumference growth in asymptomatic neonates. Recent findings showed that head circumference does not solely rely on total caloric intake. Rather, an adequate and balanced diet for optimal child brain development is recommended rather than pursuing a specific total caloric intake. The study showed that cumulative fat and caloric intake are positively associated with fractional anisotropy in the posterior limb of the internal capsule, a measure that relates to an increase in brain volume. The same study also showed that cumulative protein intake is positively associated with higher cognitive and motor scores.[26] Therefore, from these points of view and based on our findings, we conclude that breastmilk contains the necessary calories for adequate infant brain growth as well as the required macronutrients level needed to achieve daily caloric needs.

We observed a decrease in breastmilk protein levels as the infants aged. Protein levels contained in mature breastmilk are between 0.9-1.1 g/100 ml.[27] However, breastmilk protein levels are higher at the beginning of the lactation: they start at 1.4-1.6 g/100 ml, decrease to 0.8-1.0 g/100 ml when infants reaches 3-4 months old, and further decline to 0.7-0.8 g/100 ml when the baby reaches 6 months.[28] Interestingly, the breastmilk in this study had higher protein levels even during the third month of observation (1.72 ± 0.37) g/100 ml compared to that previous report. Again, maternal diet, age, type of analyzed samples (hindmilk or foremilk), breastfeeding time, and breastmilk storage conditions post-pumping might play role in our finding, since other macronutrients (especially fat) depend on those factors.[16,22-25]

Our findings on the correlation between breastmilk protein level and body weight suggest that protein is an important energy source in earlier months, but it is less crucial compared to fat and carbohydrates at older ages. There are several studies that support this view. One showed that weight gain is lower in infants who received breastmilk with less protein compared to higher protein. However, anthropometric measurements are higher in the group that received formula milk with higher protein, a measure that is associated with a higher-than-normal body mass index.[29] Our finding is also in line within the context of a study that stated protein intake in formula-fed infants exceeds the required amount after 1-2 months of age. Further, this excess is probably responsible for the higher adiposity in older infants. The same study also showed that the breastfed infants are leaner compared to other groups.[30] However, it must be noted that most of these previous studies compared protein levels of human breastmilk to formula milk. Therefore, careful deduction is still needed when concluding whether a difference in human breastmilk protein level alone might have the same effect.

Our study has some limitations that hinder us from drawing a more generalized conclusion. First, there is still no Indonesian standard regarding breastmilk macronutrient levels, a deficiency that makes our study prone to bias when compared to other studies due to differences in population characteristics. Second, although we used a total-sampling method to enroll participants, we were only able to register thirty participants (approximately

one new participant per day). Further studies with longer sampling periods may be able to overcome this limitation. Third, our measurement method yielded no information on total breastmilk quality over 24 h, a deficit that made it difficult to calculate daily total calories available from the breastmilk. Fourth, perhaps the main drawback in our study was the unavailability of maternal diet data, which may affect breastmilk production and its quality during pregnancy and after childbirth. Finally, breastfeeding volume and frequency was defined "as the infant is satisfied with the breastfeeding" rather than a controlled bottled volume. Therefore, further studies with different designs are required to investigate about breastmilk and infant growth and overcome these limitations.

CONCLUSION

We conclude that breastmilk macronutrient levels correlate to infant growth in unique patterns. Breastmilk total calories were positively correlated with infant head circumference. Individual macronutrient levels yielded no significant correlations to infant body weight and length. Rather, the combined effect of the macronutrients manifested as total calories apparently affected growth. We also demonstrated that even lower concentrations of caloric sources (lactose and fat) compared to previous studies did not negatively affect infant growth. Therefore, we cannot fully support the idea that breastmilk causes underweight or overweight in infants less than 3 months old. Based on our findings, we support the idea of exclusive breastfeeding, since the evidence showed a positive relationship toward increased brain volume. Further studies that are able to overcome our limitations are needed to confirm our findings.

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Suitability of Enhanced Recovery after Surgery (ERAS) Protocols for Elderly Colorectal Cancer Patients

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ABSTRACT

Objective: Enhanced recovery after surgery (ERAS) provides a multimodal approach to postsurgical recovery, seeking to reduce a patient's stress response and promoting recovery. This study aimed to determine the suitability of ERAS protocols for elderly patients above 75 years of age.

Methods: This is a retrospective analysis of all patients who had undergone major colorectal resections under ERAS protocols in Khoo Teck Puat Hospital, Singapore and Faculty of Medicine Siriraj Hospital, Thailand between 2013 and 2014. Data collected included patient characteristics and outcomes, including length of hospitalization, and time to first flatus and mobilization.

Results: Of the 196 patients studied, 38 were above 75 years of age. Elderly patients were more likely to have more comorbidities, a higher ASA score and a higher POSSUM predicted mortality. They also had an increased risk of developing Clavien 2 complications (OR 2.41, 95% CI 1.10-5.29). Compared to their younger counterparts, elderly patients did not have a delay in first flatus or mobilization. However, they tended to stay longer (7.89 vs. 5.16 days, $p<0.001$). On multivariate analysis, ASA score of 3 and above was an independent risk factor for a length of stay over 1 week while age was not.

Conclusion: This study has shown that elderly patients achieve comparable functional recovery under an enhanced recovery approach. Enhanced recovery after surgery can be adopted regardless of a patient's age.

Keywords: Enhanced recovery; colorectal resections; elderly (Siriraj Med J 2020; 72: 18-23)

INTRODUCTION

Enhanced recovery after surgery (ERAS) had its roots from the 1990s in the early work of Henrik Kehlet[1], who proposed a multimodal approach to postsurgical recovery that could reduce both postoperative complications and duration of recovery. Enhanced recovery or 'fast-track' surgery challenges the conventional approach to postoperative care, and seeks to reduce the patient's stress response to surgery and promote recovery. Its key elements include preoperative counseling, avoidance of bowel preparation and premedication, reduction in preoperative fasting, maintenance of intraoperative normothermia, laparoscopic access where possible, avoidance of opioid analgesics, nasogastric and intra-abdominal drains, early removal of urinary catheters and early mobilization and feeding. At the beginning, these measures challenged what was then conventional wisdom and were met with resistance, but numerous publications

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over the years have validated its efficacy. A meta-analysis of six randomized controlled trials with 452 patients by *Varadhan et al*[2] in 2010 showed a reduction in hospital stay by 2.55 days (95% CI 1.85-3.24) and a reduction of complications with a relative risk of 0.53 (95% CI 0.44-0.64). While enhanced recovery was initially developed for colorectal surgery, it has now been evaluated or adopted in a number of other surgeries, including radical cystectomy, hepatobiliary and pancreatic surgery, total knee replacement and cardiovascular surgery.[3-7]

The management of an elderly patient undergoing surgery is an evolving challenge. In 2010, 524 million people were above the age of 65 years - 8 percent of the world's population. This number is expected to increase to 1.5 billion people, or 16 percent of the world's population by 2050.[8] A natural consequence of the demographic change has seen more major surgery being performed for elderly patients.[9,10] Surgery for the elderly is fraught with complexities as elderly patients have a higher incidence of co-morbidities, reduced functional reserves and are more likely to be frail. *Duron et al*[11] studied 3322 patients undergoing major digestive surgery in a multicenter prospective study and found that age above 65 years was shown to be an independent risk factor for mortality with an odds ratio of 2.21 (95% CI 1.36-3.59). Surgery in an elderly patient calls for a holistic approach with measures taken to address their increased postoperative risks.

This study aims to evaluate the comparative benefit of enhanced recovery after surgery (ERAS) protocols between elderly and young patients undergoing elective major colorectal resections in an Asian setting.

MATERIALS AND METHODS

All patients who had undergone elective major colorectal resections under ERAS protocols in the Khoo Teck Puat Hospital, Singapore and the Faculty of Medicine Siriraj Hospital, Thailand between January 2013 and December 2014 were reviewed. The elements of ERAS that were adopted in their care are detailed in Table 1. Data from our prospectively collected computer database was extracted and further clinical information was extracted from a review of the clinical notes. Individual comorbidities were recorded and quantified using the American Society of Anesthesiologist (ASA) system. Preoperative surgical risk was quantified with the Colorectal Physiological and Operative Severity for the enUmeration of Mortality and Morbidity (CR-POSSUM)[12] score. Body mass index (BMI), stage of malignant disease, site of surgery relative to the peritoneal reflection and surgical approach (open vs. laparoscopic) were noted.

TABLE 1. Enhanced Recovery after Surgery (ERAS) Protocol.

Variable	Age
Preoperative	Patient education and counselling
	Anaesthesia assessment
	Low residue diet until day before surgery, clear fluids until 2 hours before surgery
	Fluids for carbohydrate loading
	Avoidance of bowel preparation (except for low rectal lesion)
Intraoperative	Epidural analgesia for open surgery (upper midline)
	Mechanical venous thromboemolism and antibiotic prophylaxis
	Zero-balance fluid management
	Bilateral TAP block for laparoscopic/subumbilical incisions +/- PCA
	Removal of NG tube before extubation
Postoperative	Allow free fluids at the earliest opportunity
	Give fluids at 1 ml/kg/hr - Prompt cessation of IV fluids
	Discontinue PCA by POD2, Epidural/TAP cathethers by POD3
	Oral analgesia prescribed - Paracetamol +/- NSAIDS
	Sit out of bed and ambulation by physiotherapist from POD1
	Remove urinary cathether if there are no specific requirements

Outcome measures of morbidity were quantified with the Clavien scoring system.[13] Other outcome measures included the length of stay, day of first flatus or mobilization, the need for re-operations and postoperative mortality. Analysis for factors correlating to the development of postoperative complications and mortality were performed using factors that were identified to be useful predictors by previous studies. The outcomes of patients with age over 75 years were compared with those with a younger age.

Bivariate analysis was performed using Chi-square test in Statistical Package for the Social Sciences for Windows (SPSS Inc, Chicago, USA), version 20.0 on a personal computer. Results were expressed as odds ratios with 95% confidence intervals. Stepwise logistic regression analysis was used in multivariate analysis to identify parameters that independently had affected outcomes.

Institutional review board statement: The study was approved by the institutional review board [DSRB Reference Number: 2017/00130 and SIRB Number: Si 482/2560].

RESULTS

Among the 196 patients who underwent colorectal resections, 38 were above the age of 75 years. The demographic and characteristics of the patients who were operated under ERAS protocols are shown in Table 2. Elderly patients above 75 years of age were more likely to have two or more co-morbidities, with 44.7% of elderly patients having an ASA score of 3 and above compared to 17.7% ($p<0.001$) for younger patients. Elderly patients also had a higher mean CR-POSSUM predicted mortality of 5.86% compared to 1.79% ($p<0.001$) for younger patients. There was no significant difference in gender, BMI, stage of disease and site of surgery.

Bivariate analysis showed that elderly patients had increased risk of postoperative morbidity. The odds ratio for developing Clavien 2 complications and above was 2.41 (95% CI 1.10 – 5.29) for elderly patients (Table 3). However, age was not shown to be an independent risk factor for developing Clavien 2 complications and above on multivariate analysis (Table 4). Instead, having two or more co-morbidities and BMI above 25 were found to be independent risk factors. The elderly were not shown to

TABLE 2. Patient Demographics and Operation Characteristics.

Variable	Age		*P*-value
	Above 75	Below 75	
Male gender	39.5% (15/38)	55.5% (88/158)	0.072
2 or more co-morbidities	**63.2% (24/38)**	**28.5% (45/158)**	**<0.001**
ASA 3 and above	**44.7% (17/38)**	**17.7% (28/158)**	**<0.001**
Mean POSSUM predicted Mortality (SD)	**5.86% (4.43)**	**1.79% (1.52)**	**<0.001**
BMI > 25	21.1% (8/38)	32.3% (51/158)	0.176
Stage 3 disease and above	36.8% (14/38)	47.5% (75/158)	0.238
Below peritoneal reflection	39.5% (15/38)	50.9% (79/158)	0.244
Laparoscopic	**18.4% (7/38)**	**36.1% (57/158)**	**0.037**

TABLE 3. Patient outcomes on bivariate analysis (Odds Ratio).

Variable	Age		Odds Ratio	*P*-value
	Above 75	Below 75	(95% CI)	
Reoperation	2.6% (1/38)	1.9% (3/158)	1.40 (0.14 - 13.81)	0.774
Clavien ≥2 complications	**34.2% (13/38)**	**17.7% (28/158)**	**2.41 (1.10 - 5.29)**	**0.025**
Clavien ≥3 complications	5.3% (2/38)	3.8% (6/158)	1.41 (0.94 - 1.10)	0.682
Hospitalization death	2.6% (1/38)	0.6% (1/158)	4.24 (0.26 - 69.42)	0.271

TABLE 4. Multivariate analysis correlating to Clavien 2 or more complications and length of stay ≥1 week.

Factor	Clavien ≥2 Complications OR (95% CI, *P*-value)	Length of stay ≥1 week OR (95% CI, *P*-value)
Age >75	1.46 (0.59 – 3.63, 0.414)	1.22 (0.45 – 3.33, 0.701)
Male gender	1.02 (0.49 – 2.16, 0.950)	1.00 (0.44 – 2.27, 0.992)
2 or more co-morbidities	**2.61 (1.13 – 6.00, 0.024)**	**2.06 (0.82 – 5.18, 0.127)**
ASA 3 and above	1.66 (0.69 – 3.97, 0.256)	2.58 (1.02 – 6.54, 0.460)
BMI >25	**2.62 (1.05 – 6.52, 0.038)**	**2.50 (0.91 – 6.89, 0.076)**
Stage 3 disease and above	0.85 (0.40 – 1.81, 0.670)	1.45 (0.64 – 3.31, 0.373)
Below peritoneal reflection	0.82 (0.37 – 5.89, 0.577)	0.83 (0.36 – 1.89, 0.652)
Laparoscopic	1.29 (0.58 – 2.87, 0.529)	0.98 (0.40 – 2.42, 0.964)

be at significant risk for developing more major (Clavien 3 and above) complications. There was no statistically significant difference in the rate of reoperations or in-hospital death.

Elderly patients were found to have an increased length of stay at an average of 7.89 days compared to 5.16 days ($p<0.001$) in younger patients (Table 5), but demonstrated good functional recovery, with no significant difference in the day of first flatus or first mobilization. Once again, age was not shown to be an independent risk factor for a length of stay beyond one week on multivariate analysis (Table 4). An ASA score of 3 and above was shown to be an independent risk factor for increased length of stay.

TABLE 5. Patient outcomes (comparison of means).

Variable	Age		
	Above 75	**Below 75**	***P*-value**
Length of stay (SD)	**7.89 days (6.24)**	**5.16 days (3.42)**	**<0.001**
Day of first flatus (SD)	1.97 days (1.30)	1.88 days (1.22)	0.638
Day of first mobilization (SD)	1.50 days (0.95)	1.32 days (0.72)	0.052

DISCUSSION

This review of two cohort of patients from Singapore and Thailand showed that elderly patients 75 years of age and above undergoing major colorectal resections under ERAS guidelines were more likely to develop Clavien 2 and above complications and to have an increased length of stay. Although elderly patients experienced more complication and longer hospital stay, they could achieve comparable functional recovery as of a younger age group within an ERAS protocol. Interestingly, old age was not shown to be an independent risk factor for either outcome on multivariate analysis. In fact, two or more co-morbidities and BMI above 25 were found to be independent risk factors for major postoperative complication, and ASA score of 3 and above was an independent risk factor for increased length of stay.

While age above 75 years was associated with the development of Clavien 2 and above complications, it was not found to lead to more major complications (Clavien 3 and above) requiring admission to an intensive care unit or further procedural or surgical re-interventions. Elderly patients were also not found to have a significant difference in mortality rates. This suggests that enhanced recovery interventions can be safely applied to elderly patients. Several previous studies have shown that ERAS reduced complications and duration of hospitalization when applied to the elderly, and there was no significant difference in outcomes between the elderly and the young.[14-16] While the present findings are comparable to those in the literature, it may be subject to Type 2 sampling error given the sample size and the low probabilities of major adverse events, with only one patient in each cohort (age above or below 75 years) suffering from in-hospital death.

Another consideration for an increased length of stay in elderly patients was the reduced use of a laparoscopic approach, which reduces postoperative pain, improves functional recovery and shortens hospital stay.[17-18] In the present study, elderly patients were more likely to be selected for open surgery partly due to relative contraindications to a laparoscopic approach relating to their co-morbidities.

Despite an increased length of stay, there was no significant difference in the functional recovery of an elderly patient under an enhanced recovery program. They had similar average day of first flatus and first mobilization as their younger cohort. This suggests that the elderly derive a comparable benefit from enhanced recovery measures. Furthermore, what differentiate elderly patients from their younger counterparts is their own expectations when they agree to undergo surgery. Long-term survival is often not as important as a return to pre-morbid function and the retention of functional independence.[19] The application of ERAS protocols to reduce functional impairment after surgery could have an even greater significance in the elderly population.

CONCLUSION

Compared to a younger patient, an elderly patient may develop increased complications or require a longer duration of hospitalization if they have increased co-morbidities or a higher ASA score. Nevertheless, this study has shown that elderly patients achieve comparable functional recovery under an enhanced recovery approach. Enhanced recovery after surgery should be adopted regardless of a patient's age.

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Multifaceted Intervention to Improve the Quality of Care for Postpartum Hemorrhage

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ABSTRACT

Objective: To evaluate the effect of a multifaceted intervention on the quality of care and clinical outcomes for postpartum hemorrhage (PPH) as measured by adherence and acceptability to indicators of PPH management at district and referral levels.

Methods: A quasi-experimental study of interventions was conducted to improve healthcare for PPH in 6 district and 3 referral hospitals in southern Thailand. Multifaceted intervention included educational outreach, audit and feedback, reminders, and the involvement of an opinion leader. Physicians and nurses responsible for case management and care policies (145 individuals) in the aforementioned hospitals participated in the intervention. Medical records were reviewed considering the checklist of indicators for district and referral levels.

Results: All indicators for PPH management were accepted by at least 80% of the participants, except for surgical intervention. We reviewed the medical records of 805 women diagnosed with PPH. Of these, during the pre- and post-intervention periods, 132 and 142 were from district hospitals, and 228 and 303 from referral hospitals, respectively. The use of an indwelling bladder catheter and hemodynamic monitoring were significantly increased in the post-intervention period.

Conclusion: Quality of care for postpartum hemorrhage improved after implementing a multifaceted intervention targeting healthcare providers. The results of this study can be applied to other hospitals with a similar setting regarding the eligible criteria. Severe maternal morbidity and mortality from PPH should be monitored.

Keywords: Indicator; multifaceted intervention; postpartum hemorrhage; quality of care (Siriraj Med J 2020; 72: 24-32)

INTRODUCTION

Postpartum hemorrhage (PPH), defined as a blood loss of 500 mL or more within 24 h following parturition, is a common obstetric complication contributing to maternal near-miss morbidity and mortality.[1] A systematic review of the literature showed that PPH is a leading cause of maternal death in developed countries.[2] The global prevalence of hemorrhage in maternal deaths was reported as 13.4%, but 10%-20% in Thailand.[3] The World Health Organization (WHO) updated the guidelines for PPH prevention and treatment in 2012 focusing on uterine atony and a retained placenta, which are the most common causes of PPH.[4] However, these guidelines are recommended practices in general and are not focused on hospital contexts in particular. As a result, the guidelines are not used efficiently and clinical

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practice based on evidence-based guidelines remains a challenge.[5] Moreover, the translation of knowledge into action is limited in most developing countries.[6]

Although evidence-based guidelines for best practice to prevent and treat PPH have been promoted,[4,7] these practice guidelines are not always adhered to appropriately.[8-10] To improve the adherence to standard practices, indicators are an important tool to aid evaluating and monitoring quality improvement.[11] Scientific evidence for developing appropriate indicators to improve the quality of care is essential.[12] Acceptability of the indicators by healthcare providers is vital to develop appropriate indicators to measure the quality of a process.[13–14] We previously developed process indicators for PPH management for district- and referral-level hospitals from the evidence-based guidelines, which a healthcare provider agreed were feasible to monitor.[15] The report of a study conducted in The Netherlands described the development of quality indicators to prevent and manage PPH, but their ultimate indicators differed from those in our present study.[16] A systematic review found that didactic traditional continuing medical education or mailing the dissemination of knowledge alone did not change the behavior of healthcare professionals significantly.[17] Therefore, comprehensive methods should be used to introduce to healthcare providers the practice of implementing and correctly utilizing indicators.

A clinical audit is a commonly used method to reduce the frequency of severe complications and improve the management of PPH.[18,19] However, it has been argued that conducting an audit alone is not sufficient to change the practice of medical professionals and that the use of multiple approaches, known as a multifaceted intervention, including audit and feedback, educational outreach, the involvement of opinion leaders, and reminders, is effective.[20,21] Multifaceted intervention has also been reported as an effective strategy to improve the adherence to standard practice related to PPH.[20] However, there are a variety of interventions that influence the clinical practice depending on the context of the facilities.[21] Therefore, the present study aimed to evaluate the effect of a multifaceted intervention on the quality of care for PPH as measured by the adherence and acceptability to management indicators as well as the clinical outcomes at the district and referral levels.

MATERIALS AND METHODS

Study design and context

We conducted a quasi-experimental before-and-after study in Songkhla province, southern Thailand, which has various hospital levels and contexts, to assess the change of practice related to PPH based on management indicators. This study was approved by the Institutional Ethics Committee of the Faculty of Medicine, Prince of Songkla University (approval No. 53-108-18-1-3) and the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand (Si 45/2010) in June 2010. All the physicians and nurses participated in the study were informed and signed their consent.

A total of 9 hospitals, including 3 referral hospitals (a university, a regional, and a provincial hospital) and 6 district hospitals in Songkhla province, with a previous record of at least 30 deliveries per month and the highest complications in the province, were chosen to acquire sufficient cases of PPH. The obstetricians and the general doctors had responsibilities as the team leaders at the referral and provincial hospital, respectively. Although guidelines for PPH management existed in the participating hospitals, they were described variously, and unmonitored. A checklist of indicators, which were considered feasibly relevant, measurable, and improvable, was used to audit PPH management. Details of the development process, reliability, and validity are described in our previously published manuscript.[15]

The indicators for district hospitals included a correct diagnosis of PPH, and general management, such as the administration of intravenous fluids, monitoring of vital signs, and use of an indwelling bladder catheter. For referral hospitals, blood cross-matching was added as an indicator of general management. Specific management indicators common to both hospital levels included performing a uterine massage and providing oxytocin or methylergometrine in the case of uterine atony and after removal of the placenta in the case of a retained placenta. Prostaglandin E2, surgical and radiological interventions for uterine atony, and removal of the placenta under general anesthesia were additionally indicated at the referral level.

Intervention

The intervention included educational outreach, audit and feedback, reminders, and the involvement of an opinion leader from August to September 2010. Before educational outreach, an audit was conducted by reviewing the medical records of women with PPH in the participating hospitals. Then the research team visited the study hospitals to give information on the magnitude of PPH and the need for prompt appropriate PPH management. In addition, feedback on the audit information related to PPH management and the outcomes of practice based on the indicators was provided to healthcare providers in this educational outreach visit. In addition, a chart of quality indicators was placed in

the labor room, postpartum ward, and emergency room as a reminder of the PPH guidelines. These activities were facilitated by the opinion leaders in the hospitals.

Data collection

The medical records of women with PPH who had delivered in the participating hospitals from October 2008 to September 2009 (pre-intervention period) were audited by 2 standardized researchers using an indicator checklist. Then, educational outreach activities were conducted in each participating hospital during August and September 2010. All the physicians and nurses who were mainly responsible for the management of PPH at each hospital were invited to participate in the study. Discussions on each indicator for the management of PPH, and the challenges with possible solutions were recorded. After the intervention, the medical records of women with PPH who had delivered between October 2010 to September 2011 (post-intervention period) were audited by the same researchers using the same checklist. A diagram of the study flow and time frame is shown in Fig 1.

Variables

Information on the healthcare providers participating in the intervention, including gender, age, occupational status, and duration of work experience, were collected. The acceptability of each indicator was determined using a constructed self-administered questionnaire. The acceptability was assessed as "the degree to which they would accept the indicator in their practice" and was measured using a 5-item Likert-type rating scale, ranging from strongly unacceptable to strongly acceptable. Patient characteristics, including maternal age, parity, gestational age at delivery, and route of delivery, were recorded. Practicing each indicator was evaluated as "yes", "no", or "no data". Maternal outcomes, such as amount of blood loss in 24 h after delivery, receiving a blood transfusion, shock, hysterectomy, length of hospital stay, and referral status, were assessed. Neonatal outcomes included Apgar score < 7 at 5 min and NICU admission.

Data analysis

The sample size for the study was based on a target for improvement defined as 90% adherence to each indicator, compared with an average baseline adherence of 70% at the district level and 80% at the referral level in the pre-intervention period,[9] with a 95% confidence interval and a power of 80%. At least 72 medical records of PPH at the district level and 219 at the referral level were required for before and after the intervention.

The data were entered in EpiData Entry, version 3.1 (Lauritsen JM and Bruus MA, a comprehensive tool for the validated entry and documentation of data. The EpiData Association, Odense Denmark, 2008), and analyzed using R, version 2.10.0 (R Foundation for Statistical Computing, Vienna, Austria). The acceptability was analyzed descriptively by hospital level. The maternal characteristics, adherence to practice of each indicator, and maternal and neonatal clinical outcomes were compared before and after the intervention by hospital level using a univariate analysis. $P < 0.05$ was considered as significant in the tests of statistical inference.

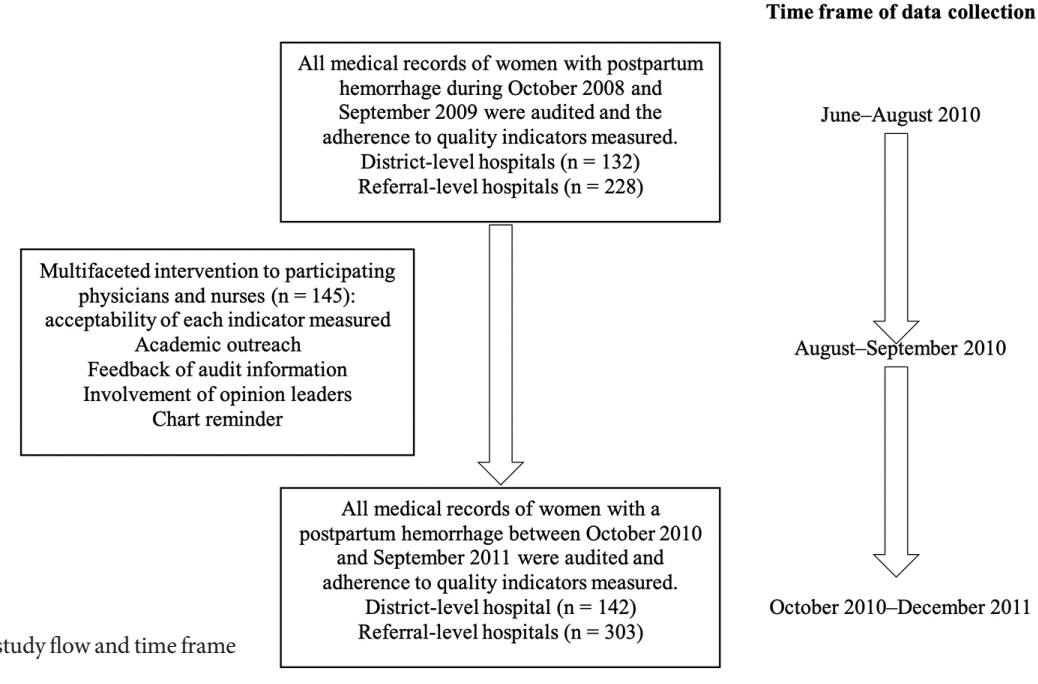

Fig 1. Diagram of the study flow and time frame

RESULTS

Acceptability of the indicators to healthcare providers

Of the 145 healthcare providers from both district and referral hospitals, 124 were women (85.5%) and 38 were physicians (26.2%). Their mean age was 34 years old, with working experience ranging from 1 to 35 years (median 8 years; IQR 3 to 14 years).

In total, 805 medical records of women with PPH were reviewed. During the pre- and post-intervention periods, 132 and 142 were from district hospitals, while 228 and 303 were from referral hospitals, respectively. As shown in Table 1, all the PPH indicators were accepted by at least 80% of the participants, except for surgical intervention. The main reason for the lower acceptability of surgical intervention was because it requires special training and high-level competency.

Use of indicators by healthcare providers

The characteristics of mothers during the pre- and post-intervention periods are shown in Table 2. In district hospitals, maternal age and parity were not significantly different, but significantly higher proportions of preterm birth and normal labor were found during the post-intervention period. However, those 2 characteristics were not significantly different in the referral hospitals.

Table 3 shows the change of adherence to the indicators for PPH. Significant improvements, particularly in the use of indwelling bladder catheter ($p < 0.001$ and $p = 0.007$) and the monitoring of vital signs ($p < 0.001$ and $p = 0.001$), were found after the intervention in both contexts. Of all the women with PPH, uterine atony was diagnosed in 78% of women attending district hospitals and 69% of women attending referral hospitals.

TABLE 1. Acceptability of quality indicators on postpartum hemorrhage rated by healthcare providers.

Indicators for postpartum hemorrhage	Type of hospital District hospitals n (%)	 Referral hospitals n (%)
Diagnosis		
Registration of estimated blood loss	75 (88.2)	58 (96.7)
General management		
Administration of intravenous fluid	85 (100.0)	60 (100.0)
Indwelling bladder catheter	74 (87.0)	54 (90.0)
Monitoring of blood pressure and pulse rate every 15 min within 2 h of diagnosis and recording urine output every hour	69 (81.2)	52 (86.7)
Cross-matching blood	NA	53 (88.3)
Specific management		
Uterine atony		
Performing uterine massage	83 (97.6)	60 (100.0)
Administering oxytocin	77 (90.5)	56 (93.3)
Administering methylergometrine	75 (88.2)	57 (95.0)
Administering prostaglandin E2	NA	52 (86.7)
Surgical intervention	NA	42 (70.0)
Retained placenta		
Manual removal of placenta	NA	53 (88.3)
Uterine massage and administration of uterotonic drugs after removing the placenta	78 (91.7)	58 (96.7)

Abbreviation: NA = not applicable

TABLE 2. Characteristics of women with postpartum hemorrhage before and after the intervention.

Intervention period	District hospitals			Referral hospitals		
	Pre-intervention (n = 132) n (%)	Post-intervention (n = 142) n (%)	*P**	Pre-intervention (n = 228) n (%)	Post-intervention (n = 303) n (%)	*P**
Age (years), mean (SD)	28.61 (6.69)	28.49 (6.72)	0.80	28.8 (6.8)	29.27 (7.15)	0.99
Age group (years)			0.49			0.39
≤20	10 (7.6)	16 (11.3)		13 (5.7)	25 (8.3)	
20-34	92 (69.7)	100 (70.4)		149 (65.4)	183 (60.4)	
≥35	29 (22.0)	26 (18.3)		66 (28.9)	94 (31.0)	
Missing data	1 (0.7)	0		0	1 (0.3)	
Parity			0.66			0.66
Nulliparity	36 (27.3)	36 (25.4)		75 (32.9)	106 (35)	
Multiparity	90 (68.2)	96 (67.6)		145 (63.6)	190 (62.7)	
Grand multiparity	6 (4.5)	10 (7.0)		8 (3.5)	7 (2.3)	
Gestational age group			0.38			0.17
<37 weeks	9 (6.8)	15 (10.6)		46 (20.2)	63 (20.8)	
≥37 weeks	122 (92.5)	127 (89.4)		182 (79.8)	236 (77.9)	
Missing data	1 (0.7)	0		0	4 (1.3)	
Route of delivery			0.02			0.86
Normal labor	92 (69.7)	112 (78.9)		123 (53.9)	151 (49.8)	
Cesarean section	25 (18.9)	26 (18.3)		82 (36.0)	107 (35.3)	
Operative delivery	15 (11.4)	4 (2.8)		23 (10.1)	33 (10.9)	
Missing data	0	0		0	12 (4.0)	

Number in the table are frequency and percent unless stated; SD, standard deviation

*Continuous data analyzed by unpaired t test; categorical data omitting missing data analyzed by Chi-square test.

The implementation of specific management for uterine atony and for a retained placenta in district hospitals was not significantly different between the two periods, while the implementation of uterine massage in uterine atony ($p < 0.001$) and manual removal of a retained placenta ($p < 0.001$) were significantly improved in the referral hospitals.

The clinical outcomes of women with PPH are shown in Table 4. Neither maternal nor neonatal outcomes were significantly changed after the intervention. More than half of those who were diagnosed in the referral hospitals had a blood loss of 1,000 mL or more and received a blood transfusion. Hysterectomy was performed in 10% of cases. Few women diagnosed as PPH showed an estimated blood loss of less than 500 mL; however, the nurse records revealed that vaginal bleeding was continuously observed within 24 h of parturition without quantitative estimation.

DISCUSSION

The management of PPH as monitored by quality indicators was improved after multifaceted intervention was implemented aimed at physicians and nurses. However, the effect on clinical outcomes was not identified in this study. A significant improvement of active care, particularly in the use of indwelling bladder catheters

TABLE 3. Percentage adherence to the quality indicators for the care of postpartum hemorrhage.

Intervention period	District hospitals			Referral hospitals		
	Pre-intervention (n = 132) n (%)	Post-intervention (n = 142) n (%)	*P**	Pre-intervention (n = 228) n (%)	Post-intervention (n = 303) n (%)	*P**
General management						
Indwelling bladder catheter	58 (43.9)	134 (94.4)	< 0.001	173 (75.9)	259 (85.5)	0.007
Monitoring of blood pressure and pulse rate every 15 min within 2 h of diagnosis and recording urine output every hour	88 (66.7)	141 (99.3)	< 0.001	209 (91.7)	297 (98)	0.001
Administration of intravenous fluid	130 (98.5)	142 (100)	0.23	228 (100)	302 (99.7)	1
Cross matching	NA	NA	NA	207 (90.8)	277 (91.4)	0.92
Specific management						
Uterine atony	**n = 104**	**n = 109**		**n = 158**	**n = 208**	
Performing uterine massage	103 (99)	102 (93.6)	0.07	105 (66.5)	174 (83.7)	< 0.001
Administering uterotonic drugs	101 (97.1)	109 (100.0)	0.12	156 (98.7)	206 (99)	1
Surgical intervention						0.81
Vessel ligation	NA	NA		2 (1.3)	2 (1)	
B-Lynch	NA	NA		3 (1.9)	6 (2.9)	
TAH	NA	NA		20 (12.7)	21 (10.1)	
Refer	8 (7.7)	11 (10.1)	0.71	NA	NA	
Retained placenta	**n = 27**	**n = 32**		**n = 54**	**n = 72**	
Performing manual removal of placenta	16 (59.3)	25 (78.1)	0.20	42 (77.8)	71 (98.6)	< 0.001
Performing uterine massage and uterotonic drug given after removal of placenta	16 (59.3)	25 (78.1)	0.20	54 (100.0)	70 (97.2)	0.51
Refer	11 (40.7)	10 (31.2)	0.627	NA	NA	

Numbers in table are frequency and percent. *Analyzed by Chi-square test or Fisher's exact test as appropriate.
Abbreviations: NA = not applicable; TAH = total abdominal hysterectomy

and the monitoring of vital signs, was found after the interventions in both district and referral hospitals. The adherence to the quality indicators was related to their acceptability from the healthcare providers. However, a significant improvement of adherence to the indicators after the intervention could not be identified for all indicators due to the low prevalence of certain specific conditions (e.g., retained placenta at a district hospital) or a high baseline adherence > 90% before the intervention. On the other hand, some specific quality of care indicators (uterine massage and manual removal of a retained placenta) were significantly improved at only referral hospitals because of the low baseline adherence and higher number of cases there than in district hospitals.

A multifaceted intervention with various approaches, including audit and feedback, educational outreach,

TABLE 4. Clinical outcomes of women with postpartum hemorrhage.

Intervention period	District hospitals			Referral hospitals		
	Pre-intervention (n = 132) n (%)	Post-intervention (n = 142) n (%)	*P**	Pre-intervention (n = 228) n (%)	Post-intervention (n = 303) n (%)	*P**
Maternal complications						
Amount of blood loss (mL)			0.50			0.51
<500	7 (5.3)	3 (2.1)		13 (5.8)	11 (3.6)	
500-999	74 (56.1)	86 (60.6)		92 (41.1)	116 (38.4)	
1,000-2,499	49 (37.1)	52 (36.6)		96 (42.9)	137 (45.4)	
≥2,500	2 (1.5)	1 (0.7)		23 (10.3)	38 (12.6)	
Blood transfusion	36 (27)	28 (34)	0.39	131 (57.5)	163 (53.8)	0.45
Shock	21 (15.9)	25 (17.6)	0.83	26 (11.4)	27 (8.9)	0.42
Hysterectomy	1 (1)	1 (0.7)	1	23 (10.1)	32 (10.6)	0.97
Length of hospital stay (days)			0.70			0.91
Median, IQR	3 (2,4)	3 (2,3)		4 (3,6)	4 (3,5)	
Refer	19 (14.4)	22 (15.5)	0.93	NA	NA	
Neonatal complications						
Apgar scores <7 at 5 min after birth	2 (1.6)	2 (1.4)	1	9 (4.1)	17 (6.2)	0.41
NICU admission	NA	NA		15 (6.6)	18 (5.9)	0.91

Numbers in table are frequency and percent except for length of hospital stay (median (IQR, interquartile range)). *Analyzed by Chi-square test or Fisher's exact test as appropriate.

Abbreviation: NA = not applicable

involvement of local opinion leaders, and reminders, was chosen as the intervention in our study because there is evidence that these interventions can change the behavior of healthcare professionals.[17,21–23] A literature search in PubMed performed on October 14, 2019, using the terms "multifaceted intervention" and "postpartum hemorrhage", revealed 6 articles, including a controlled trail[24] and 2 randomized-controlled trials[25–26], as well as 3 before-and-after quasi-experimental trials.[20,27,28] Although these studies showed a variation in the outcomes monitored of PPH, the use of multifaceted intervention was a common strategy for preventing PPH and improving its management.[29]

In the present study, the healthcare providers who worked in the participating hospitals contributed to the design process to aid considering whether the management strategies were feasible and practical in their contexts and would be supported by policymakers before the strategies were implemented. Details of the development and assessment of the quality of care indicators were published previously.[15] Apart from the importance of the content disseminated, educational outreach assists the provision of an audit of the relevant indicators in the clinical setting, and contributes to an opportunity for discussion between the members of the care team. The involvement of opinion leaders and reminders are helpful for encouraging the continuity of good practice. Therefore, multiple approaches as a multifaceted intervention have been proven to be effective in changing the practice of medical professionals.[17,20,21]

The accuracy of estimating blood loss during delivery and immediately postpartum is a challenge. Visual estimation

is common practice but has low sensitivity, leading to the underestimation of PPH in 89% of cases.[30] Although various techniques were used in previous studies, no definite method is recommended in clinical practice.[31]

Guidelines for PPH management were different in each context.[18,20] Our management criteria were developed from evidence-based guidelines and based on the acceptability of healthcare providers as quality indicators.[15] Adherence to practices such as cross-matching of blood and vital sign monitoring both pre- and post-intervention periods in our study were better than those reported in a study in Malawi.[19] Significant improvements in the use of indwelling bladder catheters and the monitoring of vital signs was found after the interventions in this study. These practices are important for the early detection of hemorrhagic shock.[8]

The study has a few limitations to report. First, a study using an interventional design may be subject to possible selection and outcome bias. However, the indicators of PPH management were applied to all diagnosed cases, regardless of the patient age, parity, gestational age, or route of delivery. Second, the results of a quasi-experimental before-and-after study may be affected by temporal changes. However, the outcomes in the present study were registered immediately after intervention, which minimizes the outcome change over time. In addition, the benefit of multifaceted intervention for PPH has already been shown in randomized-controlled trials, thus a quasi-experimental interventional study is a reasonable choice for the study design. Finally, this study could not identify the effect of the improvement of the quality of care on maternal and neonatal clinical outcomes because this was not the main objective of the present study, therefore the sample size was not calculated for improving clinical outcomes. A well-designed clinical trial to determine the effect of implementing the indicators on the quality of care and the incidence of complications is thus warranted.

CONCLUSION

The use of indicators for the quality of care for PPH was acceptable to healthcare practitioners and their adherence to indicators was improved after implementing a multifaceted intervention targeting the practitioners. The guideline for the development and implementation of indicators can be applied to other hospitals with a similar setting to the eligible criteria of the present study.

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Role of Vascular Endothelial Growth Factor (VEGF) and Doppler Sub-endometrial Parameters as Predictors of Successful Implantation in Intracytoplasmic Sperm Injection (ICSI) Patients

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ABSTRACT

Objective: to investigate the expression of vascular endothelial growth factor (VEGF) in patients having infertility due to low endometrial acceptance, and to correlate it to non-invasive ultrasound variables, endometrial thickness, and sub-endometrial Doppler parameters (PI, RI, Vs/Vd).

Methods: 80 women all under the age of 40 underwent ICSI-ET; all patients were exposed to ovarian stimulation protocols. The oocytes were retrieved using an ultrasound guide, and were fertilised via injection of sperm inside the follicle (ICSI). VEGF serum level was analysed at day of embryo transfer by ELIZA test, and sub-endometrial evaluation was conducted via two-dimension power Doppler ultrasound (2D PD-US), by measuring resistance index (RI) and pulsatility index (PI) on the day of embryo transfer.

Results: There was a significantly higher VEGF level and endometrial thickness in pregnant (433± 207 and 9.72± 1.35) women, compared to non-pregnant (276± 165 and 8.95 ± 1.21) respectively as *p*-values were (0.001 and 0.01)). Additionally, there were significantly lower RI and PI in pregnant (0.584 ± 0.124 and 0.829 ± 0.301) women compared to non-pregnant (0.651±0.132 and 1.006±0.335) women, as *p*-values were (0.02 and 0.02, respectively). The level of E2 was on the day of embryo transfer and Vs/Vd in pregnant women (1402± 524 and 3.14 ± 3.75) and in the non-pregnant group (1296± 611 and 3.82 ± 3.07), as *p*-values were 0.41 and 0.38, respectively.

Conclusion: The combined analysis of endometrial receptivity was completed, and the serum level of VEGF and sub-endometrial evaluation with 2D PD-US was defined by measuring resistance index (RI) and pulsatility index (PI) on the day of embryo transfer. These can serve as useful prognostic methods for the detection of endometrial receptivity and pregnancy outcomes in infertile women undergoing ICSI protocols, and will be helpful for candidate counselling about postponing embryo transfer and cryopreservation, which may serve as a better option, to be recommended for the next cycle, when achieving better endometrial Doppler parameters.

Keywords: VEGF; Sub-endometrial doppler; infertility (Siriraj Med J 2020; 72: 33-40)

INTRODUCTION

Infertility means the inability to have a baby despite regular unprotected sex.[1] According to NICE guidelines, two years of having regular sex without the presence of a known abnormality in both partners is necessary for establishing the diagnosis of infertility.[2] Management of

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these patients have changed and improved dramatically, ranging from assistedreproduction technology to in vitro fertilisation (IVF). Intracytoplasmic sperm injection (ICSI), has helped tremendously in management of infertility due to male factors.[3] The problem of IVF arise in the failure of transfer of embryo. That's way research has focused on finding the best conditions in the embryo and the endometrium that will allow proper transfer. Discovering specific and accurate biomarkers is a primary concern to many researchers. Additionally, knowledge of the human implantation window length on days (6-10) post-ovulation, the effect of steroid hormones (oestrogen, progesterone, gonadotropins) on genetic factors, the age of a woman, and functional and morphological markers pertaining to endometrial receptivity are of crucial significance to all future studies aimed at identifying endometrial receptivity[4], studying endometrial receptivity by non-invasive methods like vaginal ultrasonography. Conventionally, pulsed Doppler sonography is used to evaluate uterine and endometrial blood flow, but non standard results have been reported for the measurement of sub-endometrial resistance index (RI) and pulsatility index (PI) at the second endometrial zone (zone 2), with serum level of estradiol at day of HCG and angiogenic factor VEGF at day of embryo transfer. This variation is correlated with endometrial receptivity and pregnancy outcome, and can contribute to making a judgment as to whether an embryo should be transferred, or whether to cryopreserve it until it reaches an optimum level of endometrial receptivity.

Due to the limited mobility of the intravaginal transducer in the small vaginal cavity, Normal ultrasound is of limited value. Real-time U/S allows study of two factors related to implantation: the thickness of endometrium and the pattern of endometrial morphology.[5] Ultrasound is crucial for predicting endometrial preparation before transfer of embryo (ET), in both fresh IVF cycles and frozen-thawed embryo transfer cycles. Frequently used parameters for endometrial sonographic assessment involve endometrial thickness, endometrial patterns, and Doppler indices.[6] At the myometrial-endometrial junction, there is a sub-endometrial region that is detected on ultrasound examination as a thin hypoechoic layer between the echogenic endometrium and myometrium; this is referred to as the junctional zone, inner myometrium, sub- endometrial halo, or sub- endometrial layer, and can be identified by either ultrasound or MRI. Research has confirmed that the sub-endometrial haloaround around the endometrium is representative of the innermost layer of the myometrium.[7] The vascularity zones are identified as follows. Zone 1: vessels are detected in the myometrium around the endometrium; zone 2: vessels penetrate the hyperechogenic endometrial edge; zone 3: vessels reach the internal hypo echogenic zone; zone 4: vessels reach the endometrial cavity, when colour mapping of the endometrial and sub-endometrial regions is absent; this means a definite implantation failure or a considerable decline in the implantation rate.[8] Doppler studies have revealed that the resistance in arteries of the endometrium is significantly reduced during the mesoluteal phase, which is the period when embryo implantation is possible. The changes in blood vessels may have a vital role in the implantation process, as they are present from the start of the embryo implantation. Vascular endothelial growth factor (VEGF), belongs to proteins binding heparin that attach to endothelial cells, and which lead to proliferation and new blood vessel formation. The VEGF also causes release of cytokines by the endothelial cells leading to dilatation of blood vessels. It acts as an angiogenic factor to promote angiogenesis in various tissues.[9] Consequently, this explains the crucial role of angiogenesis in different female reproductive processes, e.g., development of a dominant follicle, formation of a corpus luteum, endometrial growth, as well as implantation. As such, local angiogenesis is considered a major prerequisite for implantation and subsequent conception.[10] Angiogenesis was reported as it is least occurring during the menstrual phase, then there will be an increase during the early proliferative phase, reaching maximum in mid-cycle then decrease near the end of the cycle.[10,11]

MATERIALS AND METHODS

This is a prospective study was conducted in the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University. The study was approved by the Local Medical Ethical Committee of the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University. Eighty women undergoing an IVF/ICSI cycle were included in this study. At the day of embryo transfer, two dimensional Power Doppler (2D-PD) ultrasound was conducted for sub-endometrial blood flow zone 2, with serum VEGF level analysis.

IVF/ICSI procedures

Step-by-step descriptions of IVF procedures:

1. Controlled ovarian hyper stimulation (COH)
2. Oocyte retrieval (OCR)
3. Fertilisation and embryo culture
4. Embryo quality
5. Embryo transfer (ET)

Three different types of controlled ovarian hyperstimulation (COH) were used according to the demographic parameters of patients, starting a long agonist protocol, from day 21 of the preceding cycle and using a GnRH agonist (Decapeptyl® 0.1 mg, Ferring Co., Germany); then, on the second day of the menstrual cycle, stimulation was started with a daily dose of 150-450 IU rFSH (follitropin alfa, Gonal F®, Merck Serono). Secondly, a short agonist protocol was initiated, beginning with a GnRH agonist from cycle day one-to-two, then starting a daily dose of 150-450 IU rFSH (follitropin alfa, Gonal F®, Merck Serono). The third option used an antagonist protocol by starting with a daily dose of 150-450 IU rFSH (follitropin alfa, Gonal F®, Merck Serono), and when follicles reached 13-14 mm in size, a GnGH antagonist was started (Cetrotide®, Merck Serono). Patients were monitored by transvaginal sonography (TVS). HCG (Ovitrelle® 250 microgram, Merck Serono) was given when three or more follicles reached a diameter of 18 mm. Oocytes retrieval was performed using a transvaginal probe 34-36 hours following the HCG injection, immediately prior to the rupture of follicles. Oocytes were aspirated by transvaginal ultrasound guided oocyte retrieval (TUGOR); oocytes at retrieval can be either the germinal vesicle (GV), which is the most immature, or from metaphase I (MI), at which the oocyte is an immature egg. The absence of a polar body or germinal vesicle indicates it to be at the MI stage, which is an intermediate stage between the GV and MII (mature) stages, or metaphase II oocyte (MII), which is mature. Generally, prior to OCR, a semen sample is prepared for sperm extraction, following a minimum of two days and a maximum of seven days' sexual abstinence. Testicular sperm extraction (TESE) is a surgical sperm retrieval procedure used in infertility treatment for men with azoospermia.

At the IVF laboratory, aspirated follicles were examined. Flushing was performed, and the follicles are kept one-to-two hours in a 37°C/CO_2 incubator. Later, all oocytes underwent denudation and grading in a laminar flow cabinet. Thereafter, a needle was carefully inserted through the shell of the egg into its cytoplasm, then kept in the CO_2 incubator while waiting for the results of cell division, which would be detected with the aid of a Nikon ICSI microscope. Following insemination, zygotes were observed for 18-20 hours to check for the presence of two pronuclei, and for 25-29 hours to confirm the existence of early cleavage, which was correlated with higher implantation rates. At day one, the presence of two pronuclei was considered a good prognostic sign.

At day two-or-three post-OCR, and according to the number and grading of the embryos, patients were prepared for the transfer. The patient's serum was obtained for VEGF serum level, two dimensional transvaginal ultrasound scans were done to measure endometrial thickness, regularity, and echogenicity, and sub-endometrial blood flow colour Doppler indices (PI, RI and Vs/Vd) were measured. The measurement involved both endometrial layers, excluding the surrounding low amplitude echo layer; three measurements were taken and the average value was recorded. A pulsed Doppler system was used for blood flow analysis. Sub-endometrial vessels were visualised at the endometrial periphery, sometimes penetrating the hyperechogenic endometrial edge, or even reaching the endometrial cavity.

We measured the endometrial thickness on the day of ET as we want it to be more accurately correlated with the level of VEGF which was measured on the same day.

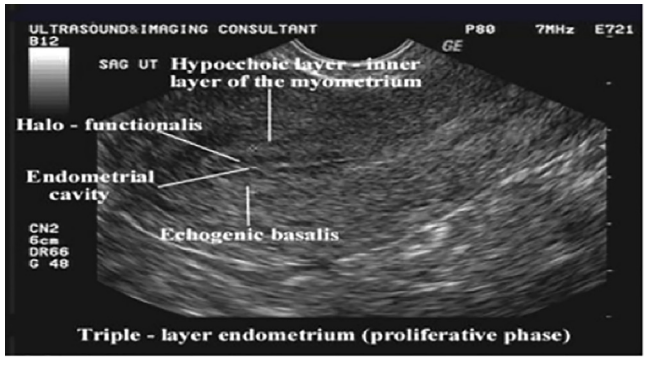

Fig 1. Ultrasound review reveals myometrial, endometrial, and sub-endometrial zones.

Blood flow velocity waveforms from the sub-endometrial vessels were obtained by placing the Doppler gate over the coloured area at zone 2 and activating the pulsed Doppler function.

$$RI = \frac{PSV-EDV}{PSV} \quad PI = \frac{PSV-EDV}{mv} \quad mv = \frac{PSV+EDV}{2}$$

Abbreviations: RI = resistance index; PSV = peak systolic velocity; EDV = end-diastolic velocity; PI = pulsatility index; mv = mean velocity

RESULTS

Demographic parameters and hormonal profile

Regarding the demographic parameters (age, BMI of patients, and duration of infertility) and the basal hormonal profile level (FSH, LH, PRL, E2, and testosterone), the statistical analysis showed no significant differences between pregnant and non-pregnant ICSI patient groups, and *p*-values of 0.516, 0.06, and 0.622, and

0.289, 0.495, 0.334, 0.782, 0.568, and 0.342, respectively (Table 1).

Vascular endothelial growth factor (VEGF) and Doppler parameters

Table 2 demonstrates the differences between some measurements in pregnant and non-pregnant women in this study. Endometrial thickness, RI, PI, and VEGF showed statistically significant differences, with *p*-values equaling 0.01, 0.021, 0.015, and 0.001, while Vs/Vd showed no statistically significant differences, with a *p*-value of 0.385.

Correlation of VEGF with other endometrial receptivity parameters

Table 3 shows that the Pearson correlation for VEGF, and E2 at day of HCG administration and endometrial thickness at day of embryo transfer, showed a positive association above zero (r= 0.325, 0.227), with a statistically significant value of association (*p*-value equal to 0.003 and 0.043). Pearson correlation for VEGF and RI, PI, and Vs /Vd showed a weak negative association below zero (r= -0.168, -0.11, -0.088), with no statistically significant value of association (*p*-value equal to 0.137, 0.331, and 0.436).

Correlation of endometrial thickness with other endometrial receptivity parameters

The Pearson correlation of endometrial thickness with Vs/Vd showed a positive association above zero (r=0.23), with a statistically significant association value (*p*-value 0.04), while Pearson correlation for endometrial thickness with RI, PI, and E2 at D. of HCG administration showed weak association above zero (r=0.062, 0.079, and 0.129), with no statistically significant association value (*p*-value=0.586, 0.489, and 0.253), as shown in Table 4.

Correlation of E2 at day of embryo transfer with endometrial receptivity parameters

Regarding E2 level at day of HCG administration, its Pearson correlation with RI, PI, and Vs/Vd showed weak negative association below zero (r=-0.01, -0.031, and -0.107, respectively), with no statistically significant association value (*p*-value=0.933, 0.786, and 0.346, respectively), as shown in Table 5.

DISCUSSION

The data for the present study show that the pregnant group had higher levels of VEGF compared to the non-pregnant group, as shown in Table 2. The rate of endometrial blood flow during the normal female reproductive cycle has been correlated with increased expression of angiogenic factors (e.g., VEGF). These are members of a family of heparin binding proteins that act directly on the endothelial cells, and induce proliferation and angiogenesis.[12] Zenneni et al. found that patients with primary infertility had a much less immunohistochemical expression of VEGF in the secretory endometrium.[13] In another study, Hannan et al confirmed the presence of thirty different types of mediators present in the myometrial cavity during the menstrual cycle, of which VEGF was much less in uterine fluid obtained during implantation from patients with infertility.[11] Schild et al. state that it is important to have good emdometrial vascularization inorder to implant.[14] In the current study, there was positive correlation between VEGF and E2 at day of HCG administration (Table 3), which is supported by authors who have noted a maximum expression of VEGF in the stroma during proliferative phase, with a peak glandular VEGF expression during the secretary phase.[15]

Additionally, in the present study, we noticed a clear positive association between VEGF and endometrial thickness at day of embryo transfer (Table 3), which is also concluded in a study conducted by Miwa et al., which indicates a 'thin' endometrium characterised by high blood flow impedance of the uterine radial artery, poor epithelial growth, decreased VEGF expression, and poor vascular development.[16] Thus, there is a positive association between endometrial thickness and VEGF; the angiogenic factor plays a role in endometrial receptivity, and this elucidates higher endometrial thickness for pregnant women compared to non-pregnant women, as well as a significant value association with Vs/Vd in our study (Table 4).

In the current study, pregnant women had a thicker endometrium than non-pregnant women. Researchers found that there is a reduced success rate of IVF in patients with a thin endometrium, even if there was no previous intrauterine surgery or infection. Some studies found that a thin EMT negatively affects pregnancy rates following fertility treatment[17], while other studies were unable to confirm this, indicating that the use of endometrial thickness as a tool for deciding on cycle cancellation or the freezing of all embryos, or cessation from further IVF treatment, appears unjustified.[18,19]

Some groups did not find a correlation between age, the number of follicles, and gonadotropin ampoules with endometrial thickness; however, in all age ranges, the chance of pregnancy was higher with an endometrial thickness of 6<ET≤10 mm.[20] Higher conception ratesoccured in patients with endometrial thickness of 10 mm and above.

TABLE 1. Comparison of demographic parameters and hormonal profile between pregnant and non-pregnant ICSI patient groups by unpaired t-test.

Parameters	Pregnant N = (36) Mean ± SD	Non-pregnant N = (44) Mean ± SD	*P*-value
Age (yrs)	28.89 ± 6.07	29.77 ± 5.97	0.52
BMI (kg/m^2)	26.05 ± 2.85	27.31 ± 2.94	0.06
Duration of infertility (yrs)	5.64 ± 3.79	6.07 ± 3.95	0.62
FSH (mIU/ml)	7.59 ± 1.94	7.02 ± 2.80	0.29
LH (mIU/ml)	4.89 ± 2.06	5.31 ± 3.36 0.49	
E_2 (pg/ml)	37.3 ± 13.6	34.3 ± 13.4	0.33
PRL (ng/ml)	15.87 ± 6.18	15.46 ± 7.03	0.78
TSH (mIU/ml)	2.275 ± 0.625	2.176 ± 0.920	0.57
Testosterone (ng/dl)	1.039 ± 0.682	1.50 ± 3.06	0.34

Abbreviations: n=number, SD=standard deviation, yrs=years, BMI=body mass index, FSH=follicle stimulating hormone, LH=luteinized hormone, E_2=estradiol hormone, PRL=prolactin hormone, TSH=thyroid stimulating hormone

TABLE 2. Comparison between pregnant and non-pregnant ICSI patient groups with ultrasound Doppler parameters and VEGF level by unpaired t-test.

Parameters	Pregnant N = (36) Mean ± SD	Non-pregnant N = (44) Mean ± SD	*P*-value
Endometrial thickness (mm)	9.72 ± 1.35	8.95 ± 1.21	0.0
RI	0.584 ± 0.124	0.651± 0.132	0.0
PI	0.829 ± 0.301	1.006± 0.335	0.02
V_s/V_d	3.14 ± 3.75	3.82 ± 3.07	0.38
VEGF (pg/ml)	433 ± 207	276 ± 165	0.01

Abbreviations: n=number, SD=standard deviation, RI=resistance index, PI=pulsatility index, V_s=peak systolic velocity, V_d=diastolic velocimetry, VEGF=vascular endothelial growth factor

TABLE 3. Correlation between VEGF with E2 at day of HCG administration, and ultrasound Doppler parameters at day of embryo transfer by Pearson correlation test.

		E_2 at Day of HCG administration (pg/ml)	RI	PI	V_s / V_d	Endometrial thickness (mm)
VEGF (pg/ml)	r	0.325	-0.168	-0.11	-0.088	0.23
	P	0.003	0.137	0.331	0.436	0.04

Abbreviations: r=Pearson correlation, *P*=p-value, E_2==estradiol hormone, HCG=human chorionic gonadotropin hormone, RI=resistance index, PI=pulsatility index, V_s=peak systolic velocity, V_d=diastolic velocimetry, VEGF=vascular endothelial growth factor.

TABLE 4. Correlation between endometrial thickness with E2 at day of HCG administration, and ultrasound Doppler parameters at day of embryo transfer by Pearson correlation test.

		E_2 at day of HCG administration (pg/ml)	RI	PI	V_s/V_d
Endometrial thickness (mm)	r	0.129	0.062	0.079	0.23
	P	0.253	0.586	0.489	0.04

Abbreviations: r=Pearson correlation, *P*=p-value, E_2=estradiol hormone, HCG=human chorionic gonadotropin hormone, RI=resistance index, PI=pulsatility index, V_s=peak systolic velocity, V_d=diastolic velocimetry

TABLE 5. Correlation between E_2 at day of HCG administration with ultrasound Doppler parameters at day of embryo transfer by Pearson correlation test.

		PI	RI	V_s/V_d
E_2 at day of HCG administration (pg/ml)	r	-0.01	-0.031	-0.107
	P	0.933	0.786	0.346

Abbreviations: r=Pearson correlation, *P*=p-value, E_2=estradiol hormone, HCG=human chorionic gonadotropin hormone, RI=resistance index, PI=pulsatility index, V_s=peak systolic velocity, V_d=diastolic velocimetry

Another study found that when the is an endometrium of less than 7 mm it is better to do cryopreservation, however if the endometrium is thin but with a good texture (triple-line pattern), other factors should be considered such as the quality of the embryo. This is in agreement with the results of the current study.[21]

The sub-endometrial RI and PI in the present study were significantly lower in pregnant patients than in non-pregnant patients. This is supported by other researchers, who found patients that became pregnant were characterised by a significantly lower resistance index; these results were obtained from sub-endometrial vessels by transvaginal colour Doppler ultrasonography.[22] The reason for this is because sub-endometrial vascularity increased significantly at day of embryo transfer, due to the effect of stimulated hormones on endometrial angiogenesis.[23] Jain et al. (2015) found that serum VEGF levels rose alongside with an increase in Doppler vascular penetration zones (zone 2, intermediate vascularity), which implies that serum VEGF concentrations can be used as a marker of endometrial receptivity. No conception was noted in patients with poor or intermediate vascularity, as identified in Doppler vascular zone 2.

This means that vascular endothelial growth factor (VEGF) is a major regulator of endothelial cell proliferation, angiogenesis, vasculogenesis, and capillary permeability. A concurrent rise in serum VEGF level was observed alongside an increase in Doppler vascular penetration zones. A receptive endometrium is a reflection of good endometrial vascularity, which signifies serum VEGF as a marker of endometrial receptivity.[24,25] This is supported by our results as shown in Table 2, where a high level of VEGF is associated with low RI, PI, and VS/Vd, and an elevated level of E2 at day of embryo transfer, as well as a thick endometrium.

CONCLUSION

Combined analysis of endometrial receptivity was conducted for the present research. The serum level of VEGF, and sub-endometrial evaluation with 2D PD-US, by measuring resistance index (RI) and pulsatility index (PI) at day of embryo transfer, can serve as useful prognostic methods for the detection of endometrial receptivity and pregnancy outcome in infertile women undergoing ICSI protocols, and will be helpful for candidate counselling with regard to postponing embryo transfer and cryopreservation, which may be a better option for a future cycle, when better endometrial Doppler parameters can be achieved.

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The Good Skin Care Practices and Emollient Use since Early Infancy as the Primary Prevention of Infantile Atopic Dermatitis among Infants at Risk: a Randomized Controlled Trial

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ABSTRACT

Objective: The study aimed to determine whether enhancing the skin barrier since early infancy could reduce the incidence of infantile atopic dermatitis among high risk infants.

Methods: We conducted a prospective, randomized, controlled trial at the Pediatric Clinic, Phramongkutklao Hospital in Bangkok. Eligible infants aged less than 10 weeks with family history of atopy were enrolled and randomly allocated to one of the two groups. The intervention group applied emollient at least once daily all over the body together with receiving good skin care practice advice, whereas the control group received only good skin care practice advice. All infants were followed up and assessed at 2, 4, 6 and 9 months old.

Results: Fifty-two infants were enrolled, 25 in the intervention group and 27 in the control group. At 9 months old follow-up, none in the intervention group had infantile atopic dermatitis, whereas 14.8% in the control group developed infantile atopic dermatitis (p-value < 0.05). The mean age at diagnosis of infantile atopic dermatitis was 5.5 months.

Conclusion: Regular emollient application together with good skin care practice since early infancy could reduce the incidence of infantile atopic dermatitis among high risk infants.

Keywords: Infantile atopic dermatitis; primary prevention; emollient (Siriraj Med J 2020; 72: 41-46)

INTRODUCTION

Infantile atopic dermatitis (IAD) is chronic inflammatory dermatosis with increasing prevalence worldwide. In 2009, the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three provided comprehensive data on the prevalence of atopic dermatitis stressing the global concern of the increasing trends both in developing and developed countries.[1] This study proposed the prevalence of atopic dermatitis in the age group 6 to 7 years ranging from 0.9% to 22.5% and 0.2% to 24.6% for the group of 13 to 14 years old. Interestingly, the high prevalence of 15% or more in the age group 6 to 7 years has been found in many countries across the globe including the Asia-Pacific region. One study conducted in Bangkok reported the prevalence of atopic dermatitis at 9.4% in the older age group.[2]

To our knowledge, factors responsible for developing of IAD are multifactorial including genetic, environment, immune dysregulation and dysfunctional skin barrier.[3] For the genetic aspect, when one or both of parents are

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diagnosed with any allergic disease, their children could have a 40 to 50% chance to develop atopic dermatitis. Infants who develop IAD before 2 years of age with persisting disease would have the risk to develop other atopic diseases as a part of the atopic march.[4-5] The chronic relapsing itchy eczematous skin with typical locations for particular age is known to be the hallmarks of atopic dermatitis, affecting the quality of life not only of the patients but also their family members.[6-7]

Various modalities for the primary prevention of IAD have been studied, for example, exclusive breastfeeding, hydrolyzed protein formula, maternal antigen avoidance, prebiotics and probiotics but without promising evidence.[8-13] The skin barrier dysfunction and immune dysregulation are known as the key pathogenesis of IAD.[14-15] Hence, the hypothesis of enhancing the skin barrier since birth or early infancy to impede penetration of allergens and consequently prevent inflammatory cytokines release may play an important role to prevent the disease. Simpson et al. investigated the effect of emollient on the infant skin barrier for the primary prevention of IAD among high risk infants with positive outcomes.[16-17] Horimukai et al. also studied the primary prevention of IAD among high risk infants in Japan and reported reduced IAD incidence among infants regularly using emollient.[18]

We conducted a study to determine whether good skin care practice together with regular emollient use since early infancy could reduce the incidence of IAD among high risk infants.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department in Bangkok (IRB RTA; Ro51h/58). A prospective, randomized, controlled trial among healthy high risk infants for whom at least one of their parents or siblings presented any allergic diseases was conducted at the Pediatric Outpatient Department of Phramongkutklao Hospital in Bangkok from 2016 to 2017. Funding was granted by Phramongkutklao Hospital, and investigators declared they had no conflict of interest. Thailand's clinical trial registration (TCTR20161208001).

Study population

Eligible infants were defined as healthy, term infants, aged less than 10 weeks old whose parent(s) or sibling(s) had a history of any allergic disease such as atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, food allergy or other allergic conditions.

Infants known to have major congenital anomalies, immunodeficiency syndrome, any skin disease other than infantile seborrheic dermatitis or neonatal acne were excluded from the study. Infants whose parents reported regular emollient use before enrollment were also excluded. Written informed consent forms were obtained from all enrolled families.

Study design and intervention

The enrolled infants were allocated to either the control or intervention group by block of 4 randomization with allocation concealment using opaque envelopes. Infants in the intervention group were assigned to regularly apply the hospital formulated emollient containing white petrolatum, stearyl alcohol, propylene glycol and glycerin, named "Cold Cream" all over the body except periorbital and perioral areas at least once daily shortly within 3 to 5 minutes after bathing and padding dry the baby skin. However, those parents or caregivers of infants in the control group were asked not to apply any skin care products on the baby skin except using the gentle liquid baby cleansers during bathing and the barrier ointment or cream on diaper areas as needed. Caregivers in both groups were given verbal advice for good skin care practice repeatedly during every visit. The good skin care practice comprised the proper duration of bathing of 5 to 10 minutes with tap or lukewarm water, bathing not more than twice daily and using only a minimal amount of gentle liquid baby cleansers of any manufactures. Bath oil, bubble bath or any bath additives were not allowed to be used in both groups.

Appointments with investigators were set up during their regular well baby clinic visits at 2, 4, 6 and 9 months old at the Pediatric Outpatient Clinic. One unblinded investigator would perform a general physical examination, growth and developmental milestone evaluation, general health supervision, routine vaccination and advice regarding good skin care practice to every caregiver of the infants in both groups. The intervention group infants aged less than 6 months received Cold Cream, 180 grams and the infants aged 6 months or older received 240 grams of Cold Cream per visit. The parents in the intervention group were asked to bring back the empty bottles of Cold Cream to confirm their compliance. During each visit, the infants in both groups would be sent to another room and receive only the skin examination and evaluation for the diagnosis of infantile atopic dermatitis by a pediatric dermatologist who was blinded as to group allocation. Neither blood test nor equipment used for transepidermal water loss or stratum corneum hydration measurements were used in this study.

Outcomes

The primary outcome was the cumulative incidence of IAD in both groups. The diagnostic criteria for atopic dermatitis was based on the atopic dermatitis guidelines by Eichenfield et al. in 2014.[6] The secondary outcomes were mean age of onset of IAD, adverse reaction of Cold Cream application and the factors associated with developing IAD. The study end points were defined when the enrolled infants developed IAD or when the infants were 9 months old.

Statistical analysis

The sample size needed to compare two proportions was calculated between groups with an expected 60% reduction in IAD incidence based on related studies using $\alpha = 0.05$ and $\beta = 0.20$.[17-18] A sample size of 70 infants (35 in each group) was required.

Statistical analysis was performed by comparing between the two groups by two-sample test proportion. Descriptive data were presented as means (with standard deviation), medians (with inter-quartile range), and percentages.

RESULTS

This study was conducted from January 2016 to April 2017. Initially, 70 eligible families were informed to recruit in this study. Of these, 17 families were unwilling to participate. One of investigators had to move to work in another hospital, then due to time limitation, the enrollment had to stop before reaching the calculated sample size of 70 infants. Then 53 infants were enrolled and randomly allocated to one of the two groups. In all, 26 infants were placed in the intervention group and 27 in the control group. One infant in the intervention group had to leave the study before 9 months old because the family had to move outside Bangkok. A diagram of the participants is shown in Fig 1. The baseline demographic data between groups were comparable (Table 1).

Regarding the primary and secondary outcomes, none of the infants in the intervention group received a diagnosis of IAD which was repeatedly evaluated during each visit up to 9 months old, whereas 4 (14.8%) infants in the control group developed IAD ($p = 0.045$; Table 2). The mean age of the 4 infants at the onset of IAD was 5.5 ± 0.55 months. The dryness of skin or xerosis, assessed by skin examination during the last follow-up visits, was comparable between groups ($p = 0.120$; Table 2). However, the skin dryness was evaluated clinically without transepidermal water loss or skin moisture measurements. None of the 4 IAD infants developed cow's milk protein allergy or any other food allergy.

The exact volume of the Cold Cream used in each infant in the intervention group was not recorded in this study. Most of the parents carried only the empty bottles of Cold Cream to present to the investigator to confirm their compliance. However, the average Cold Cream used monthly for infants less than 6 months was 90 gm and 120 gm for infants 6 months or older. No interventions related to adverse events were reported by the caregivers.

We also studied those factors assumed to have effects on developing IAD including area of residence (suburb or intown residence), feeding type (exclusive or nonexclusive breast feeding), inhouse pets (dogs or cats) and inhouse smoking and found no significant difference between the IAD and non IAD groups (Table 3). The environmental data around the time of the study in Bangkok are presented. The average temperature in Bangkok was 31°C with 66% relative humidity. The mean level of $PM_{2.5}$ (fine particulate matter) was 58.69 $\mu g/m^3$ at the open roadside areas.[19]

DISCUSSION

This comprised a randomized controlled trial conducting to demonstrate a modality for the primary prevention of infantile atopic dermatitis among high risk infants by enhancing the skin barrier with regular use of emollient and educating concerning good skin care practice to caregivers. We found that using Cold Cream or a petrolatum containing moisturizer at least once daily to the whole body of the high risk infants showed a decrease in the cumulative incidence of infantile atopic dermatitis compared with the infants in the control group receiving only the good skin care advice. We designed to enroll only term, healthy high risk infants, because manipulating the preterm or sick infant skin might increase rates of infection. Our results were in the same direction as in the related data from the studies of Simpson EL in the US and Horimukai K in Japan, although our study did not show a strongly significant difference.[17-18] This might have been a result of the small sample size in this study. The related studies demonstrated that daily emollient use among high risk infants significantly decreased the incidence of infantile atopic dermatitis.

Which emollients would be the best to use in this setting? For example, in the hot and humid geographic regions, we would not recommend using pure petrolatum to the infant skin especially during the summer months. Heat rash would be one concern. Instead we would recommend using the oil-in-water emulsions for the normal skin type and the water-in-oil emulsions such as the "Cold Cream" for the dry skin type. In this study,

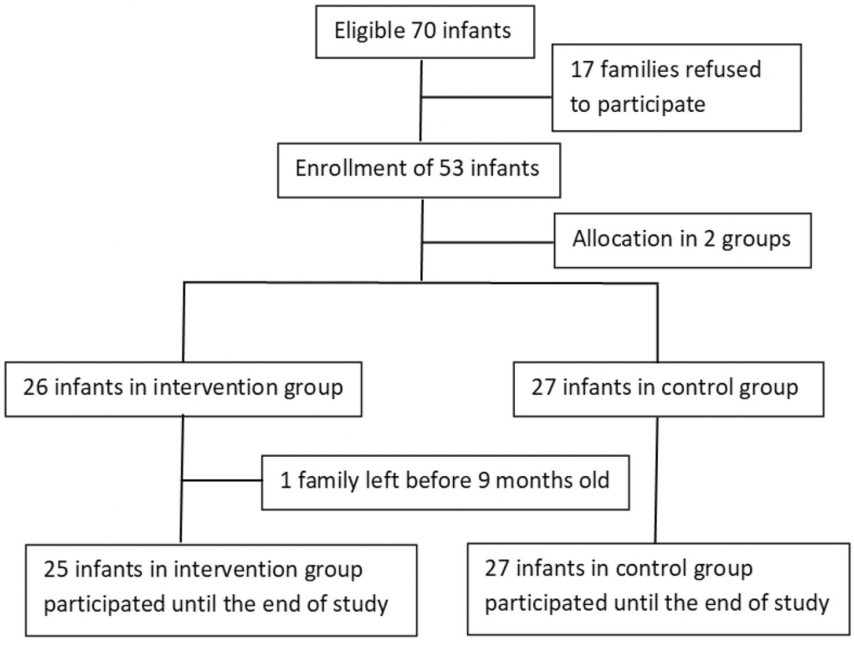

Fig 1. Study population diagram.

TABLE 1. Demographic characteristics.

Characteristics	Intervention (*n* = 25)	Control (*n* = 27)
Sex, n (%)		
Male	12 (48)	13 (48)
Female	13 (52)	14 (52)
Birthweight (g)*	2,270 ± 0.4	2,480 ± 0.7
Age at enrollment (weeks)*	4.19 ± 2.9	4.00 ± 2.9
Both parental atopy (%)	42.3	18.5
Skin at enrollment ** (%)		
Moderate to marked skin dryness	20.0	7.4
Feeding (%)		
Exclusive breast feeding	56.0	80.5
Non-exclusive breast feeding	44.0	19.5
Bathing frequency (%)		
Once daily	48.0	66.7
More than once daily	52.0	33.3
Bathing time (%)		
Up to 10 minutes	92.0	96.3
More than 10 minutes	8.0	3.7
In house pets (%)		
Pets	32.0	37.0
No pets	68.0	63.0
In house smoking (%)		
Smoking	68.0	63.0
No smoking	32.0	37.0
Area of residences (%)		
Urban areas	72.0	48.1
Suburb areas	28.0	51.9

*Data presented as mean ± standard deviation. ** By dermatologic examination.

TABLE 2. Cumulative incidence of IAD and moderate to marked skin dryness (xerosis).

Outcomes	Intervention (*n* = 25)	Control (*n* = 27)	P-value*
Infantile atopic dermatitis	0 (0%)	4 (14.8%)	0.045
Xerosis**	3 (12.0%)	8 (29.6%)	0.120

*Two-sample test of proportion, $p < 0.05$ = statistical significant.
**Evaluated by Pediatric dermatologist at the end of study.
Abbreviation: IAD = infantile atopic dermatitis

TABLE 3. The environmental or biological factors and IAD developing group.

Factors	*n in group* (N = 52)	IAD *n (%)*	P-value*
In town residential areas	31	2 (6.5)	0.683
Exclusive breast feeding	36	3 (8.3)	0.791
In house pets (cats or dogs)	14	3 (21.4)	0.162
In house smoking	34	4 (11.8)	0.130

*Multivariate analysis
Abbreviation: IAD = infantile atopic dermatitis

we did not measure neither the stratum corneum hydration nor the transepidermal water loss (TEWL). Thus, we cannot conclude using scientific data to explain the positive results in the emollient group. These were our limitations.

Scientists have unveiled many associated genes linked to atopic dermatitis such as the Filaggrin gene (*FLG*) for skin barrier dysfunction, β-defensin 1 (*DEFB1*) for the susceptibility to infections, nucleotide-binding oligomerization domain 1 (*NOD1*) and Toll-like receptor 2 (*TLR2*) genes for immune dysregulation.[15] These provide evidence stressing the importance of genetic background for developing atopic dermatitis. In this study, we enrolled high risk infants with any atopic problems among the families, even though the infants from atopic dermatitis families would have higher risk to develop IAD than infants from families with asthma or allergic rhinitis.[20] We realized that some parents could not recall having atopic dermatitis as a part of their atopic march during their childhood.

Allergic sensitization can occur through an impaired skin barrier leading to inflammatory responses and consequently developing atopic rashes. To close the critical gateways for microbes and allergens is to strengthen or to enhance the skin barrier. These strategies of enhancing the skin barrier as early as possible might constitute a convenient and effective method to implement to high risk infants to prevent infantile atopic dermatitis.

According to the ISAAC Phase Three survey, the number of patients with IAD still dramatically and continuously increases over time with higher prevalence (>15%) in many parts of big cities around the world including Asia-Pacific.[1] Because of the small sample size in this study, we could not confirm any correlation between environmental or biological factors such as feeding type, area of residence, smoking or inhouse pets and IAD incidence.

Atopic dermatitis is a public health problem for children across the globe. On the other hand, IAD is one of the noncommunicable diseases (NCDs) of childhood as we claimed metabolic syndrome for adulthood, and atopic dermatitis causes burdens in health care systems.[21] One study estimated the direct and indirect costs of atopic dermatitis to total over 5 billion dollars annually in the US.[22] The primary prevention of IAD remains a major concern.

Limitations of this study included the short time of follow-up visit, small number of participants, lack

of measurement of skin moisture or TEWL and lack of sensitization tests for allergens. More evidence for the primary prevention of IAD still needs further investigations.

CONCLUSION

This study presented evidence that regular emollient use concomitant with good skin care practice since early infancy could be an effective modality for the primary prevention of infantile atopic dermatitis among high risk infants.

What this study adds

Enhancing the skin barrier by regular emollient use together with implementing good skin care practice for caregivers of infants born in atopic families could serve as a modality for the primary prevention of infantile atopic dermatitis.

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The Impact of Active Nutritional Support for Head and Neck Cancer Patients Receiving Concurrent Chemoradiotherapy

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ABSTRACT

Objective: Malnutrition is the most common problem in head and neck cancer (HNC) patients receiving concurrent chemoradiotherapy. The radiation toxicities cause decreased food intake, with resultant severe weight loss and malnutrition. This study sought to determine whether an active nutrition improvement counseling program before and during concurrent chemoradiotherapy for HNC patients could increase the treatment completion rate without the interruptions caused by the side effects of chemoradiotherapy.

Methods: The findings of a prospective study of the effects of an active nutrition improvement program before and during concurrent chemoradiotherapy (study, n = 32) was compared with those of a retrospective chart review of HNC patients who had received definite or postoperative concurrent chemoradiotherapy (control, n = 80). The correlations between nutritional status and the number of treatment completions, number of tube feeding insertions during treatment, RTOG toxicity, nutritional status, and quality of life were obtained.

Results: There was no statistically significant difference between the concurrent chemoradiotherapy completion rates of both groups (p = 0.121; 95% CI, 0.226-1.188). The major cause of delayed or discontinued chemotherapy was oral mucositis. No significant differences were found in the tube feeding insertion rates and RTOG toxicities of both groups. However, the data showed a clinically significant difference in the concurrent chemoradiotherapy completion rate for the study group (56%), more than 15 percentage points higher than the control group's rate (40%).

Conclusion: An active nutrition improvement program before and during concurrent chemoradiotherapy is clinically beneficial for HNC patients, providing a higher treatment completion rate than otherwise.

Keywords: Head and neck cancer; radiotherapy; chemotherapy; chemoradiotherapy; nutrition. (Siriraj Med J 2020; 72: 47-58)

INTRODUCTION

Head and neck cancer (HNC) is one of the most common malignancies in the world, with high mortality rates in developing countries.[1] In 2016, Siriraj Cancer Registry reported that HNC accounted for 6.9% of newly diagnosed cancers.[2] Malnutrition as a comorbidity of cancer has been recognized. A study by Unsai et al. that evaluated the nutritional status of HNC patients receiving radiotherapy found that a quarter of the patients had malnutrition at presentation. Although the number with

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malnutrition had increased by more than three quarters by the end of the treatment, the patients subsequently demonstrated nutritional improvement by their 3- to 6-month follow-ups.[3]

Nutritional status is a modifiable factor that impacts on disease prognosis and treatment compliance. In the case of HNC, Langius et al. found that weight loss both before and during radiotherapy was an important prognostic indicator for 5-year disease-specific survival.[4] Another study found that less weight loss was experienced by radiotherapy-receiving patients with HNC or gastrointestinal cancer who had attended intensive nutrition counseling sessions than those just given standard care[5]

The aim of this study was to establish the impact of the nutritional status of HNC patients on treatment compliance, radiation toxicities, rate of any tube feeding, and quality of life.

MATERIALS AND METHODS

This study was performed at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, during 2016-2017. A quasi-experimental study design was used to compare patients receiving routine pretreatment counseling with those participating in an active nutrition improvement program conducted by a physician. The study was approved by the Ethics Committee of the Siriraj Institutional Review Board (Si 797/2016).

The candidates in this study were newly diagnosed HNC patients (nasopharyngeal, oral cavity, oropharyngeal, laryngeal, and hypopharyngeal cancers) aged 18-80 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Those patients treated with a curative aim received either prescribed concurrent chemoradiotherapy or postoperative concurrent chemoradiotherapy. We excluded patients who had early stage (T1N0M0) or distant metastatic (M1) diseases. Candidates were also excluded if they had other malignancies; had received neoadjuvant chemotherapy or previous radiotherapy; or had medical illnesses that would compromise their ability to complete the study, such as a systemic infection. Data were collected during the chemoradiotherapy treatment and through to the 3-month follow-up.

Study population

Control group (retrospective study)

A retrospective chart review was conducted of newly diagnosed HNC patients who had received definite concurrent chemoradiotherapy or postoperative concurrent chemoradiotherapy for curative intent January-December 2016. The information was collected from the records relating to the patients' first visits to the Division of Radiation Oncology, their entire treatment schedule, and the follow-up conducted 3 months after treatment completion. Those patients were all scheduled for routine, pretreatment counseling.

Study group (prospective study)

A prospective intervention was undertaken of newly diagnosed HNC patients with a curative aim who had been scheduled for definite concurrent chemoradiotherapy or postoperative concurrent chemoradiotherapy January-December 2017. At least one month before starting the radiotherapy, the patients began to participate in an active nutrition improvement program conducted by their physician. The program sessions were held at the date of enrollment, every 2 weeks before radiotherapy started, and every week during their treatment. All patients gave written, informed consent before commencing the program.

Definitions and terms

- Head and neck cancer (HNC) was one whose primary site was the nasopharynx, oral cavity, oropharynx, hypopharynx, or larynx. The tumor staging was determined in accordance with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh Edition (2010).
- The active nutrition improvement program for the study group was the nutrition counseling provided by the physician, comprising nutrition recommendations, guidance on the calculation of a proper calorie-intake (30-35 kcal/kg), and a notebook for the patients' daily dietary records. A serial assessment was performed at the first visit; the first, fourth, and last weeks of the radiation treatment; and then at the first, second, and third months after treatment completion. Two tools were used for this purpose: the Patient-Generated Subjective Global Assessment (PG-SGA), and the Functional Assessment of Cancer Therapy–Head and Neck (FACT–H&N, version 4).
- The radiotherapy techniques in this study were either the three-dimensional conformal radiation therapy or volumetric modulated arc therapy.
- The concurrent chemotherapy regimen (Cisplatin or Carboplatin) selected for each patient was based on medical oncologists' judgments.
- Treatment completion was deemed to have occurred if an HNC patient attended and finished the definite concurrent chemoradiotherapy or

postoperative concurrent chemoradiotherapy treatment sessions as scheduled, without any interruptions or postponements.

The study hypothesis and objectives

It was hypothesized that the active nutrition improvement program would lessen the incidences of treatment interruption or postponement.

The primary objective was to study the impact of nutritional status before and during the radiotherapy and chemotherapy treatment on patients' rates of treatment completion, without any interruptions or postponements resulting from treatment-related side effects.

The secondary objectives were to review the relationships between the patients' nutritional statuses before and during treatment and the feeding tube insertion rate, Radiation Therapy Oncology Group (RTOG) radiation toxicity grading, nutritional statuses (PG-SGA), and quality of life (FACT–H&N, version 4).

Statistical analysis

From the Siriraj Hospital medical record reviewed of the 45 patients with head and neck cancer, 17 (37%) of the patients experienced an interruption in concurrent chemoradiotherapy. We considered a 15% reduction in treatment interruption, so, the sample size should be 62 evaluable patients per treatment group, the study had an 80% power to detect an absolute difference of 15% in the treatment interruption rate, assuming a two-sided test and an overall significance level of 0.05.

For comparisons between the two groups, continuous variables were analyzed using Mann-Whitney U tests, whereas chi-squared or Fisher's exact tests and univariate analysis by logistic regression were used for categorical variables. A p-value of < 0.05 was considered statistically significant. The statistical analyses were conducted using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 112 HNC patients were included in the study. Of those, 80 were in the control group (the retrospective chart review of patients receiving treatment January-December 2016), but only 32 were in the study group (the prospective study of patients undergoing treatment January-December 2017). The patients in the study group were not reach the target but we had desired to stop enrolled the patients because it was at the end of the year 2017. The patients received definite concurrent chemoradiotherapy or postoperative concurrent chemoradiotherapy. Seventy-three patients in the control group and 27 in the study group remained throughout the study. In control group, 1 patient had refused the radiotherapy during the treatment period and after complete treatment, 4 patients had disease progression, 2 patients had lost to follow-up. In study group, 1 patient had refused the radiotherapy during the treatment period and 1 patient had died from hemorrhagic stroke, 2 patients had disease progression and 1 patient had lost to follow-up.

For both groups, the demographic data and patient characteristics were similar. The majority of patients were male (77.7%), and the mean age was 56.11 ± 9.94 years. Almost half of the patients were diagnosed with nasopharyngeal cancer (45.5%). Most of the patients had lymph node involvement (84.9%), and half had stage IV disease (55.4%). These patients received radiotherapy via the volumetric modulated arc therapy technique (83%), concurrent with Cisplatin (88.4%). About 18% of the patients had tube feeding before enrollment, and this was the same proportion as those who experienced significant weight loss following their diagnosis with cancer. In the case of the study group, none of the patients who enrolled in the active nutrition improvement program had severe malnutrition at the time of diagnosis (Tables 1 and 2).

A comparison of the two groups did not reveal any statistically significant difference in their treatment completion rates ($p = 0.121$; 95% CI, 0.226-1.188). Nevertheless, the completion rate for concurrent chemoradiotherapy was clinically significant for the study group (56%), being 16 percentage points better than that of the control group (40%). Similarly, the chemotherapy compliance of the study group (56.3%) was 15 percentage points better than that of the control group (41.3%). Most patients in both groups were able to attend their radiotherapy sessions without interruption, with 81.3% and 77.5% attendance rates for the patients in the study and control groups, respectively (Table 3).

Even in the multivariate analysis, adjusted by defining the prognostic factors for age ≤ 60 years versus > 60 years, nasopharyngeal cancer versus non-nasopharyngeal cancer, and stages I–III disease versus stage IV disease, the differences showed no statistical significance for both groups ($p = 0.118$; 95% CI, 0.288-1.183; Table 4).

As to patients who had their treatment delayed, 25% of the control group patients experienced oral mucositis, with half of those (55.3%) being prescribed narcotic drugs. However, just 3.1% of the patients in the study group experienced the same treatment side effect, with only 22.2% of the ones affected being given narcotic drugs (Table 5).

TABLE 1. Baseline patient characteristics: demographics.

Characteristics	Control (n = 80)	Study (n = 32)	Total (n = 112)	*P*-value
Sex				
Male	59 (73.8%)	28 (87.5%)	87 (77.7%)	
Female	21 (26.3%)	4 (12.5%)	25 (22.3%)	0.137
Age (mean ± SD)	56.11 (± 9.94)	55.88 (± 12.52)	56.04 (± 10.69)	0.916
Site				
Nasopharynx	36 (45%)	15 (46.9%)	51 (45.5%)	
Oropharynx	18 (22.5%)	4 (12.5%)	22 (19.6%)	
Oral cavity	14 (17.5%)	3 (9.4%)	17 (15.2%)	
Larynx	7 (8.8%)	5 (15.6%)	12 (10.7%)	
Hypopharynx	5 (6.3%)	5 (15.6%)	10 (8.9%)	0.267
T stage				
1	18 (22.5%)	4 (12.5%)	22 (19.6%)	
2	23 (28.8%)	5 (15.6%)	28 (25%)	
3	16 (20%)	11 (34.4%)	27 (24.1%)	
4	23 (28.8%)	12 (37.5%)	35 (31.3%)	0.160
N stage				
0	14 (17.5%)	3 (9.4%)	17 (15.2%)	
1	14 (17.5%)	6 (18.8%)	20 (17.9%)	
2	44 (55%)	19 (59.4%)	63 (56.3%)	
3	8 (10%)	4 (12.5%)	12 (10.7%)	0.768
Stage				
I	2 (2.5%)	0 (0%)	2 (1.8%)	
II	7 (8.8%)	3 (9.4%)	10 (8.9%)	
III	27 (33.8%)	11 (34.4%)	38 (43.8%)	
IVA	35 (43.8%)	14 (43.8%)	49 (43.8%)	
IVB	9 (11.3%)	4 (12.5%)	13 (11.6%)	1.000

During the treatment, about 30% of the patients in both groups required enteral tube feeding. As shown in Table 6, most of them preferred nasogastric (NG) feeding (94.1%), but 5.9% elected to be fed via percutaneous endoscopic gastrostomy (PEG).

Serial assessments of the patients' nutritional statuses were performed during the treatment and throughout the study. Looking at the body-weight changes between before-receiving the treatment and at the end of treatment, patients suffering more than 10% weight loss represented 34.2% and 16.1% of those in the control and study groups, respectively. During the first month following treatment, weight was regained, but the gain was better in the study group than in the control group. However, by 3 months, weight gain had improved equally in both groups (Table 7).

The percentage of body-weight change was calculated at each patient assessment to monitor the progression of weight loss. We used the median percentage of the body-weight change of each group as a comparable value measurement, and the dynamic weight changes were plotted on a line graph (Fig 1). Once the concurrent chemoradiotherapy started, patients experienced gradual weight losses throughout the study. There was a statistically significant difference 1 month after treatment completion: at that time, the study group patients were likely to have less weight loss than those in the control group. However, at the end of the study, there was no statistical difference in the weight changes of the two groups.

TABLE 2. Baseline patient characteristics: treatment and nutritional status.

Characteristics	Control (n = 80)	Study (n = 32)	Total (n = 112)	*P*-value
Radiation technique				
3D[1]	15 (18.8%)	4 (12.5%)	19 (17%)	
VMAT[2]	65 (81.3%)	28 (87.5%)	93 (83%)	0.580
Type of treatment				
CCRT	62 (77.5%)	26 (81.3%)	88 (78.6%)	
Postop CCRT	18 (22.5%)	6 (18.8%)	24 (21.4%)	0.801
Chemotherapy regimen				
Cisplatin	71 (88.8%)	28 (87.5%)	99 (88.4%)	
Carboplatin	9 (11.3%)	4 (12.5%)	13 (11.6%)	1.000
Tube feeding (before treatment)				
No	65 (81.3%)	26 (81.3%)	91 (81.3%)	
Yes	15 (18.8%)	6 (18.8%)	21 (18.8%)	1.000
NG[4] (n = 21)	–	1 (14.3%)	1 (4.5%)	
PEG[5] (n = 21)	15 (100%)	5 (83.3%)	20 (95.2%)	0.286
% Baseline body-weight loss				
Nil	46 (57.5%)	17 (53.1%)	63 (56.3%)	
< 5%	23 (28.8%)	9 (28.1%)	32 (28.6%)	
5%-10%	9 (11.3%)	5 (15.6%)	14 (12.5%)	
> 10%	2 (2.5%)	1 (3.1%)	3 (2.7%)	0.889
Nutritional status (PG-SGA[6])				
A	–	19 (59.4%)	19 (59.4%)	
B	–	13 (40.6%)	13 (40.6%)	
C	–	–	–	
QOL mean score (± SD)	–	71.97 (± 9.74)	–	

Abbreviations: 3D = Three-dimensional conformal radiotherapy; VMAT = Volumetric modulated arc therapy; CCRT = Concurrent chemoradiotherapy; NG = Nasogastric tube; PEG = Percutaneous endoscopic gastrostomy; PG-SGA = Patient-Generated Subjective Global Assessment

Radiation oral mucositis and radiation dermatitis were the common acute complications of the radiotherapy. The descriptive data showed that in the control group, those complications developed at the third week of treatment, which was 1 week earlier than for the study group (Figs 2 and 3).

With patients who had participated in the active nutrition improvement program (the study group), serial assessments using their nutritional status classified by PG-SGA were performed at the first visit; the first, fourth, and last week of treatment; and the first, second, and third month after finishing the treatment. The patients' nutritional statuses were divided into 3 classes: Class A, well-nourished (scores 1-8); Class B, moderately malnourished (scores 9-18); and Class C, severely malnourished (scores > 18). At the first visit, most of the patients had good nutritional status, and none had severe malnutrition. However, during the treatment, almost all of the patients became malnourished. Fortunately, their nutritional statuses improved during the three months after the completion of the treatment (Fig 4). In addition, the quality of life by functional assessment of cancer therapy (FACT-H&N, version 4) was performed. Although the mean of the quality of life score reduced gradually, the mean score fell by less than 10 points (Fig 5).

TABLE 3. Results of treatment.

Treatment	Control	Study	Total	*P*-value	Odds Ratio*	95% CI
Concurrent Chemoradiotherapy						
Complete	32 (40%)	18 (56.3%)	50 (44.6%)			
Incomplete	48 (60%)	14 (43.8%)	62 (55.4%)	0.121	0.519	0.226–1.188
Radiotherapy						
Complete	76 (95%)	31 (96.9%)	107 (95.5%)			
Incomplete	4 (5%)	1 (3.1%)	5 (4.5%)	0.515	0.484	0.54–4.312
Radiotherapy: interruption						
No	62 (77.5%)	26 (81.3%)	91 (79.1%)			
Yes	18 (22.5%)	6 (18.8%)	24 (21.4%)	0.663	0.795	0.283–2.229
≤ 7 days	8 (10%)	3 (9.4%)	11 (9.8%)	0.632	0.715	0.182–2.813
> 7 days	10 (12.5%)	3 (9.4%)	13 (11.6%)	0.813	0.8	0.126–5.092
No	63 (78.8%)	25 (78.1%)	88 (78.6%)			
Yes	17 (21.3%)	7 (21.9%)	24 (21.4%)	0.942	1.038	0.384–2.806
Chemotherapy						
Complete	33 (41.3%)	18 (56.3%)	51 (45.5%)			
Incomplete	47 (58.8%)	14 (43.8%)	61 (54.5%)	0.152	0.546	0.239–1.250
Chemotherapy compliance						
60%–100%**	73 (91.3%)	30 (93.8%)	103 (92%)			
< 60%	7 (8.8%)	2 (6.3%)	9 (8%)	0.662	0.695	0.136–3.541
Compliance of Cisplatin						
100%	27 (37.5%)	16 (57.1%)	43 (43%)	0.26	0.281	0.031–2.552
66%	39 (54.2%)	11 (39.9%)	50 (50%)	0.642	0.591	0.064–5.442
33%	6 (8.3%)	1 (3.6%)	7 (7%)			
Compliance of Carboplatin						
100%	6 (75%)	2 (50%)	8 (66.7%)	0.501	3	0.122–73.64
66%–83%	1 (12.5%)	1 (25%)	2 (16.7%)	1	1	0.020–50.39
< 50%	1 (12.5%)	1 (25%)	2 (16.7%)			

*The reference group was the control group; **Cisplatin 2/3 cycles or Carboplatin > 4/6 cycles

TABLE 4. Results of treatment: multivariate analysis by logistic regression.

Treatment	Control	Study	Total	*P*-value	Odds Ratio*	95% CI
Concurrent Chemoradiotherapy						
Complete	32 (40%)	18 (56.3%)	50 (44.6%)			
Incomplete	48 (60%)	14 (43.8%)	62 (55.4%)	0.118	0.514	0.224–1.183

*The reference group was the control group; adjusted by age ≤ 60 versus > 60 years, nasopharyngeal versus non-nasopharyngeal, and stages I, II, III versus stage IV

TABLE 5. Cause of treatment delays, and the treatments for oral mucositis.

Treatment	Control	Study	Total	*P*-value	Odds Ratio*	95% CI
No treatment delay	33 (41.3%)	18 (56.3%)	51 (45.5%)			
Cause of the treatment delay						
Oral mucositis	20 (25%)	1 (3.1%)	21 (18.8%)			
Dermatitis	1 (1.3%)	1 (3.1%)	2 (1.8%)			
Hematologic toxicity	2 (2.5%)	2 (6.3%)	4 (3.6%)			
Renal toxicity	7 (8.8%)	1 (3.1%)	8 (7.1%)			
Infection	4 (5%)	–	4 (3.6%)			
Body-weight loss	1 (1.3%)	1 (3.1%)	2 (1.8%)			
N/A	12 (15%)	8 (25%)	20 (17.9%)	0.071		
Oral mucositis treatment						
Non-narcotic drug	17 (44.7%)	7 (77.8%)	24 (51.1%)			
Narcotic drug	21 (55.3%)	2 (22.2%)	38 (48.9%)	0.091	0.231	0.042–1.262

*The reference group was the control group

TABLE 6. Tube feeding during treatment.

Results	Control	Study	Total	*P*-value	Odds Ratio*	95% CI
Tube feeding	25 (31.3%)	9 (28.1%)	34 (30.4%)	0.745	0.861	0.349–2.126
NG[1]	23 (92%)	9 (100%)	32 (94.1%)			
PEG[2]	2 (8%)	–	2 (5.9%)	1.000		

*The reference group was the control group

Abbreviations: NG = Nasogastric tube; PEG = Percutaneous endoscopic gastrostomy

TABLE 7. Percentage of body-weight loss: during treatment and follow-up

Body-weight loss	Control	Study	Total	*P*-value
Week 1				
N	80	32	112	
Nil	41 (51.3%)	22 (66.8%)	63 (56.3%)	
< 5%	25 (31.3%)	7 (21.9%)	32 (28.6%)	
5%–10%	11 (13.8%)	2 (6.3%)	13 (11.6%)	
> 10%	3 (3.8%)	1 (3.1%)	4 (3.6%)	0.42
Week 2				
N	80	31	111	
Nil	22 (27.5%)	9 (29%)	31 (27.9%)	
< 5%	44 (55%)	20 (64.5%)	64 (57.7%)	
5%–10%	13 (16.3%)	2 (6.5%)	15 (13.5%)	
> 10%	1 (1.3%)	–	1 (0.9%)	0.634
Week 3				
N	79	31	110	
Nil	8 (10.1%)	6 (19.4%)	14 (12.7%)	
< 5%	46 (58.2%)	15 (48.4%)	61 (55.5%)	
5%–10%	25 (31.6%)	9 (29%)	34 (30.9%)	
> 10%	–	1 (3.2%)	1 (0.9%)	0.143
Week 4				
N	79	31	110	
Nil	10 (12.7%)	5 (16.1%)	15 (13.6%)	
< 5%	29 (36.7%)	13 (41.9%)	42 (38.2%)	
5%–10%	36 (45.6%)	12 (38.7%)	48 (43.6%)	
> 10%	4 (5.1%)	1 (3.2%)	5 (4.5%)	0.866
Week 5				
N	77	31	108	
Nil	5 (6.5%)	4 (12.9%)	9 (8.3%)	
< 5%	27 (35.1%)	12 (38.7%)	39 (36.1%)	
5%–10%	31 (40.3%)	13 (41.9%)	44 (40.7%)	
> 10%	14 (18.2%)	2 (6.5%)	16 (14.8%)	0.330
End of treatment				
N	79	31	110	
Nil	7 (8.9%)	5 (16.1%)	12 (10.9%)	
< 5%	16 (20.3%)	6 (19.4%)	22 (20%)	
5%–10%	29 (36.7%)	15 (48.4%)	44 (40%)	
> 10%	27 (34.2%)	5 (16.1%)	32 (29.1%)	0.170
1st FU (1 month after RT)				
N	79	31	110	
Nil	4 (5.1%)	6 (19.4%)	10 (9.2%)	
< 5%	11 (14.1%)	10 (32.3%)	21 (19.3%)	
5%–10%	30 (38.5%)	5 (16.1%)	35 (32.1%)	
> 10%	33 (42.3%)	10 (32.3%)	43 (39.4%)	0.005
2nd FU (2 months after RT)				
N	76	28	104	
Nil	9 (11.8%)	6 (21.4%)	15 (14.4%)	
< 5%	14 (18.4%)	7 (25%)	21 (20.2%)	
5%–10%	16 (21.1%)	7 (25%)	23 (22.1%)	
> 10%	37 (48.7%)	8 (28.6%)	45 (43.3%)	0.284
3th FU (3 months after RT)				
N	73	27	100	
Nil	11 (15.1%)	5 (18.5%)	16 (16%)	
< 5%	12 (16.4%)	9 (33.3%)	21 (21%)	
5%–10%	11 (15.1%)	2 (7.4%)	13 (13%)	
> 10%	39 (53.4%)	11 (40.7%)	50 (50%)	0.226

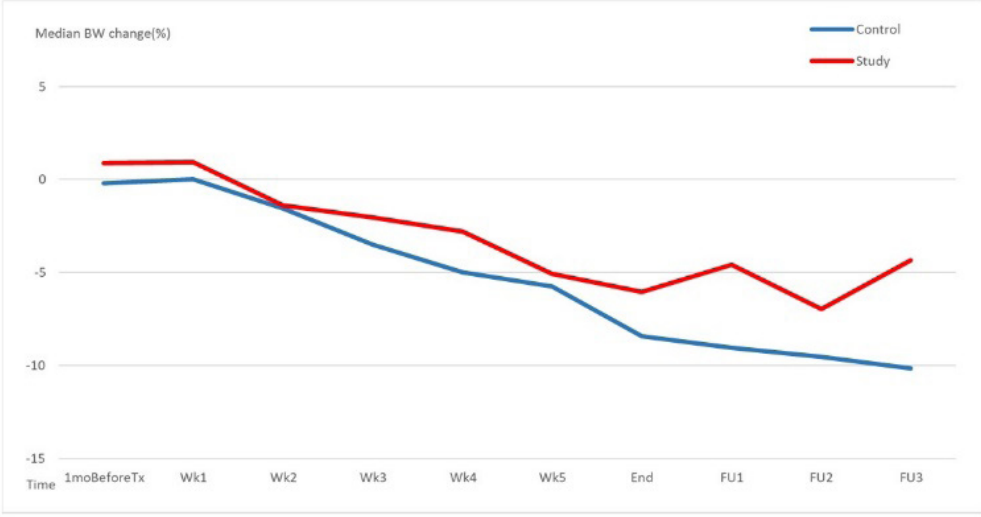

Fig 1. Median percentages of the body-weight changes.
P-value from Mann-Whitney U test

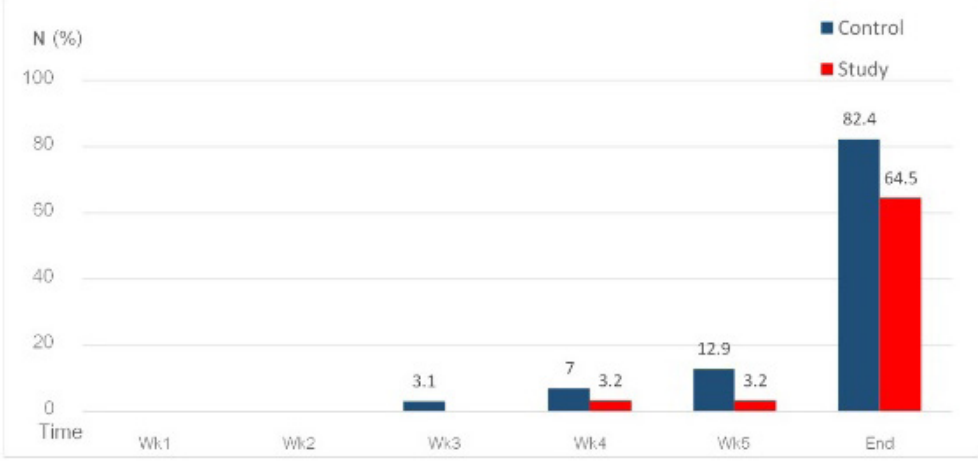

Fig 2. Acute complications: grand 2 or grade 3 radiation oral mucositis.

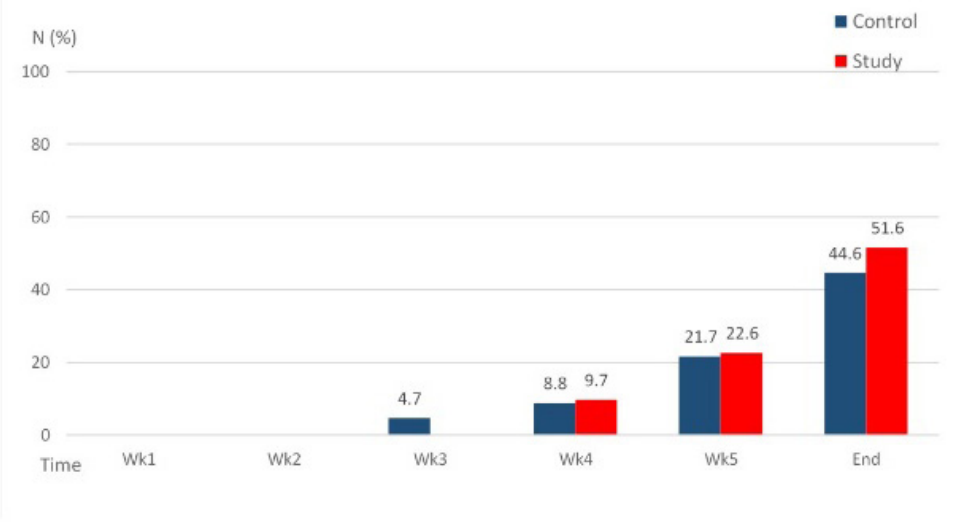

Fig 3. Acute complications: grand 2 or grade 3 radiation dermatitis.

Fig 4. Nutritional status by PG-SGA.

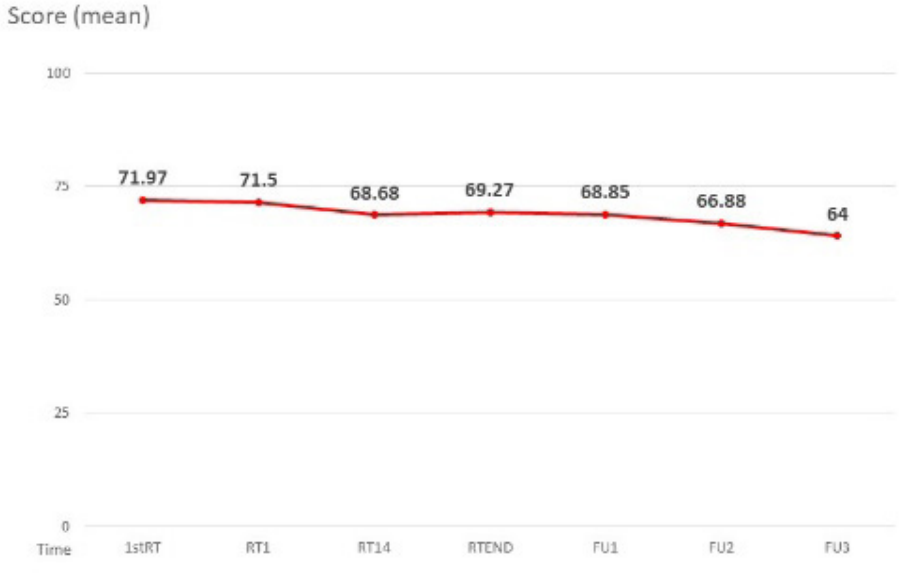

Fig 5. Mean score of quality of lfe by functional assessment of cancer therapy: mean score by FACT-H&N version 4.

DISCUSSION

Patients who have been diagnosed with cancer usually experience weight loss and/or malnutrition, especially in the case of those with HNC. White et al. identified that malnutrition could affect cancer patients' functional and quality of life outcomes.[6] They also established easy criteria to identify severe malnutrition by using the percentage of weight loss from baseline: > 5% within 1 month, > 7.5% within 3 months, > 10% within 6 months, and > 20% within 1 year. In another study, O'Neill and Shaha assessed malnutrition by using either the percentage of weight loss during the preceding 6 months (the difference between the usual weight and the actual, current weight) or the gold standard method, PG-SGA, to monitor the nutritional status of patients.[7] They recommended that malnutrition be corrected in order to reduce the morbidity and mortality rates resulting from treatment effects. Several other studies have found that HNC patients experience a reduced calorie intake and a consequential weight loss before and during treatment. The studies suggested that

early intervention (active dietary counseling, the addition of nutrition supplements, or the use of a prophylactic feeding tube) may improve patients' nutritional statuses.[8-11]

There are a number of ways to manage the nutrition of HNC patients. Many studies have explored effective ways to improve nutrition before, during, and after cancer treatment, especially concurrent chemoradiotherapy. Prophylactic enteral feeding using a PEG or NG tube, and which was done with and without a nutrition supplement before cancer treatment, demonstrated no effects on weight loss, quality of life, or nutritional improvement.[12–13] However, the prophylactic enteral feeding revealed the benefit of overall clinical outcome improvements and a decline in the incidences of serious treatment side effects. Prophylactic enteral tube feeding was indicated in those patients who were predicted to have severe malnutrition, were curative aim patients with old age and locally advanced disease (T3/T4 and/or lymph node involvement), and were undergoing post-radical surgery with a reconstruction procedure and concurrent chemoradiotherapy.[14-16]

Pretreatment weight loss is an important prognostic indicator for the overall survival of HNC patients. The benefit of individual dietary counseling is that it helps maintain good nutrition in HNC patients. Isenring et al. demonstrated that early and intense nutrition intervention in the form of individual nutrition counseling and oral supplements not only minimized weight loss and the ensuing deterioration in nutritional status, quality of life and physical function, but it also reduced the risks of infection and treatment toxicities.[5]

In this study, the primary outcome was to explore the correlation between nutritional improvement and the rate of treatment completion. There were no significant differences in the patient characteristics of the study and control groups. Most of the patients were middle-aged men who had been diagnosed with locally advanced HNC and had received volumetric modulated arc therapy concurrent with a cisplatin regimen. The active nutrition improvement program with serial nutritional assessments was introduced to the study group. There was clinical significance in the higher rate of treatments that were completed as scheduled by these study group patients. The active nutritional counseling also provided a clinical benefit by way of improved compliance with chemotherapy. The number of chemotherapy completions by the study group, 56%, was 15 percentage points higher than the corresponding figure for patients in the control group (40%), who had only been given routine counseling. We also examined whether there was a correlation between the nutrition improvement program and serial assessments and chemotherapy tolerance. To this end, the causes of treatment interruptions and postponements were studied. We found that common problems after receiving concurrent chemoradiotherapy were oral mucositis and dermatitis, mainly occurring 3 to 4 weeks after starting the radiation treatment. In the control group, the mucositis developed sooner and with more severe pain, indicated by the greater number of patients using a narcotic drug in that group than in the study group.

As to the secondary outcomes, only one-third of the patients in each group required enteral feeding. NG-tube feeding was mostly selected because it is less invasive than PEG. Approximately the same proportion of patients in each group had experienced a significant weight loss by the third week of treatment. This correlated with the onset of mucositis and dermatitis, which were the common acute complications. Unfortunately, nutritional assessments using the PG-SGA classification were only conducted for the patients in the study group. The descriptive data showed that most of the patients were well-nourished at their initial diagnosis. However, during their treatment, they became moderately to severely malnourished. We assume that was because of the natural course of the disease and/or the acute complications of the treatment, such as mucositis, which might have interfered with the patients' oral food intake. However, most of the patients recovered to a normal, or mildly malnourished, status within 3 months of treatment cessation.

CONCLUSION

The active nutrition improvement program, a noninvasive procedure conducted by a physician, was clinically beneficial. Compared to the patients receiving only routine dietary counseling, the nutrition improvement program produced a higher scheduled treatment completion rate (i.e., without interruption or postponement), improved chemotherapy tolerance, and a lower and delayed incidence of mucositis. Given that the active counseling program is not too complicated and could be easily conducted by any paramedic, we recommend that it be provided as part of treatment protocols.

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Depression and Quality of Life in Spinal Cord Injury Patients Living in the Community After Hospital Discharge

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ABSTRACT

Objective: To investigate quality of life (QoL) and the prevalence of depression, and to identify factors significantly associated with QoL and depression in spinal cord injury (SCI) patients living in the community after hospital discharge.

Methods: This prospective study included SCI patients that have a follow-up evaluation and care at the Siriraj Spinal Unit of the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during April 2015 to February 2018. Presence and level of depression and QoL were assessed using Patient Health Questionnaire-9 (PHQ-9) and World Health Organization Quality of Life Brief-Thai (WHOQOL-BREF-THAI), respectively. Age, gender, education level, income, marital status, level of impairment, injury severity, cause of injury, and time since injury were collected and recorded.

Results: One hundred and twelve spinal injury patients (64.3% male) with a mean age of 44.3±15.3 years were enrolled. The prevalence of depression was 39.3%, and the mean overall QoL was a moderate 90.3±14.7. Multivariate analysis revealed marital status to be the only independent predictor of depression after hospital discharge (odds ratio [OR]: 2.99, 95% confidence interval [CI]: 1.19-7.51; p=0.020). Regarding QoL, multivariate analysis revealed educational level (OR: 16.18, 95% CI: 3.01-87.03; p=0.001), level of impairment (OR: 9.20, 95% CI: 1.84-46.13; p=0.007), and depression (OR: 50.39, 95% CI: 7.94-319.83; p<0.001) to be independent predictors of quality of life.

Conclusion: Depression was observed in 39.3% of SCI, and most study patients had moderate QoL. Marital status predicts depression; and, educational level, level of impairment, and presence of depression predict QoL.

Keywords: Quality of life; depression; spinal cord injury; community; postdischarge (Siriraj Med J 2020; 72: 59-66)

INTRODUCTION

Depression is a psychological complication that is regularly observed among spinal cord injury (SCI) patients.[1] Early onset depression may be found after SCI and is considered a normal part of the patient adaptation process[2], Prevalence of depressive symptoms in SCI in in-patient ward (clinic) was report about 30%.[3] Moreover, almost 20% of patients were found to have a continuation of depressive symptoms after hospital discharge[4], and that percentage increased to 25-30% after these patients returned to live in a community setting.[5] The prevalence of depression was reported to be three times higher among SCI patients living in the community than among general population.[6]

One of the negative consequences of depression in SCI patients is reduced quality of life.[7] Craig, *et al.*

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reported a decrease in quality of life and an increase in anxiety and/or depression in patients who sustained a spinal cord injury.[3] Several studies found depression to be associated with reduced quality of life in SCI patients.[8,9,10,11] Holicky and Charlifue studied 225 English SCI patiens who had lived with SCI for 26 or more years. They found a decrease in the level of depression among patients who got married. They also found a higher level of life satisfaction, overall mental health, and quality of life in married SCI compared to unmarried SCI.[12]

Depression in SCI patient dose not spontaneous resolved, therefore continuation of treatment is necessary for SCI patients after hospital discharge.[13] Accordingly, follow-up to monitor for depressive symptoms among SCI patiens living in the community is essential. Moreover, SCI patients are now living longer[14], which highlights the need for long-term support to improves in patient quality of life. Improved understanding about depression and quality of life in this patient population will improve the mental health evaluation and treatment processes among SCI patiens living in a community setting. The aim of this study was to investigate quality of life and the prevalence of depression, and to identify factors significantly associated with quality of life and depression in SCI patients living in the community after hospital discharge.

MATERIALS AND METHODS

Participants

The study population consisted of SCI patients who received follow-up evaluation and care at the Siriraj Spinal Unit of the Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the April 2015 to February 2018. Patients that met all of the following criteria were included: (1) age greater than 18 years; (2) having good consciousness; and, (3) having good ability and a willingness to answer the PHQ-9 questionnaire and the WHOQOL-BREF-THAI. Patients that have a history or diagnosis of depression before SCI occurred and active psychosis patients were excluded.

Assessment instrument

The PHQ-9 questionnaire is a self-report depression screening tool that consists of 9 items that are derived from DSM-IV depression diagnostic criteria. There are four levels of scoring for each item that include: "Not at all" (score = 0); "Some days, not often" (score = 1); "Quite regularly" (score = 2); and, "Nearly every day" (score = 3). The overall score can range from 0-27. Based on studies conducted in Thailand, a participant with a score of 9 or more was diagnosed as having depression (sensitivity = 0.84, specificity = 0.77).[15] In the present study, a participant with a score higher than 7 was considered to have depressive symptoms.

World Health Organization Quality of Life Brief-Thai (WHOQOL-BREF-THAI) is a 5-point rating scale instrument. It is comprised of 26 items, of which 23 questions are positive, and 3 questions are negative. The positive questions are scored, as follows: "Not at all" (score = 1), "Slightly" (score = 2), "Moderate" (score = 3), "Very" (score = 4), and "Extremely" (score = 5). The 3 negative questions are scored, as follows: "Not at all" (score = 5), "Slightly" (score = 4), "Moderate" (score = 3), "Very" (score = 2), and "Extremely" (score = 1). The instrument measures four domains of quality of life, including: physical health, psychological well-being, social relationships, and environment. Quality of life is classified by score into one of the three following categories, including: poor quality of life (score 26-60), moderate quality of life (score 61-95), or good quality of life (score 96-130). Its reliability (Cronbach's alpha coefficient) was 0.84, and the validity was 0.65 when tested against the Thai version of the WHOQOL-100. This questionnaire is officially approved by WHO.[16] Moreover, the WHOQOL-BREF-THAI is widely used in the study of SCI patients. Thus, it is considered a suitable tool for assessing the QoL of patients who have sustained a spinal cord injury.[17]

After receiving study approval from the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 233/2015), written informed consent was obtained from all enrolled study participants. The following data were collected from patient medical records: age, gender, education level, income, marital status, level of impairment, injury severity, cause of injury, and time since injury. Patient level of depression and quality of life was assessed using the PHQ-9 questionnaire and WHOQOL-BREF-THAI, respectively.

Statistical analysis

The prevalence of depression among spinal injury patients was reported as number and percentage, and the depression and quality of life scores were reported as mean ± standard deviation (SD). Student's t-test was used to compare continuous data, and chi-square test or Fisher's exact test was used to compare categorical data. Factors with a p-value less than 0.20 in univariate analysis were included in multivariate analysis. The results of multivariate analysis are presented as adjusted odds ratio (OR) and 95% confidence interval (CI). All data

analyses were performed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA), and a p-value<0.05 was regarded as being an indicator of statistical significance.

RESULTS

One hundred and twelve spinal injury patients with a mean age of 44.3±15.3 years (range: 18-84) were enrolled. Of those, 64.3% were male and 35.7% were female. One-quarter (25.9%) of patients had an elementary-level education, 40.2% were married, and the average income was 11,810.9±18,197.7 Thai baht per month (range: 0-100,000). Regarding the cause of injury and outcome, 57.1% of patients were injured in traffic accidents and 37.1% became paraplegic. The majority of patients (41.1%) had incomplete injury, and the mean duration of disease after injury was 55.8±64.4 months (range: 1 month to 28 years), as shown in Table 1.

The prevalence of depression was 39.3%, and the mean depression score was 5.8±4.4. Regarding quality of life, the majority of patients (59.8%) had a moderate level of quality of life, followed by good quality of life (38.4%) and poor quality of life (1.8%). The mean quality of life score was 90.3±14.7. The mean quality of life score in each domain was, as follows: physical domain: 23.4±4.9, psychological domain: 22.2±3.8, social relationship domain: 9.8±2.2, and environmental domain: 28.2±4.9. The quality of life in each domain was observed to be moderate (Table 2).

Univariate analysis that included age, gender, educational level, marital status, income, cause of injury, time since injury, severity of impairment, and severity of injury as factors potentially associated with depression revealed only marital status to be significantly associated with depression (p=0.026). We then included all factors from univariate analysis with a p-value less than 0.20 in multivariate analysis (i.e., gender, marital status, and time since injury). That analysis revealed marital status to be the only independent predictor of depression after hospital discharge. More specifically, patients who were married had a 2.99 times (95% CI: 1.19-7.51, p=0.020) greater probablity of developing depression than patients who were single (Table 3).

Univariate analysis revealed educational level (p=0.001), income level (p=0.019), level of impairment (p=0.004), severity of injury (p=0.005), and depression (p<0.001) to be significantly associated with quality of life. Multivariate analysis that included factors from univariate analysis with a p-value less than 0.20 (i.e., educational level, income level, time since injury, depression, severity of injury, and level of impairment) revealed educational level, level of impairment, and depression to be independent predictors of quality of life. Patients with an undergraduate degree or higher had a 16.18 times (95% CI: 3.01-87.03, p=0.001) greater probability of having good quality of life when compared to patients with a lower level of education. Patients with non-severe disability had a 9.20 times (95% CI: 1.84-46.13, p=0.007) greater probability of having good quality of life when compared to patient with tetraplegia. Lastly, patients with an absence of depressive symptoms had a 50.39 times (95% CI: 7.94-319.83, p<0.001) greater probability of having good quality of life when compared with patients with depression (Table 4).

DISCUSSION

The present study found the prevalence of depression among SCI patients after discharge from Siriraj Hospital to be 39.3%. The prevalence of depression reported in this study is far higher than the 18%[4], 20%[18], and 22% rates reported from other countries.[19] However and importantly, a score of 10 or greater reflected the presence of depressive symptoms in those studies, while a score greater than 7 reflected the presence of depressive symptoms in our study. Moreover, we used diagnostic criteria established and recommended by the Thailand Department of Mental Health. Concerning the measurement of quality of life among SCI patients after discharge from the hospital, we selected the WHOQOL-BREF Questionnaire as a tool to demonstrated level of QOL, because it is widely used in the study of SCI patients and it has proven acceptable reliability.[20] The results of our study showed the overall QoL and the QoL for each domain to be at moderate level, which is similar to the results from previous studies conducted in Thai SCI population.[17,21,22,23,26]

Considering factors related to depression among SCI patients, the current study found marital status to be significantly associated with depression. More specifically, we found that married patients were more likely to develop depression than unmarried SCI. Similarly, Tzanos, *et al.*[25] investigated depressive mood among SCI patients in Greece, and they found that having a spouse did not play an important role in the prevention of depression. On the contrary, In some previous study found marriage to be significantly associated with a low level of emotional distress.[26] In some instances, SCI patients experience an adverse change in marital status – a divorce. A previous study found that divorced SCI patients were more likely to have depressive mood when compared with other groups of SCI patients.[27] Other previous findings revealed family relationship and family support are represent key factors that influence a reduction in depression among SCI patients.[28]

TABLE 1. Demographic and clinical characteristics of included spinal injury patients.

Variables	Mean ± SD or n (%)
Age (years)	44.3±15.3
Male gender	72 (64.3%)
Education	
No education	3 (2.7%)
Primary school	29 (25.9%)
Secondary school	27 (24.1%)
Vocational certificate	20 (17.9%)
Undergraduate	27 (24.1%)
Postgraduate	6 (5.4%)
Marital status	
Single	41 (36.6%)
Married	51 (45.5%)
Divorced/Separated/Widowed	20 (17.9%)
Income (Thai baht/month)	11,810.9±18,197.7
Cause of injury	
Traffic accident	64 (57.1%)
Fall	36 (32.1%)
Violence	7 (6.3%)
Other	5 (4.5%)
Level of impairment	
No	37 (33.0%)
Paraplegia	43 (38.4%)
Tetraplegia	32 (28.6%)
Severity of injury (n=75)	
Complete	29 (25.9%)
Incomplete	46 (41.1%)
Time since injury (months)	55.8±64.4

Abbreviation: SD = standard deviation

TABLE 2. Quality of life scores of included spinal injury patients.

Domains	Level of QOL			QOL score		
	Poor (%)	Moderate (%)	Good (%)	Mean±SD	Range	Level
Physical health	31 (27.7%)	73 (65.2%)	8 (7.1%)	23.4±4.9	11-34	Moderate
Psychological	50 (44.6%)	60 (53.6%)	2 (1.8%)	22.2±3.8	12-30	Moderate
Social relationship	25 (22.3%)	67 (59.8%)	20 (17.9%)	9.8±2.2	4-15	Moderate
Environmental	48 (42.9%)	63 (56.3%)	1 (0.9%)	28.2±4.9	18-40	Moderate
Overall QOL	43 (38.4%)	67 (59.8%)	2 (1.8%)	90.0±14.7	52-126	Moderate

Abbreviations: QOL= quality of life; SD = standard deviation

TABLE 3. Univariate and multivariate analysis for factors significantly associated with depression.

Factors	No depression (n=68)	Depression (n=44)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Gender			***0.160***		0.301
Male	40 (55.6%)	32 (44.4%)		1.59 (0.66-3.81)	
Female	28 (70.0%)	12 (30.0%)		1.00	
Education			0.832		
Lower than bachelor's degree	47 (59.5%)	32 (40.5%)			
Bachelor's degree or higher	21 (63.6%)	12 (36.4%)			
Marital status			***0.026***		
Single	30 (73.2%)	11 (26.8%)		1.00	
Married	24 (47.1%)	27 (52.9%)		2.99 (1.19-7.51)	***0.020***
Divorced/separated/widow	14 (70.0%)	6 (30.0%)		1.00 (0.29-3.40)	0.997
Income level (Thai baht/month)			0.377		
No income	21 (55.3%)	17 (44.7%)			
<15,000	21 (56.8%)	16 (43.2%)			
≥15,000	26 (70.3%)	11 (29.7%)			
Cause of injury			0.209		
Fall	40 (62.5%)	24 (37.5%)			
Traffic accident	24 (66.7%)	12 (33.3%)			
Violence	2 (28.6%)	5 (71.4%)			
Other	2 (40.0%)	3 (60.0%)			
Level of impairment			0.233		
Paraplegia	26 (60.5%)	17 (39.5%)			
Tetraplegia	16 (50.0%)	16 (50.0%)			
Normal	26 (70.3%)	11 (29.7%)			
Severity of injury			0.235		
Complete	18 (62.1%)	11 (37.9%)			
Incomplete	24 (52.2%)	22 (47.8%)			
Normal	26 (70.3%)	11 (29.7%)			
Time since injury (months)			***0.137***		
<60	48 (57.8%)	35 (42.2%)		1.00	
60-120	6 (50.0%)	6 (50.0%)		2.81 (0.71-11.12)	0.141
>120	14 (82.4%)	3 (17.6%)		4.89 (0.81-29.41)	0.083

Factors with a *p*-value <0.2 in univariate analysis were included in multivariate analysis
A *p*-value<0.05 in multivariate analysis indicates statistical significance
Abbreviation: CI = confidence interval

TABLE 4. Univariate and multivariate analysis for factors significantly associated with quality of life.

Factors	Good (n=43)	Poor/moderate (n=69)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Gender			0.547		
Male	26 (36.1%)	46 (63.9%)			
Female	17 (42.5%)	23 (57.5%)			
Education			***0.001***		
Lower than bachelor's degree	22 (27.8%)	57 (72.2%)		1.00	
Bachelor's degree or higher	21 (63.6%)	12 (35.4%)		16.18 (3.01-87.03)	***0.001***
Marital status			0.560		
Single	18 (43.9%)	23 (56.1%)			
Married	19 (37.3%)	32 (62.7%)			
Divorced/separated/widow	6 (30.0%)	14 (70.0%)			
Income level (Thai baht/month)			***0.019***		
No income	11 (28.9%)	27 (71.1%)		0.79 (0.18-3.54)	0.756
<15,000	11 (29.7%)	26 (70.3%)		0.84 (0.19-3.67)	0.817
≥15,000	21 (56.8%)	16 (43.2%)		1.00	
Cause of injury			0.379		
Fall	28 (43.8%)	36 (56.3%)			
Traffic accident	13 (36.1%)	23 (63.9%)			
Violence	1 (14.3%)	6 (85.7%)			
Other	1 (20.0%)	4 (80.0%)			
Level of impairment			***0.004***		
Tetraplegia	7 (21.9%)	25 (78.1%)		1.00	
Paraplegia	14 (32.6%)	29 (67.4%)		2.97 (0.81-10.94)	0.102
Normal	22 (59.5%)	15 (40.5%)		9.20 (1.84-46.13)	***0.007***
Severity of injury			***0.005***		
Complete	9 (31.0%)	20 (69.0%)			
Incomplete	12 (26.1%)	34 (73.9%)			
Normal	22 (59.5%)	15 (40.5%)			
Time since injury (months)			***0.142***		
<60	32 (38.6%)	51 (61.4%)		0.83 (0.18-3.89)	0.813
60-120	2 (16.7%)	10 (83.3%)		0.21 (0.02-2.06)	0.181
>120	9 (52.9%)	8 (47.1%)		1.00	
PHQ-9			***<0.001***		
Depression	3 (6.8%)	41 (93.2%)		1.00	
No depression	40 (58.8%)	28 (41.2%)		50.39 (7.94-319.83)	***<0.001***

Factors with a *p*-value <0.2 in univariate analysis were included in multivariate analysis
A *p*-value<0.05 in multivariate analysis indicates statistical significance
Abbreviations: CI = confidence interval; PHQ-9 = Patient Health Questionnaire-9

Concerning factors related to the QoL of SCI patients, the present study found having a bachelor degree or higher, having non-severe disability, or having no depressive symptoms to be significantly associated with patients having a good QoL score. Similarly, previous studies conducted in other countries and in Thailand found the factors that influence QoL are the educational level[24], severity of disability[21,30,31], and presence of depression. Tzanos, *et al.*[25,29] found that high educational level enabled SCI patients to acquire skills necessary for learning new knowledge, and to better understand the steps required for using assisting technology. Furthermore, higher education level promoted greater access to technology, and influenced a tendency toward higher income. Employment and sufficient income were factors that helped to facilitate a better QoL. In contrast, low educational level may effectuate or worsen social barriers among SCI patients, and this may further limit all varieties of potential opportunities that could improve their state of mind and overall well-being. Regarding severity of disability, people who become disabled due to an injury are more likely to have a lower level of quality of life than people in the general population.[21] After sustaining an injury, the physical performance of patients decreases, and this adversely affects their coping skills, which consequently decreases their quality of life their quality of life.[23] An absence of depressive symptoms was reported to be a factor significantly associated with good quality of life.[26] Tzanos, *et al.*[25] found the PHQ-9 score to be negatively related with the QoL score in every domain (WHOQOL-BREF). Similarly, Tate, *et al.*[32] also found good quality of life to be significantly related to reduced prevalence of depression.

The limitation of this study is its cross-sectional design, which means that the data was collected at one point in time. However, the study participants selected the answers that they felt best described their situation and state of mind, so further elicitation to extract additional information was not required.

CONCLUSION

The prevalence of depression among study participants was 39.3% according to PHQ-9. Primary care, based on the depression diagnostic criteria of the Thailand Department of Mental Health, includes managing emotions and consulting a psychiatrist, psychologist or some other type of training mental health professional. Moreover, self-assessment must be elicited when a patient is receiving follow-up services. Having an undergraduate degree or higher, presence of non-severe disability, and no presence of depressive symptoms were found to be significantly related with good quality of life among SCI. Moreover, the educational level and severity of disability variables were personal and illness-related factors that cannot be easily prevented or treated among these patients. However, depression, which is a factor that was found to be associated with good quality of life, can be screened for and prevented prior to its development. If depression is identified, it can be treated, and this will lead to improved QoL in patients with SCI that return to living in the community after their discharge from the hospital.

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Comparison of Computed Tomography Angiography (CTA) Findings in Post-Endovascular Aortic Aneurysm Repair CTA between Persistent and Transient Type II Endoleak

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ABSTRACT

Objective: To compare first post-endovascular aortic aneurysm repair (EVAR) computed tomography angiography (CTA) imaging characteristics between transient and persistent type II endoleaks.

Methods: This retrospective study enrolled patients who underwent EVAR and were diagnosed with type II endoleak from first post-operative CTA during January 2005 to October 2017 at the Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Aneurysmal sac size, aneurysmal sac growth, and endoleak were recorded among patients whose endoleak disappeared within 6 months (transient group), and among patients whose endoleak persisted for more than 6 months (persistent group).

Results: Eighty-eight patients with a mean age of 75.3±7.3 years were included. Of those, 12 and 76 patients were in the transient group and persistent group, respectively. There were 71 males and 17 females. Univariate analysis showed number of feeding arteries (odds ratio [OR]: 9.9, p=0.012) and presence of inferior mesenteric artery (IMA) as an endoleak source (OR: 4.3, p=0.026) to be found more frequently in the persistent group than in the transient group; however, neither factor survived multivariate analysis. No significant difference between two groups was seen for endoleak diameter, endoleak complexity, or aneurysmal sac enlargement.

Conclusion: The number of feeder arteries and presence of IMA as an endoleak source on first postoperative CTA to be more likely found in patients with persistent type II endoleak. Further prospective study in a larger study population is necessary to identify any existing statistically significant differences and/or associations.

Keywords: Comparison; computed tomography angiography; CTA; post-endovascular aortic aneurysm repair CTA; persistent and transient type II endoleak (Siriraj Med J 2020; 72: 67-73)

INTRODUCTION

Endovascular aortic aneurysm repair (EVAR) is now generally accepted worldwide as a treatment procedure for abdominal aortic aneurysm because it has a lower rate of perioperative mortality than open surgical repair.[1,2] However, despite EVAR being shown to have superior perioperative survival advantage, its most well-known complication – endoleak, which is defined as continuous

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perfusion within the aneurysm sac – can cause aneurysmal sac expansion that can lead to compromised long-term survival outcome.

Type II endoleaks originate from retrograde flow from collateral arteries to the aneurysmal sac. Typical aortic side branches that cause type II endoleaks are the inferior mesenteric artery (IMA), the lumbar arteries (LAs), the median sacral artery, and the accessory renal arteries. Early-onset type II endoleak is defined as an endoleak found within 90 days after EVAR, while late-onset type II endoleak is detected after 90 days. Early-onset type II endoleak can be classified as transient (one that spontaneously resolves within 6 months) or persistent (endoleak that lasts longer than 6 months after EVAR) type II endoleak.

Persistent type II endoleaks have been reported as a cause of late adverse outcome including aneurysmal sac diameter enlargement, the need for switching to open repair/ reintervention and rupture.[3] Researchers have investigated for factors that predict persistent type II endoleaks. In addition to demographic and patient characteristics that have been discussed and reported in previous studies as predictors of persistent type II endoleak4, several other studies examined preprocedural imaging findings to identify factors that predict this particular variety of endoleak.[5-9]

The objective of this study was to identify the relation of computed tomography angiography (CTA) findings in first post-EVAR CTA between transient and persistent type II endoleaks.

MATERIALS AND METHODS

Patients

This study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University (Si 051/2018). The study retrospectively enrolled patients who were diagnosed with type II endoleak from first post-operative CTA during January 2005 to October 2017 at the Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University. The first post-operative CTA should be performed within 90 days after EVAR to evaluate for early-onset type II endoleak, and the next post-operative CTA should be performed at least 6 months after EVAR according to the criteria for persistent type II endoleak. A search of our center's database and radiology reporting system revealed 88 patients (mean age 75.3±7.3 years, 71 males and 17 females) that met the inclusion criteria. Patients with other types of endoleak or who were lost to follow-up were excluded.

Imaging study

Two sessions of CTA were interpreted. The first postoperative CTA within the first 90 days after EVAR was used for measurement of CTA findings, and the follow-up CTA was used to assess the outcome. CT scans were obtained using helical CT scanners (1. Somatom Definition dual source CT; Siemens, Forchheim, Germany or 2. Discovery CT 750HD; GE Healthcare, Milwaukee, USA or 3. Revolution CT, GE Healthcare, Milwaukee, USA). The CTA protocol consists of unenhanced CT scan, contrast-enhanced CTA phase, and delayed phase. Contrast-enhanced CTA phase was used by bolus-tracking technique with a threshold of 150 Hounsfield units (HUs) at abdominal aorta proximal to the endovascular stent graft. Delayed phase was performed 2 minutes after bolus trigger.

Imaging interpretation

Evaluation and measurement of CTA findings were performed by two radiologists who separately interpreted the image findings on our center's Picture Archive Communication System (PACS). The following CTA findings were analyzed from the first postoperative CTA: size of the aneurysmal sac, name of feeder artery and total number of arteries feeding the endoleak, endoleak complexity, diameter of endoleak, attenuation of the endoleak, and attenuation of aorta.

Aneurysmal sac diameter was measured using electronic caliper to the nearest millimeter. Measurement of the orthogonal sac diameter using double oblique short axis was performed (Fig 1). The number of feeder arteries included all visible arterial feeders. A common vessel of lumbar arteries, and a common vessel of the fourth lumbar artery and the median sacral artery were counted as one feeding artery. Endoleak complexity was classified into simple type and complex type. A simple type endoleak was defined as an endoleak that is fed by a single artery, while a complex type endoleak was defined as being fed by two or more arteries. Measurement of endoleak diameter was performed in axial plane of delayed phase CT images. The maximal diameter was measured and recorded (Fig 2). Attenuation of endoleak and aorta was measured using the greatest possible circular region of interest (ROI) on both CTA and delayed phases in Hounsfield units. Relative attenuation of endoleak was calculated using the following formula: (endoleak cavity attenuation on CTA and delayed phases – endoleak cavity attenuation on unenhanced images) / (attenuation of stent graft lumen on CTA and delayed phases – attenuation of stent graft lumen on unenhanced images). The outcome

(transient or persistent type II endoleak and aneurysmal sac diameter enlargement) was recorded based on the findings from CTA study performed 6 months after EVAR.

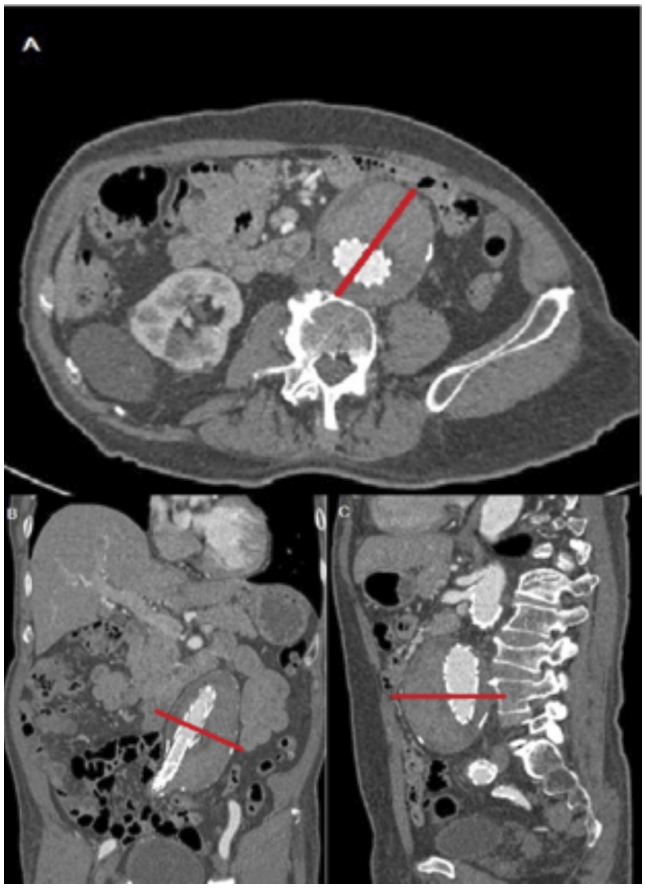

Fig 1. Post-EVAR CTA images show the method used to measure the aneurysmal sac. (A) Double oblique axial view used to measure the orthogonal diameter of the aneurysm. (B) and (C) Coronal and sagittal reformatted images, respectively.

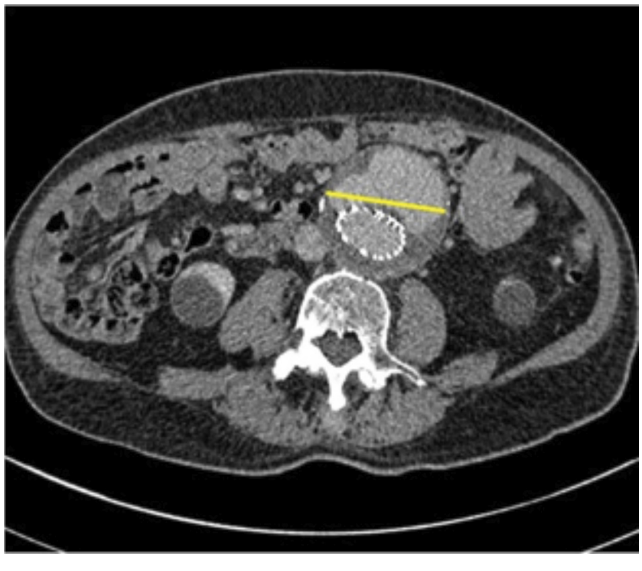

Fig 2. Post-EVAR CTA, delayed phase, axial plane image demonstrates measurement of endoleak diameter.

Statistical analysis

All data analyses were performed using SPSS Statistics software (SPSS, Inc., Chicago, IL, USA). Values are shown as mean and/or standard deviation or number and percentage, as appropriate. Univariate analysis was performed using chi-square test, *t*-test or Mann-Whitney U test, and multivariate analysis was done using logistic regression analysis to identify factors independently associated with persistent type II endoleak. Interobserver agreement of aneurysmal sac diameter measurement, number of feeder arteries, endoleak diameter measurement, and attenuation measurement was calculated using intraclass correlation coefficient (ICC, *r*). The *r* values were classified, as follows: 1.0, perfect agreement; 0.81-0.99, almost perfect agreement; 0.61-0.80, substantial agreement; 0.41-0.60, moderate agreement; 0.21-0.40, fair agreement; and, less than 0.2, slight agreement. Interobserver agreement of endoleak complexity, presence of each feeder, and aneurysmal sac enlargement were calculated using kappa statistic. The kappa values (*k*) were interpreted, as follows: 0.81-1.00, very good agreement; 0.61-0.80, good agreement; 0.41-0.60, moderate agreement; 0.21-0.40, fair agreement; and, less than 0.20, poor agreement. A p-value < 0.05 was considered statistically significant.

RESULTS

Patients

Eighty-eight patients were included. There was no significant difference in age between the transient and persistent groups (73.92±7.15 years vs. 75.57±7.30 years, respectively). Of the 88 early-onset type II endoleak patients, 12 patients had spontaneous resolution (transient group), and 76 patients still had type II endoleak on the 6-month follow-up CTA (persistent group). There was no significant difference in gender distribution between groups (p=0.236). Patient demographic data are shown in Table 1.

Endoleak characteristics

Initial mean aneurysmal sac diameter in the transient group and persistent group was 57.0±11.57 mm and 58.92±14.34 mm, respectively (p=0.66). In terms of endoleak complexity, simple endoleak was found in 7 transient type II endoleak patients, and in 24 persistent type II endoleak patients. Complex endoleak was observed in 5 transient type II endoleak patients, and in 52 persistent type II endoleak patients (p=0.103).

The number of arterial feeders of endoleak was separated into two groups: 2 or less arterial feeders, and more than 2 feeders. The transient type II endoleak

TABLE 1. Patient characteristics.

	Type II endoleak during follow-up		*P*-value
	Transient (n=12)	Persistent (n=76)	
Mean age (years)	73.92±7.15	75.57±7.30	0.468
Gender			
Male	8 (66.7%)	63 (82.9%)	0.236
Female	4 (33.3%)	13 (17.1%)	

A *p*-value<0.05 indicates statistical significance

group had a significantly greater proportion of 2 or less arterial feeders than the persistent group (91.7% *vs*. 52.6%, respectively; odds ratio [OR]: 9.9, 95% confidence interval [CI]: 1.217-80.526; *p*=0.012).

Regarding endoleak sources (different arterial feeders), presence of inferior mesenteric artery (IMA) was found more frequently in the persistent group (68.4%) than in the transient group (33.3%) (OR: 4.3, 95% CI: 1.18-15.8; *p*=0.026). However, there was no significant difference between two groups for presence of lumbar artery (LA), median sacral artery, or accessory renal artery as an arterial feeder of type II endoleak.

Endoleak diameter showed no significant difference between groups. Median diameter of type II endoleak in the transient group and persistent group was 15 mm and 13 mm, respectively (*p*=0.87). The mean attenuation of the endoleak cavity was not significantly different between the transient and persistent groups in unenhanced (43.0 *vs*. 43.8 HUs), arterial (281.6 *vs*. 273.7 HUs), and delayed (140.1 *vs*. 128.9) phases. The relative attenuation of endoleak in both the arterial and delayed phases was also not significantly different between two groups. The data are shown in Table 2. Regarding aneurysmal sac enlargement, the persistent type II endoleak group had 6 patients (7.9%) with enlarged aneurysmal sac, while the transient type II endoleak group had no patients (0%) with enlarged aneurysmal sac (*p*=0.591).

Multivariate analysis

Univariate analysis revealed statistically significant differences in three variables, including endoleak complexity, number of arterial feeders, and presence of inferior mesenteric mesentery feeder. However, when entered into multivariate analysis, none of these factors was found to be an independent predictor of persistent type II endoleak. The odd ratio for endoleak complexity, number of arterial feeders, and presence of inferior mesenteric feeder was 1.302 (95% CI: 0.318-5.333), 5.532 (95% CI: 0.487-62.797), and 2.285 (95% CI: 0.557-9.365), respectively (Table 3).

Interobserver agreement

Intraclass correlation coefficient (ICC) revealed almost perfect agreement for aneurysmal sac diameter measurement (*r*=0.961) and endoleak diameter measurement (*r*=0.922). There was substantial agreement in the counting of the number of arterial feeders (*r*=0.635). Attenuation measurement was moderate to substantial agreement (*r*=0.413-0.781). Cohen's kappa was used to calculate the kappa value. Presence of type II endoleak on follow-up study, endoleak complexity, and identification of arterial feeders showed good agreement (*k*=0.779-0.855). Aneurysmal sac enlargement evaluation showed moderate agreement (*k*=0.482).

DISCUSSION

A few studies[10,11] investigated type II endoleak and found no significant association relative to age, gender, or initial postoperative aneurysmal sac diameter in both transient and persistent type II endoleak – all of which is similar to our study.

Type II endoleaks can be classified into two subtypes, simple and complex subtypes based on number of inflow/outflow vessels. The authors compared simple and complex type II endoleak and found complex type II endoleak to be observed more frequently in the persistent group (68.4%) than in the transient group (41.7%). However, the difference between two groups was not statistically significant. This result is not directly comparable to that reported by Muller-Wille R, *et al*.[8] because they used a different method of outcome measurement. Muller-Wille R, *et al*.[8] classified simple and complex type II endoleak into four subtypes, and they found complex IMA-LA subtype to be significantly associated with aneurysmal sac enlargement (OR: 20.8, 95% CI: 4.9-88.9; *p*<0.001).

TABLE 2. Endoleak CTA characteristics.

	Type II endoleak during follow-up		Odds ratio (95% CI)	*P*-value
	Transient (n=12)	Persistent (n=76)		
Aneurysmal sac diameter (mm), mean±SD	57.0±11.57	58.92±14.34		0.66
Endoleak complexity, n (%)				
Simple	7 (58.3%)	24 (31.6%)	3.03(0.87-10.5)	0.10
Complex	5 (41.7%)	52 (68.4%)		
Number of feeders, n (%)			9.9 (1.217-80.526)	0.012
≤2	11 (91.7%)	40 (52.6%)		
>2	1(8.3%)	36 (47.4%)		
Endoleak source, n (%)				
IMA	4 (33.3%)	52 (68.4%)	4.3 (1.18-15.8)	0.026
LAs	10 (83.3%)	60 (78.9%)	0.75 (0.15-3.77)	1
Median sacral artery	0 (0.0%)	2 (2.6%)	0.86 (0.79-0.94)	1
Accessory renal artery	0 (0.0%)	2 (2.6%)	0.86 (0.79-0.94)	1
Endoleak diameter (mm), median (range)	15 (6, 23)	13 (3, 62)		0.87
Attenuation (HU±SD)				
Unenhanced	43±9.4	43.86±13.77		0.835
Arterial phase	281.58±100	273.7±104.2		0.807
Delayed phase	140.1±27.14	128.9±27.47		0.257
Relative attenuation CTA	0.638±0.278	0.693±0.394		0.64
Relative attenuation delay	1.058±0.601	0.914±0.307		0.248
Sac enlargement, n (%)	0 (0.0%)	6 (7.9%)	0.854 (0.78-0.934)	0.591

A *p*-value<0.05 indicates statistical significance
Abbreviations: CTA, computed tomography angiography; CI, confidence interval; SD, standard deviation; IMA, inferior mesenteric artery; LAs, lumbar arteries; HU, Hounsfield unit

TABLE 3. Multivariate analysis.

	Odd ratios (95%CI)	*P*-value
Complexity	1.302 (0.318-5.333)	0.714
Number of feeders	5.532 (0.487-62.797)	0.168
IMA feeder	2.285 (0.557-9.365)	0.251

A *p*-value >0.05 indicates statistical significance
Abbreviations: CI, confidence interval; IMA, inferior mesenteric artery

TABLE 4. Interobserver agreement.

	Intraclass correlation coefficient (ICC, r)
Sac diameter	0.961
Number of feeders	0.635
Endoleak diameter	0.922
Attenuation measurement	0.781
	Kappa value (k)
Presence of type II endoleak	0.782
Endoleak complexity	0.779
Presence of each feeder	0.855
Aneurysmal sac enlargement	0.482

Number of feeder arteries showed a significantly greater proportion of 2 or less arterial feeders in the transient group (91.7%) than in the persistent group (52.6%); $p = 0.012$. The authors found this result to be similar to that from a study by Maeda, *et al.*[10] Maeda, *et al.*[10] found multiple vessels responsible for type II endoleak to be a significant factor for prediction of persistent type II endoleak. In the present study, that relationship did not survive multivariate analysis. This difference in results may be due to the small size of our transient group that influenced a widely ranging 95% confidence interval.

Regarding sources of type II endoleak, we found a significantly greater proportion of inferior mesenteric artery feeder in the persistent group (68.4%) than in the transient group (33.3%). According to a study by Muller-Wille R, *et al.*[8] (despite this result being not directly comparable due to differences in outcome measurement between studies), presence of inferior mesenteric artery as a feeder artery was shown to be more frequent in the aneurysm enlargement group than in the non-enlargement group.

In contrast to Timaran, *et al.*[11], Keedy, *et al.*[12], and Dudeck, *et al.*[13], the endoleak diameter measured on axial CT in our study was not significantly different between the groups. Timaran, *et al.*[11] found maximum endoleak cavity diameter more than 15 mm to be associated with increased risk of increase aneurysmal sac diameter (relative risk [RR]: 11.1, 95% CI: 1.4-85.8; p=0.02). Keedy, *et al.*[12] reported transverse diameter of the endoleak cavity in the intervention group to be significantly greater than in the nonintervention group (1.85±1.01 *vs.* 1.13±0.83 cm, respectively; p=0.007). Dudeck, *et al.*[13] also identified diameter and area of endoleak nidus in the reintervention group to be significant greater than in the surveillance group. However, our endoleak diameter study result was similar to reports from Mursalin, *et al.*[7] and Muller-Wille R, *et al.*[8], both of which reported that simple evaluation of diameter and area of endoleak cavity was not of predictive value.

Attenuation measurement of endoleak from our study showed no significant difference between that transient and persistent groups for both absolute measurement and relative attenuation. The results of absolute attenuation measurement corresponded to a report from Muller-Wille R, *et al.*[8] that reported no significant difference between the no aneurysm enlargement group and the aneurysm enlargement group.

Presence of aneurysmal sac enlargement in the present study showed no significant difference between the transient and persistent groups, and this corresponds with the findings of Kaley Pippin, *et al.*[14] However, both our study and that study had a small sized study population.

Limitations

This study has three major limitations. First, the retrospective design of this study made it difficult to control the CT protocol. Second, the small number of patients in the transient type II endoleak group may have adversely affected the ability of our statistical analysis to detect significant differences between groups. Third, our results cannot be applied in late-onset type II endoleak because we included only patients with early-onset type II endoleak.

CONCLUSION

The results of this study revealed endoleak complexity, the number of feeder arteries and presence of IMA as an endoleak source on first postoperative CTA to be more likely found in patients with persistent type II endoleak. Further prospective study in a larger study population is needed to identify any existing statistically significant differences and/or associations.

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Performance of Two Commercial Dengue NS1 Rapid Tests for the Diagnosis of Adult Patients with Dengue Infection

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ABSTRACT

Objective: to determine the diagnostic performance of two commercially available dengue NS1 antigen rapid detection tests (RDTs); namely the SD BIOLINE Dengue NS1 RDT and the ImmuneMed Dengue NS1 Rapid, for the diagnosis of adult patients with dengue infection.

Methods: The study was performed by using archived samples from 237 patients with the laboratory-confirmed dengue infection. Archived, well-characterized samples from an additional 208 febrile individuals from Thailand were used as the control group. Reference testing to confirm the diagnosis in dengue patients included RT-PCR and in-house NS1 ELISA, in-house IgM and IgG capture ELISAs.

Results: The sensitivity of the SD BIOLINE Dengue NS1 RDT was 100%, and the specificity was 99% (95%CI 96.6 to 99.7%). False positive was found in 2 samples from patient with scrub typhus. The sensitivity and specificity of the ImmuneMed Dengue NS1 Ag Rapid were 97.4% (95% CI, 95.5 to 99.5%) and 96.6% (95%CI 93.5 to 98.4%) respectively. False positive results were found in 7 patients with murine typhus, scrub typhus, and influenza.

Conclusion: Both RDTs showed comparable sensitivity and specificity in this study population. Data from this study could be used to facilitate data-driven laboratory test choices for managing patient care during dengue outbreaks.

Keywords: Dengue infection; nonstructural protein -1; adult patients; rapid detection test (Siriraj Med J 2020; 72: 74-78)

INTRODUCTION

Dengue fever is an arboviral disease that is a public health priority in most tropical countries including Thailand.[1] Dengue fever is caused by the dengue virus (DENV), a flavivirus that can be classified into four predominant serotypes (DENV-1, -2, -3, and -4).[2] DENV comprises three structural proteins (capsid, membrane, and envelope) and seven nonstructural (NS) proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5NV. DENV is transmitted by mosquitoes, principally *Aedes aegypti* and *Aedes albopictus*. Clinically, dengue fever is characterized by fever, headache, myalgia, arthralgia, rash, leukopenia, and sometimes thrombocytopenia.[2,3] The severity of the disease varies from asymptomatic or mild to severe with high fever, hemorrhage, and shock.[2,3] There is no antiviral drug to cure dengue fever.[2] The only available treatment options are supportive therapies, including bed rest, fluids, and symptomatic relief using

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analgesics. As many patients present with nonspecific fever requiring differential diagnosis, laboratory confirmation using a rapid, accurate, and relatively low-cost diagnostic test is especially important.[3] Laboratory diagnosis for DENV infection includes detection of the virus, genome, NS-1 antigen or IgM/IgG antibodies, or a combination of these tests.[2-4] Rapid diagnostic tests (RDTs), using immunochromatographic assay (ICT) to detect antigen and/ or IgM, IgG, are commonly used for DENV diagnosis because of their simplicity and rapidity.[4] Several RDTs are now widely available from different manufacturers. The sensitivities of these NS1 RDTs vary among different DENV serotype and duration of illnesses.[5] The SD BIOLINE Dengue NS1 Ag RDT (Standard Diagnostic Incorporation, Gyeonggi-do, Republic of Korea) and the ImmuneMed dengue NS1 Ag rapid (ImmuneMed, Inc., South Korea) are among the widely use RDTs in Thailand. We reported here the comparative performance of these two RDTs in adult patient with dengue infection.

MATERIALS AND METHODS

Patient population

Plasma samples were obtained from 237 adult patients with laboratory-confirmed dengue infection, as part of the clinical study of dengue infection, carried out at Siriraj Hospital, Bangkok and Loei Hospital, Loei Province, Thailand. The diagnosis of dengue infection was confirmed by RT-PCR in all patients. The dengue serotype was determined by both reverse transcriptase quantitative PCR (RT-qPCR) protocol and NS1 serotype specific ELISA.[6-9] For control group, plasma samples were collected from patients (male: female = 2:1), aged 15- 84 years (mean age 45 years) with acute febrile illnesses from Siriraj Hospital, and 4 more hospitals in Thailand (Maharaj Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, Loei Hospital, Loei Province, and Banmai Chaiyapod Hospital, Burirum Province). Blood samples were collected as a part of studies investigating the causes of fever.[10-12] All of these samples were tested by indirect immunofluorescent assay (IFA) for the diagnosis of leptospirosis, scrub typhus, and murine typhus. Details of the test and interpretation of IFA is as described previously.[10-12] In addition, 2 aerobic blood cultures were done in patients with suspected septicemia or bacteremia. All patients in the control group had negative NS1 and IgM and IgG test for dengue. These clinical studies were approved by the Ethical Review Subcommittee of the Public Health Ministry of Thailand and Siriraj Institutional Review Board Faculty of Medicine Siriraj Hospital, Mahidol University (Si 148/2019). All patients provided the informed written consent before sample collection. Plasma from patients in both groups were divided for immediate use and the leftover samples were stored at –70°C. until further used. The present study protocol was approved Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

The IFA assay for the laboratory confirmation of leptospirosis, scrub typhus, and murine typhus was performed as described previously.[6,11,12] The *Leptospira interrogans*, serovar autumnalis; pooled *O. tsutsugamushi* from Karp, Kato and Gilliam strains; and *Rickettsia typhi* (Wilmington strain) were used as the antigens for the detection of IgM and IgG antibodies for the diagnosis of leptospirosis, scrub typhus, and murine typhus respectively.

The SD BIOLINE dengue NS1 RDT and the ImmuneMed Dengue NS1 Ag Rapid were performed according to the company's instruction. In brief, approximately 80 µL of plasma was applied to the ICT sample well of each RDT, and then approximately 2 drops (80 µL) of sample diluent was added into the sample well immediately. The results were interpreted visually at 15 minutes. The test result was considered negative if only the control band was stained. If the test and control bands were stained, the test result was considered positive. Weakly positive of both RDTs was considered as positive in this study.

Statistical methods

The analysis was performed on admission samples of all patients. The standard diagnostic accuracy indices of sensitivity, specificity, with the 95% confidence intervals (CIs) were calculated, using the SPSS18.0 software (SPSS Inc., Chicago, IL, USA). We did not calculate the positive and the negative predictive value for both rapid ICT because we used the stored samples collected from various hospitals, at different period of times. As a result, the proportion of samples from patients with dengue infection did not represent the true prevalence of dengue infection among patients with acute fever in Thailand.

RESULTS

In dengue group, sample from 237 patients (M: F= 135: 102, median age 24, range 15-72 years) were tested. The median duration of fever was 2 days (range 1-5 day). Dengue -4 was the most common (n=129 or 54.4%, all secondary infection) serotype found during the collection period, followed by DENV-3 (n=52 or 21.9%, with 11.5% primary infection), DENV-2 (n=34 or 14.3%, with 8.8% primary infection), and DENV-1 (n= 22 or 9.3%, with 13.6% primary infection). The distribution of cases by

day of onset of illness and DENV serotype is shown in Fig 1. For control group, there were 208 patients with confirmed other infections including; scrub typhus, n= 65, 31.3%; murine typhus, n= 43, 207%; leptospirosis, n=41, 19.7%; influenza infection, n=24, 11.5%; zika virus infection, n= 18 (8.7%), bacteremia from various bacteria such as Escherichia coli, n=10, 4.8%, and malaria, n=7, 3.4%.

The sensitivity of SD BIOLINE Dengue NS1 Ag RDT was 100% and the specificity was 99.0% (95% CI 96.6%- 99.7%). There were 2 samples from patients with scrub typhus that had false positive SD BIOLINE Dengue NS1 Ag RDT. The sensitivity and specificity of the ImmuneMed dengue NS1 Ag Rapid were 97.4% (95.5- 99.5%) and 96.6% (95% CI 93.2-98.4) respectively. Six dengue patients with secondary infection (5 patients with DENV-4, and 1 patient with DENV-3) had false negative test. False positive test results occurred among 7 patients; murine typhus (3), zika virus infection (1), leptospirosis (1), scrub typhus (1). Details of results of the analysis is shown in Table 1.

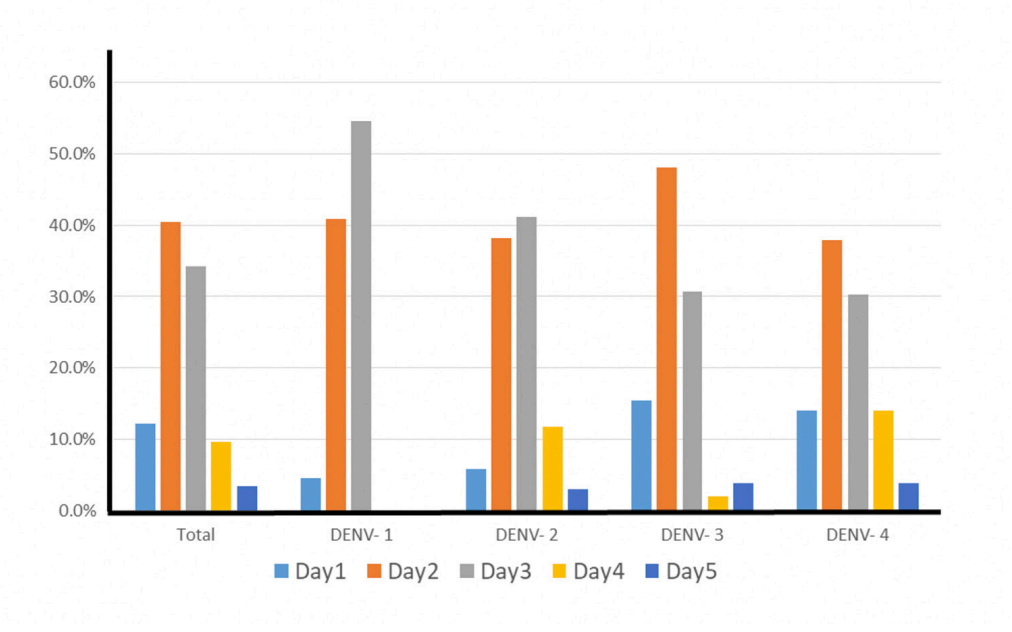

Fig 1. The distribution of samples (%) of patients with dengue infection by duration of illness in day and DENV- serotypes.

TABLE 1. Sensitivities (95%CI) and specificities (95%) compared between two RDTs for the rapid diagnosis of dengue infection in adults.

Group RDT	Dengue infection (n=237)	Other Infections (n= 208)	Total
SD BIOLINE NS1 RDT			
Positive, n	237	2	239
Negative, n	0	206	206
Total, n (%)	237 (100%)	208 (99.0%)	445
ImmuneMed NS1 RDT			
Positive, n	231	7	238
Negative, n	6	201	207
Total, n (%)	237 (97.5%)	208 (96.6%)	445

DISCUSSION

Dengue is a common cause of fever in adult patients in tropical countries. The incidence of dengue among non-malaria fever varied from 5 to 9% in these countries. In addition, recent report from Thailand indicated that a number of adult patients who died of dengue virus are misdiagnosed as severe sepsis and septic shock.[13] Thus diagnosis of dengue based on clinical features alone is difficult. Rapid NS1 antigen detection, using ICT method, is the most widely used method for the diagnosis of dengue in endemic areas.[4,5] However, the sensitivity and specificity of NS1 antigen vary, due to the different study population (children or adult), serotype circulation, immune status (primary or secondary infection) and onset of illness.[5,14,15] These factors vary from place to place and time to time. Thus we evaluated the sensitivity and specificity of two NS1 Ag RDT that are currently used in Thailand. The gold standard diagnosis of dengue infection in this study included both RT-PCR and NS1 ELISA. In this population where most adult patients had DENV-4 infection and secondary infection. Both RDT showed a comparable sensitivities and specificities. False positive of either RDTs should not explained by the coinfection of dengue with scrub typhus or murine typhus or influenza because none of them had positive of both RDTs. In addition we performed NS1 antigen detection using in-house ELISA, and none of them had detectable NS1. The SD BIOLINE NS1 RDT showed a consistent performance with the previous reports.[4,5,16] On the other hand, this is the first study for the evaluation of the ImmuneMed Dengue NS1 Ag Rapid. Although the comparable performance with the more widely used, SD BIOLINE NS1 RDT was shown, more studies with broader population ranges, to confirm result of the performance of ImmuneMed Dengue NS1 Ag Rapid, are needed.

There was a selection bias of sample of dengue patient in this study because all sample tested were collected from patient who had positive SD BIOLINE NS1 RDT as the inclusion criteria of those clinical studied. Therefore, it was not possible to calculate the true sensitivity and 95% CI of this RDT in this study. Another limitation of this study is that we only enrolled patient within 5 days of onset of illness. Although patient with suspected dengue infection were commonly presented to the hospital within this period of illness, sensitivity and specificity of both RDT beyond this duration were not determined in this study.

In conclusion, we found that both commercially point-of care NS1 antigen detection RDTs had consistent performance for the initial diagnosis of adult patient with dengue infection in the early phase of illness. This information could be used to facilitate data-driven laboratory test choices for managing patient care during dengue outbreaks.

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Comparison of an Automated Thermodynamic Treatment System (LipiFlow) and Warm Compresses for the Treatment of Moderate Severity of Meibomian Gland Dysfunction

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ABSTRACT

Objective: To compare the efficacies of a single thermodynamic treatment system (LipiFlow®) and warm compresses used for 3 months in patients with a moderate severity of meibomian gland dysfunction (MGD).

Methods: This prospective, randomized, controlled clinical study enrolled 28 patients (22 females, 6 males; mean age, 53.9 ± 14.8 years) diagnosed as having moderate MGD by plugging at the meibomian gland orifices between one-third and two-thirds of lid margins and at least one of the following: a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of 6-12; a lipid layer thickness (LLT) score of 40-70 Interferometric Color Units; upper eyelid meiboscore of 1-2; and 3-6 expressible meibomian glands (EMGs) in the lower eyelid. Both eyes of each patient were randomized into study and control eyes. Study eyes were treated with a single, 12-minute LipiFlow® system, while control eyes received 5-minute warm compresses twice daily for 3 months. The dry eye symptoms, the number of EMGs, and LLTs were evaluated.

Results: There were no significant differences in the dry eye symptoms, number of EMGs, and LLTs for both groups at baseline and at each follow-up. However, the total SPEED scores for the LipiFlow® group reduced significantly from baseline at each follow-up until 6 months. As to the warm compress group, the total SPEED scores reduced significantly from baseline at each follow-up until 3 months.

Conclusion: The single LipiFlow® treatment and twice-daily warm compresses relieved the dry eye symptoms of patients with a moderate severity of MGD compared with their baseline symptoms, despite no statistical differences in the dry eye symptoms, number of EMGs, and LLTs of both treatments.

Keywords: Meibomian gland dysfunction; warm compresses; automated thermodynamic treatment system; LipiFlow® (Siriraj Med J 2020; 72: 79-86)

INTRODUCTION

Meibomian gland dysfunction (MGD) is a chronic, diffuse, terminal duct obstruction of the Meibomian glands (MGs) involving qualitative or quantitative changes in glandular secretions.[1] It results in an alteration of the tear film and causes the majority of evaporative dry eyes, ranging from 38% to 68% of the population.[2] Patients with MGD experience eye irritation, a burning sensation, difficulty opening the eyelids, and blurred vision. The management of MGD includes the replacement of the MG

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secretion with topical oil emulsion formulations, the use of ocular ointments, the release of the MG obstruction, and the restoration of normal MG secretion. Current methods to relieve MG obstruction include eyelid margin cleansing, eyelid warming and eyelid massaging twice daily[3,4] and practitioner-administered manual expression.[5]

However, it is difficult to maintain warm compresses at a constant temperature between 32°C and 40°C (the reported melting temperature range of normal MG secretions) for 5 minutes.[6] Moreover, patients find that the twice-daily administration of an effective warm compress is both inconvenient and time-consuming, resulting in poor compliance. Although practitioner-administered manual expressions of MGs are more effective at releasing MG obstructions, their application is limited due to the associated pain. A new treatment modality, the LipiFlow® Thermal Pulsation System (TearScience Inc., Morrisville, NC, USA), may help to solve the limited success rate of warm compresses. This technology involves a single, 12-minute treatment that allows heat to be applied to the palpebral surfaces of the upper and lower eyelids directly over the MGs while simultaneously applying graded, pulsatile pressure to the cutaneous eyelid surfaces, thereby expressing the MGs during heating.[7-9] Many studies have shown that a single LipiFlow® treatment results in sustained improvement in both the signs and symptoms of MGD at 1 month,[10-12] 3 months,[9,13-15] 6 months,[16] 9 months[17] and 1 year post-treatment.[18-19] However, Finis and colleagues found that this single LipiFlow® treatment poorly benefited patients with severe MGD or MG atrophy.[16] Because of the high cost of this single LipiFlow® treatment, it is essential to identify potential non-responders or poor responders before treatment. To our knowledge, there has been no prospective, randomized, controlled clinical study of the efficacy of this treatment in patients with a moderate severity of MGD. Thus, this study evaluated the efficacy of this new treatment and compared it with the twice-daily application of warm compresses for patients with moderate MGD.

MATERIALS AND METHODS

This prospective, observer-masked, randomized, controlled clinical trial was conducted at Siriraj Hospital, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between January 2015 and June 2016. The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki for research involving human subjects (Si 725/2014; Thai clinical trial registration number: TCTR 20170905001). Written, informed consent was obtained from all patients before enrollment. The inclusion criteria were patients at least 18 years of age who had a moderate severity of MG obstruction, defined in this study as follows: the presence of plugging at the MG orifices between one-third and two-thirds of total lid margin area and at least one of the following: (1) a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of 6-12[15,20-21]; (2) a lipid layer thickness (LLT) score of 40-70 ICU (Interferometric Color Units), measured by using a LipiView® interferometer (TearScience Inc., Morrisville, NC, USA)[22]; (3) an upper eyelid meiboscore of 1-2, obtained by using a Meibography® (Oculus, Wetzlar, Germany), using the grading scales developed by Arita et al.[23]; and (4) 3-6 expressible MGs (EMGs) in the lower eyelid.[15,21] The exclusion criteria were patients with systemic diseases resulting in dry eyes (such as systemic lupus erythematosus, rheumatoid arthritis, and allergic diseases); patients who had eyelid abnormalities, previous ocular surgery, or trauma; and patients who used systemic medications affecting dry eyes (for instance, antihistamines, tetracycline derivatives, isotretinoin, and topical cyclosporine A) or steroids in the preceding month.

All patients completed the SPEED questionnaires by themselves. Then, the MGs of all patients were evaluated using a Meibography® and LLTs were measured using a LipiView® interferometer. Both the meiboscores and LLTs were measured by one examiner (P. Chonpimai). Complete ocular examinations of the anterior and posterior segments, including an assessment of the expression of the MGs of the lower eyelids of both eyes using a Meibomian Gland Evaluator (TearScience Inc., Morrisville, NC, USA), were performed by cornea specialists (W.B., P.P., S.C., and P.K. and two cornea fellows (P.N. and W.T.).

Dry eye symptoms were recorded as total SPEED scores, derived from the sum of the frequency and severity scores for all symptoms over a range from 0 to 28. A higher score represented more frequent and/or more severe symptoms.[20,24]

The number of EMGs was quantified, as described by Korb and Blackie.[21] The MGs of the lower eyelids were expressed by the Meibomian Gland Evaluator, being pressed with approximately 1.2 g/mm^2 of pressure along the distal end of the MGs at the nasal, central, and temporal parts of the lower eyelids. Each part consisted of 5 consecutive MG orifices, which meant that a total of 15 MGs were expressed. The number of EMGs was recorded.

The LLTs were ascertained by using a LipiView® interferometer, as described by Blackie et al.[22] The patients' tear film interference patterns were recorded and analyzed

as a value of interferometric color units (ICU; 1 ICU refers to approximately a 1-nm thickness of lipid layer).

The right and left eyes of each patient were randomized into a study eye and a contralateral control eye. The study eye was treated with a single, 12-minute, LipiFlow® Thermal Pulsation System, whereas the control eye was treated with a 5-minute warm compress twice daily for 3 months. The LipiFlow® treatment was utilized as described in detail by Lane et al.[11] Briefly, two drops of a topical anesthetic (0.5% tetracaine hydrochloride) were applied to the study eye prior to treatment. The LipiFlow® device applied heat (42.5°C) to the upper and lower inner eyelid surfaces directly over the MGs, while a pulsating pressure was simultaneously applied to the outer eyelids using an inflatable air bladder.[11] This device was capable of melting the MG contents without thermal injury, and of simultaneously evacuating the MGs of the upper and lower eyelids. The control eye was treated with warm compresses. The patients were instructed to soak a hand towel or washcloth in hot water, wring out the excess water, and then place the warm towel or cloth over the skin of the closed eyelids of the control eye, applying gentle pressure for 5 minutes.[6]

The study parameters were the dry eye symptoms determined by using the total SPEED scores and an assessment of the MG function, measured by the number of EMGs and the LLT scores. These three parameters were evaluated at baseline and at the follow-up times of 1 day, 1 week, 1month, 6 weeks, 3 months and 6 months.

Artificial tear eye drops (0.18% sodium hyaluronate) were prescribed for application into both eyes every 2 hours for all patients during the study.

Sample size

To calculate the sample size, a power analysis and the effect size using the data of Lane et al.,[11] which showed the improvements in the number of EMGs, were performed. On this basis, the minimum sample size was 20 patients per group. However, to ensure adequate reliability and to compensate for patient loss, 30 patients per group were enrolled.

Statistical analysis

Descriptive statistics were used to demonstrate the patients' baseline characteristics. The categorical data were described as numbers with percentages, while the continuous data were presented as mean with standard deviation (SD) or mean differences with the corresponding 95% confidence interval. The unpaired t-test was utilized to compare the continuous data of the LipiFlow® and control groups, whereas the paired t-test was used to compare the continuous data within the groups. All analyses were performed using PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA). All tests of significance were two tailed, and a p-value<0.05 was considered statistically significant.

RESULTS

A total of 33 patients were enrolled. However, only 28 completed the study because 3 patients were lost to follow-up after the baseline examination, and 2 patients did not return for the 6-month follow-up. Twenty-two patients were female (78.6%), and six were male (21.4%). The mean age was 53.9±14.8 years. There were no statistical differences in the meiboscores of the LipiFlow® and warm compress groups at baseline (p=0.745).

As to the total SPEED scores, there were no statistically significant differences between the LipiFlow® and the warm compress groups at baseline and at each follow-up (Table 1). However, in the case of the LipiFlow® group, there was a statistically significant, greater reduction in the total SPEED scores at each follow-up until 6 months, compared to the scores at baseline (Table 1). Similarly, the warm compress group showed a statistically significant, greater reduction in the total SPEED scores at the 1-week, 1-month, 6-week and 3-month follow-ups, compared to those at baseline (Table 1). However, after stopping the warm compresses at the 3-month follow-up, the total SPEED scores for the warm compress group were not changed significantly at the 6-month follow-up, compared to those at baseline (Table 1). In other words, the total SPEED scores for the warm compress group returned to near-baseline level at the 6-month follow-up after the application of the warm compresses ceased at the 3-month time point.

In a comparison of the number of EMGs of the two groups, the LipiFlow® group showed a greater increase in the number of EMGs than the warm compress group at every follow-up. Nevertheless, those greater increase were statistically significant on only two occasions: at the 1-day and the 3-month follow-ups (p=0.048 and p=0.049, respectively; Table 2).

Regarding the LLTs, there were no statistically significant differences in the LLTs of both groups at baseline and at each follow-up (Table 3). However, the warm compress group had a statistically significant greater reduction in the LLT scores at the 1-day and 1-week follow-ups, compared to those of baseline (p=0.004 and p=0.031, respectively; Table 3).

TABLE 1. Comparison of the dry eye symptoms (SPEED scores) for both groups and between baseline and at each follow-up for each group.

	SPEED scores (mean ± SD)		
	Warm compresses	**LipiFlow®**	**P-value[a]**
Baseline	9.2 ± 4.4	9.5 ± 4.5	0.781
Follow-up time			
1 day	7.4 ± 5.2	7.8 ± 4.2	0.531
Δ 1 day	-1.6 ± 4.4	-1.8 ± 2.9	
p-value[b]	0.062	0.003	
1 week	7.4 ± 4.7	7.1 ± 4.5	0.924
Δ 1 week	-2.1 ± 4.0	-2.7 ± 3.8	
p-value[b]	0.007	0.001	
1 month	6.3 ± 4.6	5.8 ± 4.1	0.731
Δ 4 weeks	-2.5 ± 4.1	-3.3 ± 3.6	
p-value[b]	0.006	<0.001	
6 weeks	6.7 ± 4.7	6.5 ± 4.2	0.777
Δ 6 weeks	-2.3 ± 5.2	-3.0 ± 4.5	
p-value[b]	0.035	0.003	
3 months	6.7 ± 4.4	6.7 ± 4.4	1.000
Δ 3 months	-2.7 ± 4.2	-2.7 ± 3.5	
p-value[b]	0.004	0.001	
6 months	7.9 ± 5.8	7.8 ± 5.3	0.954
Δ 6 months	-1.3 ± 5.1	-1.9 ± 4.7	
p-value[b]	0.238	0.034	

[a]comparison of SPEED scores for both groups, [b]comparison of SPEED scores between baseline and at each follow-up for each group, Δ = mean change in SPEED scores from baseline to each follow-up for each group

Adverse events

There were no serious, device-related, adverse events in the LipiFlow® group, and no adverse events in the warm compress group. The only device-related, adverse event was eye discomfort or pain, which occurred among patients with small eyes, narrow palpebral fissure, or deep-set eyes.

DISCUSSION

The present study showed that both the single, 12-minute, thermodynamic treatment system (LipiFlow®) and the twice-daily warm compresses were able to relieve the dry eye symptoms of patients with a moderate MGD compared to their baseline symptoms, despite there being no statistical differences in the dry eye symptoms for both treatments. In fact, the dry eye symptoms of the LipiFlow® group decreased faster at the first day post-treatment, and they continued to decrease to 6 months post-treatment. In contrast, the dry eye symptoms of the warm compress group began to reduce later, at the one-week follow-up, and sustained the reduction only while the participants applied the warm compresses twice daily for 3 months. When they stopped the warm compresses, their symptoms reappeared. Many studies[9-19] have reported that a single LipiFlow® treatment had a statistically significant greater reduction in dry eye symptoms than warm compresses at 1 month until 1 year post-treatment. In contrast to those findings, the

TABLE 2. Comparison of the number of expressible meibomian glands (EMGs) for both groups and between baseline and at each follow-up for each group.

	The number of EMGs (mean ± SD)		
	Warm compresses	LipiFlow®	P-value[a]
Baseline			
Follow-up time	2.5 ± 2.3	2.6 ± 2.8	0.885
1 day	2.0 ± 2.0	3.0 ± 2.0	0.048
Δ mean (95%CI)	-0.7 (-1.6, 0.2)	0.3 (-1.2, 1.7)	
p-value[b]	0.156	0.536	
1 week	2.5 ± 2.1	3.7 ± 3.3	0.153
Δ mean (95%CI)	-0.1 (-1.1, 1.0)	1.3 (-0.5, 3.0)	
p-value[b]	0.951	0.152	
1 month	2.6 ± 2.2	3.5 ± 3.1	0.471
Δ mean (95%CI)	0.1 (-1.1, 1.3)	0.7 (-0.8, 2.2)	
p-value[b]	0.847	0.352	
6 weeks	2.3 ± 2.4	2.4 ± 2.3	0.827
Δ mean (95%CI)	-0.4 (-1.7, 0.9)	-0.6 (-2.1, 1.0)	
p-value[b]	0.556	0.660	
3 months	2.3 ± 2.0	3.6 ± 2.2	0.049
Δ mean (95%CI)	-0.3 (-1.4, 0.8)	0.8 (-0.5, 2.0)	
p-value[b]	0.494	0.066	
6 months	2.7 ± 2.2	3.1 ± 2.1	0.369
Δ mean (95%CI)	0 (-1.2, 1.2)	0.3 (-1.1, 1.6)	
p-value[b]	0.862	0.557	

[a]comparison of the number of EMGs for both groups, [b]comparison of the number of EMGs between baseline and at each follow-up for each group, Δ mean (95%CI) = mean change in the number of EMGs from baseline to each follow-up for each group (95% confidence interval)

results of the present study were the same as those of other reports[16,25] that did not demonstrate a statistically significant difference in the dry eye symptoms between the single LipiFlow® treatment and the twice-daily warm compresses, nor in the number of EMGs and LLTs, despite a tendency to improve those three parameters in the patients receiving the LipiFlow® treatment. The current study could not demonstrate a statistical difference in the dry eye symptoms of both treatments, and the mean SPEED scores found in this study were less than those reported by other researches.[8-12,17-18] This may be due to the small sample size and the enrollment of only patients with a moderate MGD.

Concerning the MG function, the number of EMGs and LLT scores were evaluated. The number of EMGs was derived from the number of MGs in which the obstructed meibum had been melted and was able to be squeezed through the opening of the MG ducts. This implied that the MG obstruction was relieved by melting the stagnated lipid of MGs, which subsequently flowed through the ducts and passed out their openings. Consequently, LLTs should be increased as per a report[26] that showed a significant correlation between EMGs and LLTs. Although the present study found that the LipiFlow® treatment resulted in a greater number of EMGs than the warm compresses at each follow-up, those greater

TABLE 3. Comparison of lipid layer thicknesses (LLTs) for both groups and between baseline and at each follow-up for each group.

	LLT scores (mean ± SD)		
	Warm compresses	**LipiFlow®**	**P-value[a]**
Baseline			
Follow-up time	74.9 ± 18.8	70.3 ± 19.9	0.368
1 day	65.4 ± 19.6	65.5 ± 19.0	0.984
Δ mean (95%CI)	-9.4 (-15.6, -3.2)	-6.4 (-13.1, 0.3)	
p-value[b]	0.004	0.062	
1 week	69.0 ± 18.8	65.5 ± 15.9	0.491
Δ mean (95%CI)	-8.5 (-16.1, -0.9)	-5.5 (-15.0, 3.9)	
p-value[b]	0.031	0.238	
1 month	65.0 ± 18.4	69.7 ± 19.9	0.520
Δ mean (95%CI)	-7.6 (-15.7, 0.4)	-2.4 (-12.7, 8.0)	
p-value[b]	0.062	0.630	
6 weeks	73.8 ± 18.0	75.7 ± 16.7	0.798
Δ mean (95%CI)	-1.3 (-15.0, 12.3)	-1.4 (-7.4, 4.6)	
p-value[b]	0.834	0.613	
3 months	80.6 ± 17.8	76.4 ± 13.3	0.491
Δ mean (95%CI)	1.9 (-6.8, 10.7)	5.6 (-5.3, 16.4)	
p-value[b]	0.642	0.286	
6 months	67.1 ± 23.0	66.9 ± 21.2	0.979
Δ mean (95%CI)	-8.0 (-16.9, 0.8)	-2.2 (-12.3, 8.0)	
p-value[b]	0.073	0.662	

[a]comparison of LLT scores for both groups, [b]comparison of LLT scores between baseline and at each follow-up for each group, Δ mean (95%CI) = mean change in LLT scores from baseline to each follow-up for each group (95% confidence interval)

numbers were only statistically significant at the 1-day and 3-month follow-ups. In other words, our study demonstrated that the automated LipiFlow® began to be effective at an earlier time than the warm compresses. As the result of releasing the MG obstruction, LLTs should be evaluated. The current study did not show a statistically significant difference in the LLTs of both groups at baseline and at each follow-up, which is different from the findings of previous studies.[16,27] Although the LLT scores post-LipiFlow® treatment increased insignificantly from baseline, the LLT scores for the warm compress group surprisingly decreased significantly at the 1-day and 1-week follow-ups. This may be due to the small sample size, difficulties in controlling the temperature of the warm compresses, or the enrollment of only patients with a moderate MGD. With that MGD severity, the obstructed meibum needs a higher temperature than the heat provided in a recent program of LipiFlow® and the warm compresses in order to achieve the melting point of the obstructed meibum for severely-affected patients, as reported by Bron et al.[6] and Finis et al.[16] Moreover, the application of the warm compresses needs a great deal of attention to the procedures described in previous studies[3,4] to achieve constant and sufficient heat, and the warm compresses hardly provide a high enough degree of heat to melt the obstructed meibum in patients with moderate to severe MGD. This may explain the surprising result of the significant decrease

in the LLT scores at the 1-day and 1-week follow-ups for the warm compress group. In addition to inadequate temperatures, the formulation of the lipid or meibum in cases of moderate MGD is not normal lipid.[6] Thus, it cannot be easily expressed through the MG duct to its opening to increase the LLT. Even though the results of our study could not show that the effectiveness of the single LipiFlow® treatment was significantly superior to that of the warm compresses, the dry eye symptoms and the number of EMGs of the patients with moderate MGD tended to improve better when they were treated with the LipiFlow® system. The advantages of a single, 12-minute, automated thermodynamic LipiFlow® treatment are that it is less painful than manually expressing the MGs, less time-consuming than the warm compresses, and convenient due to the absence of any self-administered treatment, Moreover, a single treatment has been reported to have a prolonged effect by easing MGD for at least the following 6 months and for up to 3 years.[16-19,28] Nevertheless, the LipiFlow® treatment has several disadvantages: its high cost; the LipiFlow® devices' use of too large an eye cup and lid warmer parts for Asian eyes; and its potentially lower effectiveness for moderate and severe degrees of MGD or MG atrophy, as reported by earlier studies.[16,25,29]

The limitations of this study were its small sample size; a high female to male ratio; the enrollment of only patients with a moderate MGD; no assessment of the tear break-up time; no ocular surface staining; no Schirmer test and an incapacity to monitor the temperature of the hot water and the warm compress procedures performed by the patients at home. There were also disadvantages in having the study eye and the contralateral control eye in the same patient, such as the possibility of an inter-eye interaction and an inability to mask the patients to the specific treatment given to each eye. This may have had some impact on the subjective results, such as the SPEED scores. Since the patients with a moderate severity of MGD had obvious symptoms of dryness, a long follow-up duration of 6 months without any tear supplements might have caused corneal complications. However, the application of the artificial tear eye drops every two hours by the patients in both groups could have improved some of the symptoms of dry eyes, resulting in better SPEED scores being reported by both groups.

On the other hand, the advantages of the present study were that it was a prospective, observer-masked, randomized, controlled clinical trial comparing both treatments in the same patient, which enabled control of the internal factors of both trial groups and provided a long follow-up time of 6 months.

CONCLUSION

The single LipiFlow® treatment and the twice-daily warm compresses relieved the dry eye symptoms of the patients with moderate MGD compared with their baseline symptoms, despite there being no statistical differences in the dry eye symptoms, the number of EMGs, or the LLTs of both treatments.

Further studies should be conducted with a larger sample size and investigated by classifying the patients as having mild, moderate and severe degrees of MGD. In the future, the LipiFlow® system should develop a new program for the treatment of moderate and severe degrees of MGD by slightly increasing the heat or increasing the duration of the treatment or its repetition during a specific time period. Moreover, the eye cup and lid warmer parts of the LipiFlow® system should be available in an optional, smaller size for Asian eyes in order to apply an adequate amount of heat and effectively massage the eyelids.

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Overview of Surgical Therapies for Obstructive Sleep Apnea: a Concise Review Literature

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ABSTRACT

The surgical therapy of Obstructive Sleep Apnea (OSA) requires addressing anatomical obstructions or collapse of the pharyngeal airway by skeletal and soft tissue surgeries. Numerous surgical options have been documented for OSA therapy with varying success. OSA surgery is vital when patients refuse continuous positive airway pressure (CPAP). The aim of this article is to review surgeries for OSA and the effectiveness of each surgery in terms of Epworth sleepiness scale (ESS), Apnea Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) reduction.

Keywords: Obstructive sleep apnea; continuous positive airway pressure; epworth sleepiness scale; apnea hypopnea index; respiratory disturbance index (Siriraj Med J 2020; 72: 87-94)

INTRODUCTION

Obstructive sleep apnea (OSA) is a medical condition characterized by episodes of partial (hypopnea) or complete (apnea) constriction of the upper airway during sleep. Patients with untreated OSA are usually afflicted by excessive daytime sleepiness (EDS), which is a symptom that has been associated with an increased risk of motor-vehicle[1] and workplace accidents.[2] Moreover, several reports have linked OSA with various cardiovascular events such as stroke,[2,3] myocardial infarction,[4] and hypertension.[5] Nowadays, the usual first-line therapy for OSA is continuous positive airway pressure (CPAP). Although CPAP is still regarded as the gold-standard therapy for OSA the non-adherence rate of patients to CPAP has been documented to be as high as 34.1% (based on studies over a twenty-year time frame).[6] Consequently, CPAP non adherent patients are then managed by surgery either to increase CPAP compliance[7] or to effectively reduce the Apnea Hypopnea Index (AHI) or Respiratory Disturbance Index (RDI) to a level that alleviates the need for CPAP.[8] However, each surgical modality comes with distinct pros and cons, and it is up to the clinician to weigh them for the patient's best interest. This article serves to review the surgical treatments for OSA.

Diagnosis of OSA

Polysomnograhy (PSG) is the most accurate method for diagnosing the presence of OSA, and the severity of OSA is usually based on the Apnea Hypopnea Index(AHI): Mild OSA (5-14.9), Moderate OSA (15-29.9) and Severe OSA(≥30).[9] The PSG is incapable of determining the exact anatomical location of the obstruction or collapse. Anatomical obstructions could be well demarcated deformities of the soft tissues that

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TABLE 1. The abbreviations were used in this concise review literature.

Full name word	Abbreviation
Obstructive sleep apnea	OSA
Excessive daytime sleepiness	EDS
Continuous positive airway pressure	CPAP
Apnea hypopnea index	AHI
Respiratory disturbance index	RDI
Polysomnograhy	PSG
Drug induced sleep endoscopy	DISE
Velum, oropharynx lateral wall, tongue base and epiglottis	VOTE
Uvulopalatopharyngoplasty	UPPP
Genioglossus advancement	GGA
Laser assisted uvulopalatoplasty	LAUP
Radiofrequency ablation	RFA
Radiofrequency	RF
Maxillomandibular advancement	MMA
Bilateral sagittal split ramus osteotomy	BSSRO
Hypoglossal nerve stimulation	HGNS
Transoral oral robotic surgery	TORS

can be visualized through physical examinations, fiber optic pharyngoscopy and lateral cephalograms. These obstructions generally remain constant, regardless of whether the patient is awake or sleeping.[10] Some forms of obstructions or collapse occur as a result of a narrowing of certain anatomical sites such as the lateral pharyngeal wall or tongue during sleep.[10] Complete concentric collapse of the velum during sleep is one of the main determinants of failure of OSA surgery.[11] Therefore, drug induced sleep endoscopy (DISE) has become vital for selecting the right treatment plan in OSA cases.[12] The main anatomical structures that are visualized and evaluated via DISE are the Velum, Oropharynx lateral wall, Tongue base and Epiglottis (VOTE).[12] Besides aiding in diagnosis, DISE post-operation gives an objective and dynamic visualization of the airway, and provides a key marker for success which is the stability of the lateral pharyngeal wall.[13]

Tracheostomy

The tracheostomy as a procedure for resolving hypoventilation was first proposed in 1965 by Valero and Alroy, and the case report featured a 55 year old male with chronic traumatic micrognathia who complained of excessive sleepiness which improved after tracheostomy.[14] Multiple preceding reports up until the early of 1980s reaffirmed the tracheostomy as the surgery of choice for OSA, particularly in morbidly obese patients.[15-17] However, the complications of tracheostomy include minor hemorrhage, cuff leakage, and in severe cases tube obstruction which could lead to death.[18] There is an inevitable reduction in the quality of life of patients following tracheostomy due to speech problems, body image issues, and daily physical limitations.[19] Therefore, the American Academy of Sleep Medicine recommended that tracheostomy should only be used when all other treatment options have been exhausted and failed or when clinically urgent.[20]

Nasal surgeries

The consensus on nasal surgery as a stand-alone procedure for OSA is that it improves daytime sleepiness and snoring, but does not reduce AHI scores.[21] Nevertheless, OSA patients with increased nasal resistance from hypertrophic inferior turbinate and deviated septum are often non-adherent to CPAP.[22] Nasal surgeries increase the nasal airflow and reduce the pressure requirements on CPAP therefore improving CPAP adherence.[21,22] Nakata et al.,[22] found significant reduction of nasal resistance measured via Rhinomanometry after inferior turbinectomy and submucus resection of nasal septum was done on CPAP non-compliant patients. ESS scores post-op improved from 11.7±4.1 to 3.3 ±1.3.

Uvulopalatopharyngoplasty

The Uvulopalatopharyngoplasty (UPPP) is a surgery that was first developed by Ikematsu in the 1950's for the reduction of snoring, his findings were later published in 1964.[23] In 1981 Fujita et al.,[24] introduced the UPPP technique (Fig 1) to English-speaking surgeons.

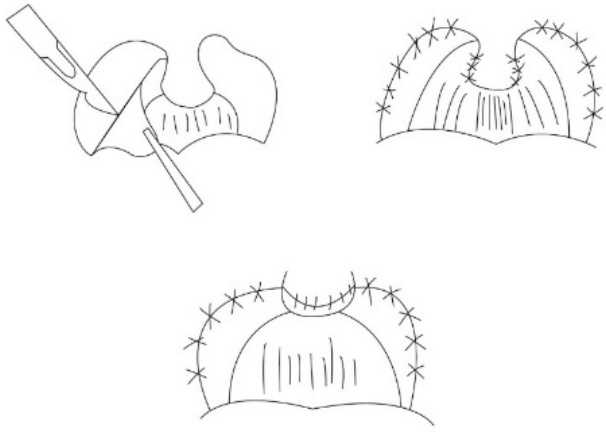

Fig 1. Fujita Uvulopalatopharyngoplasty.

Thereafter, the UPPP became a common procedure despite the lack of evidence supporting its efficacy especially as a stand-alone surgery in the treatment of moderate to severe OSA.[20] Sher et al., concluded in a meta-analysis that only 40.79% of patients who had undergone UPPP exhibited success in terms of AHI reduction of 50 % or AHI less than 20.[25] The UPPP entails the widening of the oropharynx space by means of shortening the uvula thus, long-term side effects include dysphagia, nasal regurgitation, dysphonia, and throat pain.[26] When a staging system that is based on the anatomy of the palate is used, the success of the UPPP could be more predictable.[27] Friedman et al., had success in 80.6% of Friedman stage 1 (entire uvula, tonsils or pillar are visible when tongue is in a neutral position) cases that had UPPP. [28]

Genioglossus advancement with/without hyoid myotomy

Riley et al., first documented success with genioglossus advancement (GGA) and hyoid myotomy as part of a multi-step surgical protocol. GGA was done via a genial tubercle rectangular window which was advanced and rotated before fixation whereas hyoid myotomy involved the suspension of the hyoid bone over the thyroid cartilage.[29] Neruntarat replicated the same technique under local anesthesia on 31 OSA patients with hypopharynx obstruction as diagnosed by polysomnography and awake nasopharyngoscopy, and the RDI improved from 48.2±10.8 to 14.5±5.8.[30] Both studies utilized additional UPPP for the correction of retropalatal obstructions. In 2017 Vargo et al.,[31] documented recently GGA as a stand-alone surgery for OSA with success in terms of mean AHI reduction (36/h to 4.3/h). Vargo et al., also advocated a sliding genioplasty (Fig 2) as opposed to genial tubercle window in isolated GA cases for better cosmetic outcomes and the possibility of larger advancements with glossoplexy sutures.[31]

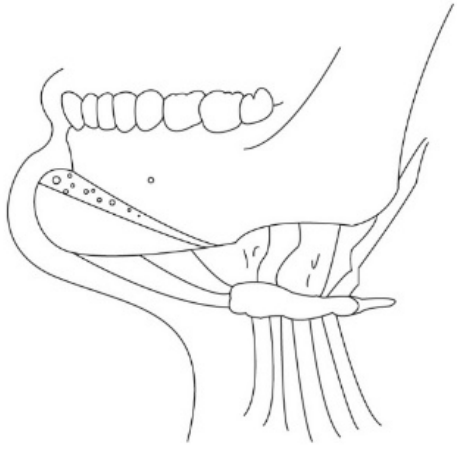

Fig 2. Sliding Genioplasty. The genial osteotomy should involve the anterior inferior border of the mandible to advance the genioglossus and suprahyoid muscles.

Laser assisted uvulopalatoplasty

Laser assisted uvulopalatoplasty (LAUP) is an outpatient procedure for OSA therapy that could be performed under local anesthesia without the risk of hemorrhage. Kamami[32] was the first proponent of the LAUP as a treatment modality for OSA. In a 1994 publication' Kamami[32] documented 43.4% resolution of OSA, with only 13% non-responders after multi session LAUP. In a similar vein, Peng et al., reported a 79.17% rate of effectiveness based on polysomnography results

from 96 patients who had received LAUP.[33] Contrarily, Göktas Ö et al., found worsening AHI scores (>5/h) post LAUP in 12 out of 25 patients.[34] A recent meta-analysis and systematic review by Camacho et al., recommended clinicians either to abandon LAUP as a therapy for OSA or to perform it with caution because individual data revealed 44% of cases with worsening AHI following LAUP.[35] Camacho et al., attributed the deterioration of OSA after LAUP to the destruction of the soft palate surface which leads to the reduction of the reflexogenic dilation of the upper airway.[35]

Radiofrequency ablation

Radiofrequency ablation (RFA) is considered a conservative procedure that involves the insertion of a Radiofrequency (RF) electrode probe into the submucosa of the soft palate or the tongue to decrease the size of these structures. RFA is usually delivered at low temperatures to prevent post-operative pain and discomfort. Powell et al., pioneered the use of RFA in mild sleep disordered breathing in 1998 by inserting a custom RF electrode to the soft palate under local anesthesia, and after 8 to 12 weeks, radiographic results showed a mean shrinkage of 5.5±3.7 mm which objectively improved ESS scores (8.5±4.4 to 5.2±3.3) and the mean 95th percentile inspiratory nadir (-19.71±5.29 cm to -12.78±6.28) cm H_2O.[36] Powell et al., followed up in 1999 with the RFA of the dorsal surface of the tongue demonstrating positive results in tongue size reduction (-17%), mean RDI (39.6 to 17.9) and mean SaO_2 nadir (81.9% to 88.3%).[37] Additionally, Riley et al., found promising results (mean AHI 35.1 to 15.1) after multiple RFA applications to the ventral and dorsal surface of the tongue. In a study on Thai patients, Sonsuwan et al., documented 16 out of 51 patients that had AHI scores of < 5 following RFA of the soft palate. These 16 patients had lower baseline AHI scores pre-op which was inferred as a key factor of success in RFA for OSA.[38]

Maxillomandibular advancement

Maxillomandibular advancement (MMA) routinely involves a Lefort 1 osteotomy (Fig 3) and Bilateral Sagittal Split Ramus Osteotomy (BSSRO) (Fig 4) with or without genioplasty advancement. Although MMA is usually performed on moderate to severe OSA patients with retrognathic maxilla and mandibles, some OSA cases with class 1 skeletal relationships could be candidates for MMA as well.[39] Morbidly obese patients who are non-adherrent to CPAP have been documented to respond favorably after MMA.[40,41] Despite morbid obesity not being a definite contraindication for MMA, the effectiveness of MMA in this group of patients remains inconclusive due to the lack of data and insufficient studies.[42] Clear indications to perform MMA as a first line surgical therapy includes retrognathic jaws, severe OSA and cases with complete concentric closure of the velum and lateral pharyngeal wall diagnosed with DISE.[38]

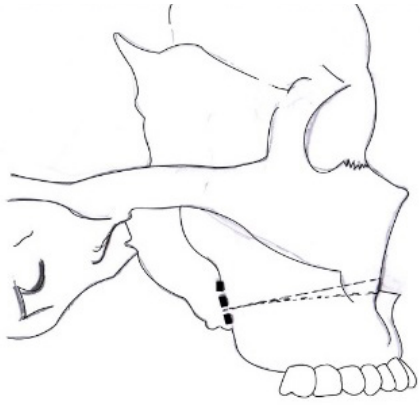

Fig 3. Lateral view (1 side) of a Lefort 1 osteotomy. The thick dotted lines show the osteotomies at the pterygomaxillary junction. The thin dashed lines show the horizontal osteotomies that form a wedge shape which facilitates anti-clockwise movement of the maxilla.

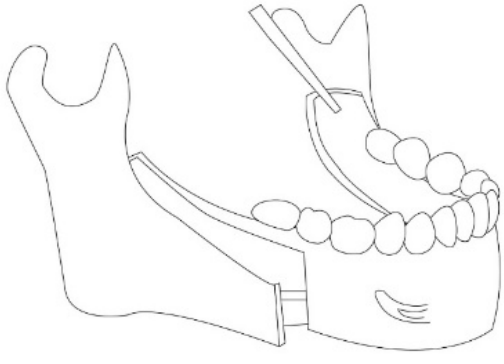

Fig 4. Bilateral sagittal split osteotomy of the mandible. Necessary precautions are necessary to prevent inferior alveolar nerve injury.

The Stanford MMA technique developed by Powell and Riley has allowed larger advancements, up to 10 mm in the maxilla and 11 mm in the mandible which effectively expands the upper airway space without the need for hyoid suspension.[43] An updated version of this technique involves Lefort 1 and Bilateral Sagittal split osteotomies with the maxillomandibular complex rotated in an anti-clockwise manner to maximize esthetic results and tension of the lateral pharyngeal wall.[39]

The success rate of MMA for OSA when performed in either phase 1 or phase 2 of the Stanford protocol has been reported to be more than 90% in patients with BMI<40 and 81% in patients with BMI>40.[43] Studies that conducted 3-dimensional Computer Tomography analysis of the upper airway in a static model post MMA

documented improvement in retropalatal and retroglossal parameters.[44,45] With the aid of DISE, dynamic measurements were recorded post MMA which revealed the lateral pharyngeal wall tension during sleep as a significant marker for success.[13] Kastoer et al., documented promising results with MMA for treating OSA patients with complete concentric collapse of the velum by eliminating the complete closure thereby reducing the AHI values by 9.9 ± 7.2 events per hour from a baseline of 40.2 ± 25.6 events per hour.[46]

Despite the high success rates and predictability of MMA as a treatment for OSA, the advancement of the maxillomandibular complex will undoubtedly alter the facial aesthetics of an individual. Li et al., conducted a questionnaire survey on patients 6 to 12 months after MMA for OSA, and 55% (24/44) of the patients reported feeling more attractive or youthful whereas 4 patients felt unfavorable changes to their facial appearance.[47] Large Lefort 1 advancements causes nasal flaring. Liu et al., reported the need for corrective nasal surgery in 18.7% of patients after MMA.[48] These unfavorable cosmetic results after MMA could be more pronounced in Asians, because Asians tend to have lips that are more outwardly projected[49] and flatter nasal bridges.[50] With this in mind, Liao et al., proposed a modified MMA technique for Asians that added anterior segmental osteotomies from premolar extraction sites, and they found a marked reduction in mean AHI scores (41.6±19.2/h to 5.3±4.0/h) with improved facial aesthetics post operation.[50] Nonetheless, according to Liu et al., MMA in Asians improves their facial appearance therefore surgeons should not be deterred from using MMA as a modality to resolve OSA in Asians as long as proper planning is done prior to surgery.[51]

Recently, a prospective multicenter study which evaluated the success of MMA for OSA reported significant improvements in mean ESS (13.3 to 4.9) and AHI (39.6 to 7.9) values.[52] These results are consistent with the 2016 meta-analysis by Zaghi et al., which documented 98.8% improvement in AHI and RDI values after MMA, based on 45 studies with a total of 518 unique cases.[53] Every surgery carries risks and potential complications, likewise MMA is an invasive surgery that could cause numbness, pain and swelling around the maxillofacial region.[53] Adverse events such as plate exposure and wound infection especially in the mandible may arise following MMA surgery.[52]

Hypoglossal nerve stimulation

In 1993 the influence of hypoglossal nerve stimulation (HGNS) on the upper airway was first studied in cats by Schwartz et al.[54] In 2011 Eastwood et al., conducted the first human trials with HGNS, with 21 CPAP non-compliant patients with moderate to severe OSA who were included in that trial, and 19/21 had polysomnography results at baseline and 6 months after HGNS device installation. AHI scores improved from 43.15±17.5/h to 19.5±16,7/h, ESS scores reduced from 12.1±4.7 to 8.1±4.4.[55] Subsequently, a multicenter prospective single-group clinical trial (STAR trial) with 126 participants was performed to assess the efficacy of HGNS for moderate to severe OSA, and the mean AHI demonstrated improvement after 12 months of HGNS (32.0±11.8 to 15.3±16.1).[56] Additionally, 116 of the 126 participants from the STAR trial were reviewed again after 36 months, and 98 agreed to a polysomnography test at 36 months after HGNS implantation. The results demonstrated stable AHI and ODI in these participants, thus, proving the long-term effectiveness of HGNS for moderate to severe OSA.[57] HGNS offers CPAP non-compliant OSA patients who are averse to facial skeletal changes from MMA, an effective second-line treatment option. However, one of the contraindications in HGNS is the complete concentric closure of the velum during DISE examination, so these cases are best treated with MMA.[39]

Palatal implants

Palatal implants or pillar implants are plastic implants that are inserted into the soft palate to stiffen the soft palate in OSA or snoring (Fig 5). Pillar implants have been largely effective in mild to moderate OSA.[58,59] In 2008 A randomized double-blinded placebo clinical trial was conducted by Friedman et al., with encouraging results after palatal stiffening with polyester implants (AHI reduction was -7.9±7.7).[58] In 2013, a meta-analysis published by Choi et al., found improved ESS and AHI scores post pillar implantation in mild and moderate OSA. Pillar implants were also found to have an overall low complication rate which was mostly trivial in nature.[59]

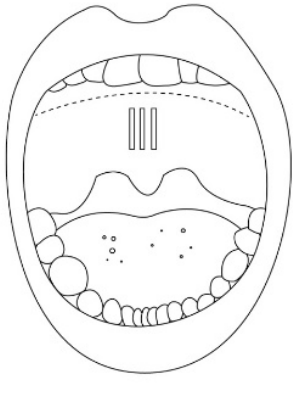

Fig 5. Pillar/palatal implants. The implants help stiffen the palate to prevent collapse.

Transoral robotic surgery

Transoral oral robotic surgery (TORS) was introduced by Vicini et al., and they documented tongue base reduction, supraglottoplasty, nasal surgeries and UPPP with the Da Vinci Robot.[60] Vicini et al., reported AHI reduction in 8 out of 10 patients after TORS, although 2 patients had worsening AHI.[60] In 2019, Vicini et al described TORS supraglottoplasty and tongue base reduction in detail, and they advocated TORS due to the precise dissection and acceptable surgical time (30minutes for tongue base reduction, and 15 minutes for Supraglottoplasty).[61] Despite accurate and minimally invasive surgeries, TORS is still not cost effective enough to warrant widespread use. Because of the price of the Da Vinci Surgical System, only selected OSA cases with tongue base hypertrophy and epiglottis collapse could potentially benefit from TORS.

DISCUSSION

CPAP is recommended as the first-line therapy in adult OSA cases but non-compliance remains a tough conundrum for patients and clinicians. McEvoy et al., published an alarming study in the New England Journal of Medicine which documented the ineffectiveness of CPAP for preventing cardiovascular events in moderate to severe OSA cases.[62] These findings coupled with the CPAP non-compliance rate could surmise a need for a shift in ideology wherein surgery is placed as a first-line therapy which fixes the etiology of OSA, particularly in cases with notable anatomical obstructions. Rotenberg et al., concluded in a systematic review that CPAP should no longer be regarded as gold-standard therapy, because of the high non-compliance and the long-term success of various surgical options. A glaring deficiency in the majority of CPAP studies is the short-term follow-up compared to the longer follow-up period in many surgical trials.[63]

MMA is currently deemed as the most effective surgical modality aside from tracheostomy for moderate to severe OSA. The advancement of the maxillo-mandibular complex causes an increase in the width of the upper airway length and tension of the lateral pharyngeal wall at the expense of facial aesthetics for some patients. Therefore, proper treatment planning and careful consideration of the baseline skeletal anatomy is needed for an acceptable outcome. Although a modified MMA technique with anterior segmental osteotomies to accommodate Asian anatomy showed promising results,[50] further research with long-term follow ups and larger samples are required to generalize this effectiveness. UPPP is very effective in selected mild to moderate OSA cases based on Friedman's staging system. CPAP non-compliant patients require thorough examination of their nasal anatomy via nasal endoscopy because nasal surgeries are proven to increase CPAP compliance. Some OSA patients that are ideal candidates for MMA may refuse MMA, in these cases, OSA can be managed with a combination of UPPP, nasal surgeries and HGNS.[64]

OSA is a chronic disease with no definite cure, and Liu et al., proposed an extension of the Stanford protocol when they documented for the first time a case of relapsed OSA in a 65 years male previously treated with 2 phases of surgeries: MMA when he was 49; UPPP, septoplasty and RFA of tongue when he was 60.[65] The latest surgery on the patient was the implantation of a HGNS device which reduced ESS to 6 and effectively reduced AHI to 1 or less depending on sleep position.[65] The authors of this review believe that customized treatment planning and multiple surgeries are necessary for the long-term stabilization of moderate to severe OSA. Therefore, ENT surgeons and oral and maxillofacial surgeons who deal with OSA should be equipped with all the surgical skills to offer patients the most appropriate treatment plan.

CONCLUSION

CPAP non-compliant patients with moderate to severe OSA require surgical therapy to either resolve OSA or to increase CPAP adherence. Further research in each surgical modality for OSA should be conducted for assessing the efficacy and long-term success rates. Currently, MMA is the only surgical modality aside from tracheostomy that could provide consistent AHI and RDI reduction in moderate to severe OSA caused by multilevel obstructions, although research documenting MMA as an isolated first line procedure is scarce. As of today, we can conclude that moderate to severe OSA in CPAP non-compliant patients is best treated with surgeries that fix multilevel obstructions. Additionally, Hypoglossal nerve stimulation could play a more important role in the future in cases with relapsed OSA who have already undergone multiple surgeries.

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