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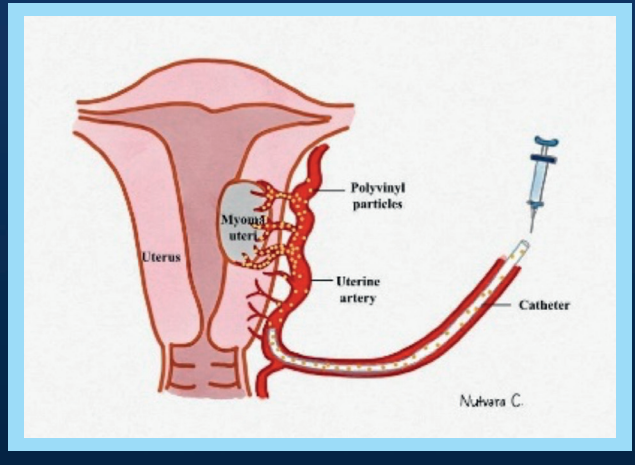

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A Randomised Controlled Trial of the Efficacy and Safety of 0.25% Desoximetasone Cream (Topoxy) Compared with 0.25% Desoximetasone Cream (Topicorte) for the Treatment of Scalp Psoriasis

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ABSTRACT

Objective: To compare the efficacy and safety of a generic desoximetasone cream (Topoxy) with the reference form, Topicorte, for the treatment of scalp psoriasis.

Methods: A randomised, double-blind, controlled study was conducted. Altogether, 105 patients with psoriasis lesions covering more than 10% of the scalp were randomised into three groups. The first, second and third groups received a placebo, Topoxy and Topicorte, respectively. The scalp psoriasis severities were assessed at weeks 0, 2, 4 and 8, using the Investigator Global Assessment (IGA) scale and Total Sign Score (TSS). The safety profiles of the products were assessed by the patients and physicians.

Results: Topoxy and Topicorte were significantly more effective than the placebo in achieving at least a two-grade improvement in the IGA score from baseline at weeks 2, 4 and 8, and there were no significant differences between Topoxy and Topicorte. The TSS of both creams were significantly lower than that of the placebo at weeks 2, 4 and 8. All patients tolerated well to the therapy.

Conclusion: Topoxy and Topicorte had comparable efficacies for scalp psoriasis. The medications were superior to the placebo in all parameters, and had a good safety profile.

Keywords: Desoximetasone cream; scalp psoriasis; topicorte; topoxy (Siriraj Med J 2020; 72: 371-379)

INTRODUCTION

Psoriasis is a chronic, immune-mediated, skin condition that is caused by an abnormal proliferation and differentiation of the epidermis. It affects 2%–3% of the global population, depending on the geographic area being studied.[1] Scalp psoriasis is found in up to 80% of psoriasis patients, and it proves to be troublesome and frustrating to most patients.[2] It is characterised by erythematous plaques with silvery scales that cause itching and discomfort.[3] Scalp psoriasis is generally hard to treat because the affected areas are mostly covered with hairs, which act as a physical barrier to topical medications.[2] The medications currently used to treat scalp psoriasis are topical corticosteroids, topical vitamin D analogues and tar shampoo.[4] Monotherapy with a topical steroid has proven to be acceptable for use as a short-term therapy

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for scalp psoriasis.[4] Topical moderate- to high-potency corticosteroids such as 0.05% clobetasol propionate, 0.25% desoximetasone, 0.1% betamethasone valerate and 0.05% betamethasone dipropionate are recommended for adult patients.[2] Cutaneous side effects of topical steroids on the scalp are rare.[5-7] Some of the reported adverse effects are skin discomfort, irritation, skin atrophy and telangiectasia.[8]

The topical corticosteroid desoximetasone is used for scalp psoriasis because of it has high efficacy with limited side effects.[9-11] Several formulations of the medication are available in the market. Topical 0.25% desoximetasone cream (Topicorte) is the reference form and is widely used. Recently, a generic formulation of the 0.25% desoximetasone cream, Topoxy, has been developed. However, Topoxy is relatively new, and its efficacy and safety have never been tested in a randomised control trial. Therefore, we conducted the present study to compare the efficacy and safety of 0.25% desoximetasone cream, Topoxy, with the reference form, Topicorte.

MATERIALS AND METHODS

Study design

A double-blinded, randomised, and placebo- and active comparator-controlled drug trial was conducted October 2016 to December 2018 at the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University. The trial was registered with ClinicalTrials.gov identification number NCT02749656. Patients were randomised into 3 groups using GraphPad Prism 5.00 for Windows (GraphPad Software, San Diego, CA). The first group received a placebo with tar shampoo; the second received Topoxy with tar shampoo; and the third was given Topicorte with tar shampoo. Patients were requested to apply the scalp cream twice daily with the recommended dosage of 1 ml or 3.5 grams of product per ten percent of total area of scalp affected and to use the tar shampoo regularly.

Subjects

This study enrolled 105 scalp psoriasis patients. The inclusion criteria were as follows: being over 18 years of age; having had a dermatologist give a diagnosis of scalp psoriasis with more than 10% of the scalp involved; and having mild to severe scalp psoriasis, according to the Investigator Global Assessment (IGA) scale, scoring a moderate-to-severe severity for at least one parameter out of redness, thickness or scaling.[12] The washout periods were 2 weeks for topical therapy; 2 weeks for phototherapy (narrow-band ultraviolet B or psoralen plus ultraviolet A); 4 weeks for oral systemic agents (methotrexate, acitretin and cyclosporine); and 6 months for biological agents. The exclusion criteria consisted of having a skin infection or skin atrophy on the scalp; currently receiving medications that might affect psoriasis (such as beta-blockers, antimalarial drugs or lithium); being pregnant or lactating; being unable to attend follow-up visits; having communication problems; or having a history of an allergic reaction or hypersensitivity to desoximetasone. The withdrawal or termination criteria comprised a patient being unwilling to continue to participate, missing more than 2 follow-up visits, or having an allergic reaction to the Topoxy or Topicorte cream. All patients gave their written informed consents prior to participating in the study.

Assessments

The scalp lesions were assessed by two dermatologists at weeks 0, 2, 4 and 8 using IGA, the Total Sign Score (TSS) and the area of scalp involved. With the IGA score, the following labels were assigned: 0, absence of disease; 1, very mild disease with only mild redness; 2, mild disease with evident redness along with mild thickness and scaling; 3, moderate disease with evident redness, thickness and scaling; 4, severe disease with inflammatory erythematous plaques along with severe thickness and scaling; and 5, very severe disease with severe inflammatory erythematous plaques.[12] The TSS was derived from the summation of the scores for the severity of redness, thickness and scaling.[12] Each parameter was graded on a scale of 0 - 4, with 0 representing no signs and 4 signifying severe signs. In cases of discordant assessments by the 2 dermatologists, an assessment by a third blinded dermatologist was requested to reach a consensus. In addition patients assessed their disease severity using the Patient Global Assessment (PGA) at weeks 0, 2, 4 and 8.[12] The PGA score is graded using the same scale as the IGA score (range, 0-4), but it differs in that the PGA score is determined by patients rather than medical staff. The efficacy of the results of the various grading systems (IGA, PGA, redness score, thickness score, and scaling score) were assessed based on the percentage of patients achieving a response of at least a 2-grade improvement from week 0.

Safety was assessed by monitoring patients' side effects, such as skin discomfort and irritation. Skin atrophy and telangiectasia were assessed by physicians. Photographs were taken at weeks 0 and 8. Patients were asked to bring their bottles of Topoxy or Topicorte cream to each follow-up visit; the amount of cream that was left at each visit was measured to assess the levels of treatment compliance.

Statistical analysis

Efficacy analysis

The patients' baseline characteristics (gender, underlying disease, family history of psoriasis, and smoking and alcohol-drinking habits) and the percentage of patients who achieved at least a 2-grade improvement in IGA, PGA, redness, thickness and scaling were presented as n (%) and were analysed using Fisher's exact test or the Chi-square test. The patients' baseline characteristics (age and duration of scalp psoriasis), TSS and area of scalp involved were presented as medians (minimum, maximum) and analysed using the Kruskal - Willis test. Differences were further analysed using the pairwise comparison method, with significance values adjusted by the Bonferroni correction for multiple tests. A *p* value of less than .05 was selected as the significance level for all statistical analyses.

Safety analysis

The safety parameter was described as the percentage of patients who experienced side effects, and it was analysed using Fisher's exact test or the Chi-square test. A *p* value of less than .05 was deemed to be statistically significant.

RESULTS

Patient disposition

In all, 105 scalp psoriasis patients were randomised equally into three groups. The first group received a placebo with coal tar shampoo (n = 35), the second group was given Topoxy with the tar shampoo (n = 35), while the third group was administered Topicorte with the tar shampoo (n = 35). Overall, 94.2% (n = 33) of the patients in the first group, 94.2% (n = 33) in the second group and 94.2% (n = 33) in the third group completed the study. Of the 99 patients who completed the study, 90 attended all four follow-up visits, while the remaining 9 patients had either two or three visits. Six patients (two from each group) were lost to follow up. Fig 1 (the study flow chart) illustrates the flow of participants through the study.

Patient demographics and baseline characteristics

The demographic data were compared across the three treatment arms (Table 1). Female was found in 66.7%, 51.5%, and 36.4% of patients in The topoxy-with-tar-shampoo treatment group, the placebo-with-tar-shampoo treatment group, and the Topicorte-with-tar-shampoo treatment group respectively. The median ages of the three groups ranged between 35 and 50 years. The durations of the scalp psoriasis ranged from 4 to 5 years. The most common underlying disease among each group was hypertension. The baseline disease characteristics (Table 2) were compared across the treatment arms. Most patients in each group had a baseline IGA score of either 3 or 4; a PGA score of either 3 or 4; a redness score of either 2 or 3; a thickness score of either 2 or 3; and a scaling score of either 2 or 3. The median TSS of each group ranged from 7 to 8 (range, 2-11). The median of the percentage of the scalp involved was 50% (range, 10%-100%) for each group. There were no statistical differences between any of the baseline disease characteristics of the 3 groups.

Efficacy (Table 3)

IGA of disease severity: The Topoxy-with-tar-shampoo treatment and the Topicorte-with-tar-shampoo treatment were significantly more effective than the placebo-with-tar-shampoo therapy in achieving at least a two-grade improvement from the baseline IGA score at week 2 (p=.002) and week 4 (p=.007), with no differences between Topoxy and Topicorte. At week 8, Topoxy was significantly more effective than the placebo in achieving at least a two-grade improvement from the baseline IGA score (p=.013).

PGA of disease severity: The Topicorte-with-tar-shampoo therapy was significantly more effective than the placebo-with-tar-shampoo treatment in achieving at least a two-grade improvement from the baseline PGA score at week 2 (p=.05). Topicorte and Topoxy were significantly more effective than the placebo in achieving at least a two-grade improvement from the baseline PGA score at week 4 (p=.004)

Redness score: The Topoxy-with-tar-shampoo treatment and the Topicorte-with-tar-shampoo therapy were significantly more effective than the placebo-with-tar-shampoo treatment in achieving at least a two-grade improvement from the baseline redness score at week 2 (p=.014), with no differences between Topoxy and Topicorte.

Thickness score: At week 2 and week 8, the Topoxy-with-tar-shampoo therapy was significantly more effective than the placebo-with-tar-shampoo therapy in achieving at least a two-grade improvement from the baseline thickness score (p=.018 for week 2, and .025 for week 8). At week 4, the Topoxy-with-tar-shampoo treatment and the Topicorte-with-tar-shampoo therapy were significantly more effective than the placebo-with-tar-shampoo treatment (p=.004), with no differences between Topoxy and Topicorte.

Scaling score: The Topoxy-with-tar-shampoo therapy was significantly more effective than the placebo-with-

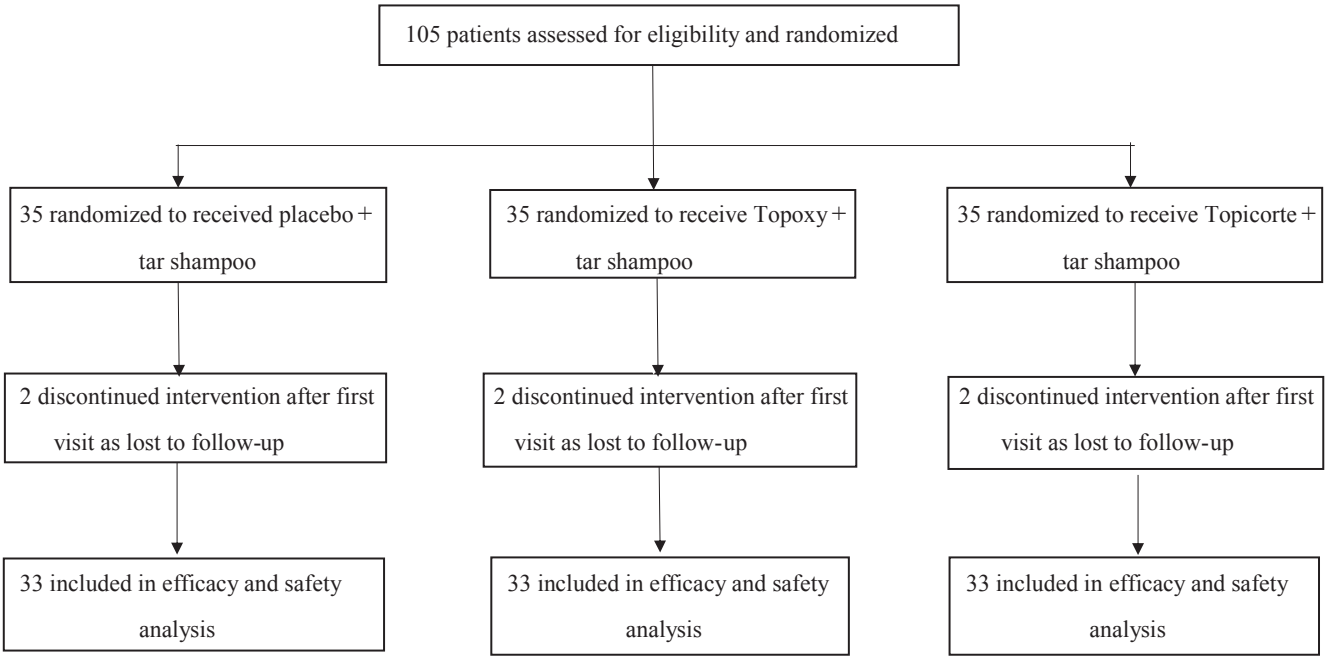

Fig 1. Flow of participants in a randomised clinical trial of 0.25% desoximetasone cream (Topoxy) compared with 0.25% desoximetasone cream (Topicorte) and a placebo.

TABLE 1. Summary of patients' baseline demographic characteristics.

Patient characteristics	Placebo (n = 33)	Topoxy (n = 33)	Topicorte (n = 33)	*P*-value
Age, years	35 (19, 66)	50 (21, 90)*	46 (20, 72)	.027
Female gender	17 (51.5%)	22 (66.7%)**	12 (36.4%)	.048
Duration of scalp psoriasis, years	5 (0.25, 21)	5 (0.08, 37)	4 (0.08, 20)	.739
Underlying disease				
Hypertension	5 (15.2%)	9 (27.3%)	6 (18.2%)	.443
Dyslipidemia	4 (12.1%)	7 (21.2%)	3 (9.1%)	.445
Diabetes mellitus	5 (15.2%)	4 (12.1%)	0 (0%)	.072
Obesity	1 (3.0%)	2 (6.1%)	4 (12.1%)	.496
Renal disease	1 (3.0%)	0 (0%)	1 (3.0%)	1.000
Malignancy	0 (0%)	0 (0%)	1 (3.0%)	1.000
Family history of psoriasis	7 (21.2%)	6 (18.2%)	6 (18.2%)	.937
Current smoker	2 (6.1%)	3 (9.1%)	3 (9.1%)	1.000
Current alcohol drinker	8 (24.2%)	4 (12.1%)	5 (15.2%)	.397

*differed significantly comparing to the placebo group; **differed significantly comparing to the Topicorte group

p value for gender, underlying disease, family history of psoriasis, current smoker, and current alcohol drinker were analyzed using Fisher's exact test or the Chi-square test. *p* value for age and duration of scalp psoriasis were analyzed using Kruskal–Willis test. Differences were further analysed using the pairwise comparison method, with significance values adjusted by the Bonferroni correction for multiple tests.

TABLE 2. Summary of patients' baseline disease characteristics.

Baseline disease characteristics	Placebo (n = 33)	Topoxy (n = 33)	Topicorte (n = 33)	*P*-value
IGA, n (%)				.220
0	0 (0%)	0 (0%)	0 (0%)	
1	0 (0%)	1 (3%)	2 (6.1%)	
2	2 (6.1%)	5 (15.2%)	9 (27.3%)	
3	16 (48.5%)	13 (39.4%)	11 (33.3%)	
4	14 (42.4%)	14 (42.4%)	11 (33.3%)	
5	1 (3%)	0 (0%)	0 (0%)	
PGA, n (%)				.437
0	0 (0%)	1 (3%)	0 (0%)	
1	0 (0%)	1 (3%)	2 (6.1%)	
2	3 (9.1%)	7 (21.2%)	4 (12.1%)	
3	13 (39.4%)	15 (45.5%)	15 (45.5%)	
4	14 (42.4%)	9 (27.3%)	10 (30.3%)	
5	3 (9.1%)	0 (0%)	2 (6.1%)	
Redness, n (%)				.797
0	0 (0%)	0 (0%)	1 (3%)	
1	8 (24.2%)	4 (12.1%)	7 (21.2%)	
2	12 (36.4%)	16 (48.5%)	13 (39.4%)	
3	12 (36.4%)	13 (39.4%)	11 (33.3%)	
4	1 (3%)	0 (0%)	1 (3%)	
Thickness, n (%)				.139
0	0 (0%)	1 (3%)	0 (0%)	
1	4 (12.1%)	6 (18.2%)	9 (27.3%)	
2	17 (51.5%)	10 (30.3%)	16 (48.5%)	
3	11 (33.3%)	16 (48.5%)	7 (21.2%)	
4	1 (3%)	0 (0%)	1 (3%)	
Scaling, n (%)				.151
0	0 (0%)	0 (0%)	0 (0%)	
1	2 (6.1%)	4 (12.1%)	5 (15.2%)	
2	11 (33.3%)	5 (15.2%)	14 (42.4%)	
3	17 (51.5%)	19 (57.6%)	10 (30.3%)	
4	3 (9.1%)	5 (15.2%)	4 (12.1%)	
Total sign score	7 (4, 11)	8 (2, 10)	7 (3, 11)	.175
Area of scalp involvement (%)	50 (10, 100)	50 (10, 100)	50 (10, 100)	.889

Abbreviations: IGA, Investigator Global Assessment; PGA, Patient Global Assessment

p value for IGA, PGA, Redness, Thickness, and scaling were analyzed using Fisher's exact test or the Chi-square test. *p* value for Total Sign Score and Area of scalp involvement were analyzed using Kruskal–Willis test. Differences were further analysed using the pairwise comparison method, with significance values adjusted by the Bonferroni correction for multiple tests.

TABLE 3. Treatment efficacy shown by number and percentage of patients achieving a response of at least a 2-grade improvement from week 0 for their IGA score, PGA score, and scalp psoriasis signs (redness, thickness and scaling), and the median of the Total Sign Score and percentage of area of scalp involvement.

	Week 2			
	Placebo (n = 32)	**Topoxy (n= 32)**	**Topicorte (n = 33)**	***P*-value**
IGA	5 (15.6%)	17 (53.1%)*	17 (51.5%)*	.002
PGA	8 (25.0%)	12 (37.5%)	18 (54.5%)*	.050
Redness	1 (3.1%)	8 (25%)*	10 (30.3%)*	.014
Thickness	4 (12.5%)	14 (43.8%)*	12 (36.4%)	.018
Scaling	5 (15.6%)	16 (50.0%)*	13 (39.4%)	.013
Total Sign Score	5 (1, 11)	3 (0, 8)*	3 (0, 8)*	<.001
Area of scalp involvement (%)	40 (5, 100)	20 (0, 90)*	15 (0, 100)*	.021
	Week 4			
	Placebo (n = 32)	**Topoxy (n= 32)**	**Topicorte (n = 33)**	***P*-value**
IGA	9 (28.1%)	20 (64.5%)*	19 (59.4%)*	.007
PGA	11 (34.4%)	22 (71.0%)*	22 (68.8%)*	.004
Redness	7 (21.9%)	15 (48.4%)	12 (37.5%)	.087
Thickness	6 (18.8%)	18 (58.1%)*	16 (50.0%)*	.004
Scaling	9 (28.1%)	18 (58.1%)*	16 (50.0%)	.047
Total Sign Score	4.5 (1, 11)	2 (0, 7)*	2 (0, 9)*	.001
Area of scalp involvement (%)	25 (1, 100)	9 (0, 90)*	10 (0, 95)*	.001
	Week 8			
	Placebo (n = 32)	**Topoxy (n= 32)**	**Topicorte (n = 33)**	***P*-value**
IGA	10 (32.3%)	21 (70.0%)*	16 (50.0%)	.013
PGA	15 (48.4%)	21 (70.0%)	23 (71.9%)	.102
Redness	6 (19.4%)	13 (43.3%)	10 (31.3%)	.130
Thickness	8 (25.8%)	18 (60.0%)*	13 (40.6%)	.025
Scaling	10 (32.3%)	19 (63.3%)	15 (46.9%)	.052
Total Sign Score	5 (1, 8)	2 (0, 9)*	2 (0, 9)	.001
Area of scalp involvement (%)	20 (1, 100)	5 (0, 100)*	5 (0, 90)*	<.001

Abbreviations: IGA, Investigator Global Assessment; PGA, Patient Global Assessment

*differed significantly comparing to the placebo group

p value for IGA, PGA, redness, thickness, and scaling were analyzed using Fisher's exact test or the Chi-square test. *p* value for Total Sign Score and Area of scalp involvement were analyzed using Kruskal–Willis test. Differences were further analysed using the pairwise comparison method, with significance values adjusted by the Bonferroni correction for multiple tests.

tar-shampoo treatment in achieving at least a two-grade improvement from the baseline scaling score at week 2 (p=.013), and at week 4 (p=.047)

Total Sign Score: At week 2 and week 4, the Topoxy-with-tar-shampoo treatment and the Topicorte-with-tar-shampoo treatment were significantly more effective than the placebo-with-tar-shampoo therapy in improving the median TSS (p<.001 for week 2 and p=.001 for week 4), with no differences between Topoxy and Topicorte. At week 8, the Topoxy-with-tar-shampoo therapy was significantly more effective than the placebo in improving the median TSS (p=.001)

Area of scalp involvement: The Topoxy-with-tar-shampoo treatment and the Topicorte-with-tar-shampoo treatment were significantly more effective than the placebo-with-tar-shampoo treatment in decreasing the area of scalp involved at week 2 (p=.021), week 4 (p=.001) and week 8 (p<.001), with no differences between Topoxy and Topicorte.

Pictures for each group of the scalp area at baseline and after eight weeks of treatment are presented in Fig 2.

Safety evaluation

Table 4 details the side effects experienced by each treatment arm. In the placebo-with-tar-shampoo treatment group, 3 (9.4%) patients at week 2 and week 4 and 2 (6.5%) patients at week 8 reported of having skin discomfort with no statistical difference from other groups. Telangiectasia was reported in 1 (3.3%) patient and 1 (3.1%) patient from the Topoxy-with-tar-shampoo treatment group and the Topicorte-with-tar-shampoo treatment group respectively with no statistical difference between two groups and to the placebo-with-tar-shampoo treatment group. No patients discontinued the treatment because of the side effects.

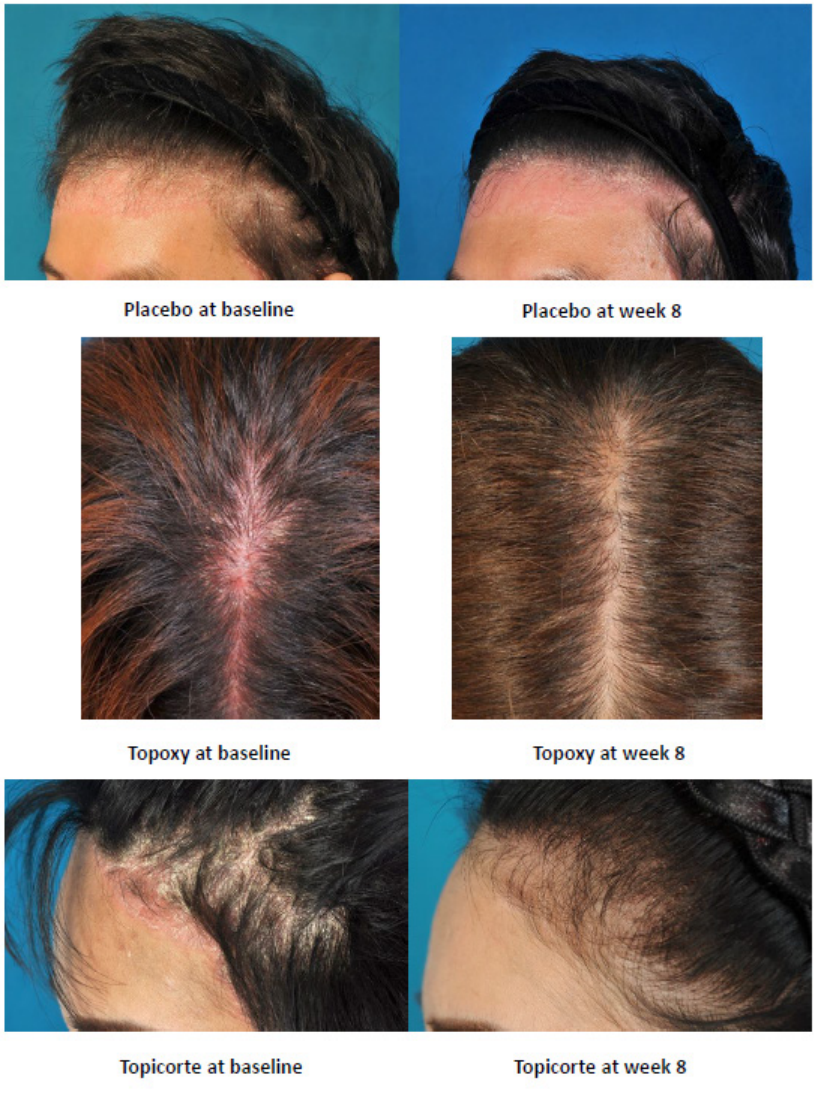

Fig 2. Pictures comparing the scalp at baseline and after eight weeks of treatment for each group. In the placebo group, minimal improvement was seen after treatment. In the case of the Topoxy and Topicorte groups, marked reductions in redness and scaling were observed.

TABLE 4. Summary of reported side effects from week 2 to week 8 of treatment.

Side effects	Placebo (n = 32)	Week 2 Topoxy (n = 32)	Topicorte (n = 33)	*P*-value
Skin discomfort, n (%)	3 (9.4%)	0 (0%)	2 (6.1%)	.281
Skin atrophy, n (%)	0 (0%)	0 (0%)	0 (0%)	–
Telangiectasia, n (%)	0 (0%)	0 (0%)	0 (0%)	–
Side effects	**Placebo (n = 32)**	**Week 4 Topoxy (n = 32)**	**Topicorte (n = 33)**	***P*-value**
Skin discomfort, n (%)	3 (9.4%)	0 (0%)	0 (0%)	.066
Skin atrophy, n (%)	0 (0%)	0 (0%)	0 (0%)	–
Telangiectasia, n (%)	0 (0%)	0 (0%)	0 (0%)	–
Side effects	**Placebo (n = 32)**	**Week 2 Topoxy (n = 32)**	**Topicorte (n = 33)**	***P*-value**
Skin discomfort, n (%)	2 (6.5%)	0 (0%)	0 (0%)	.210
Skin atrophy, n (%)	0 (0%)	0 (0%)	0 (0%)	–
Telangiectasia, n (%)	0 (0%)	1 (3.3%)	1 (3.1%)	.768

p value were analyzed using Fisher's exact test or the Chi-square test. Differences were further analysed using the pairwise comparison method, with significance values adjusted by the Bonferroni correction for multiple tests.

DISCUSSION

Topoxy was proved to be equally effective to the reference form of desoximetasone cream, Topicorte, in achieving treatment success by reducing all signs of psoriasis (redness, thickness and scaling) throughout the study. By the first two weeks, all of the parameters (IGA, PGA, redness, thickness, scaling, TSS and area of scalp involved) had improved significantly for both the Topoxy and Topicorte groups, without any significant differences between the two. After four weeks, Topoxy and Topicorte were statistically significantly superior to the placebo for all parameters except the redness score. These results proved the efficacies of Topoxy and Topicorte compared with the placebo. However, the PGA, redness score and scaling score showed no significant differences between the three groups by treatment week eight. This might be because topical steroid could lose its efficacy over time due to the down-regulation of receptor resulting in the phenomenon called tachyphylaxis.[13] Thus, the short course of corticosteroid treatment with no longer than 2-4 weeks' duration is recommended. If symptoms persist, the re-evaluation of disease is needed.[14]

Rajabi-Estarabadi et al. studied clobetasol lotion in scalp psoriasis and showed that it could lead to improvement of symptoms assessed by Psoriasis Severity Index and decreasing of transepidermal water loss.[15] However, because scalp is not the thick skin area such as palms and soles, therefore, the super potent topical steroid might not be needed.[14] Less potent topical steroid such as desoximethasone was also proved to be effective.[16] Bagel et al. studied the desoximetasone topical spray 0.25% in patients with scalp psoriasis. The results showed that it could lead to significant improvement in scalp IGA and PGA and decreasing of area of scalp involvement at 4 and 16 weeks after the product use.[16] Our results were in line with previous studies. These also showed that several formulations of desoximethasone, whether spray, or cream such as in our study worked well in scalp psoriasis.[16]

The Topoxy was found to be acceptable to, and well-tolerated by, all patients, with none experiencing skin discomfort. However, one patient in the Topoxy group experienced telangiectasia, which is a common side effect of topical steroid use. We also found telangiectasia in one patient from the Topicorte group.

It should be noted that the efficacies of Topoxy and Topicorte in our study might be higher than their efficacies in a real-life situation for 2 reasons. Firstly, tar shampoo was provided to all groups for ethical reasons. This shampoo has anti-inflammatory and antipruritic properties that are beneficial to the treatment of scalp psoriasis. These might have contributed to the relatively high efficacies of the therapies based on Topoxy and Topicorte in our study. Secondly, it is generally accepted that most patients adhere well to treatment when they are included in a research study. The limitation of this study is it was conducted in a single centre with a limited number of patients; the results may therefore not be generalisable.

CONCLUSION

The efficacies of the Topoxy and Topicorte creams were comparable, showing their treatment success through improved results for the grading systems employed (IGA, PGA, redness score, thickness score, scaling score and TSS) as well as a decrease in the area of scalp involved from treatment week 2 to week 8, compared to the placebo. Both the Topoxy and Topicorte creams were well tolerated by all patients and had a good safety profile.

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Conflicts of interest: All of the authors declare that there are no conflicts of interest.

REFERENCES

1. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, et al. National Psoriasis Foundation clinical consensus on disease severity. Arch. Dermatol 2007;143:239-42.
2. Ortonne J, Chimenti S, Luger T, Puig L, Reid F, Trueb RM. Scalp psoriasis: European consensus on grading and treatment algorithm. J Eur Acad Dermatol Venereol 2009;23:1435-44.
3. Fitzpatrick TB, Wolff K. Fitzpatrick's Dermatology in general medicine. 9th ed. New York: McGraw-Hill Medical; 2019.
4. Schlager JG, Rosumeck S, Werner RN, Jacobs A, Schmitt J, Schlager C, et al. Topical treatments for scalp psoriasis: summary of a Cochrane Systematic Review. Br J Dermatol 2017;176:604-14.
5. Reygagne P, Mrowietz U, Decroix J, de Waard-van der Spek FB, Acebes LO, Figueiredo A, et al. Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. J Dermatolog Treat 2005;16:31-36.
6. Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. J Cutan Med Surg 2003;7:185-92.
7. Andres P, Poncet M, Farzaneh S, Soto P. Short-term safety assessment of clobetasol propionate 0.05% shampoo: hypothalamic-pituitary-adrenal axis suppression, atrophogenicity, and ocular safety in subjects with scalp psoriasis. J Drugs Dermatol 2006; 5:328-32.
8. Jarratt M, Breneman D, Gottlieb AB, Poulin Y, Liu Y, Foley V. Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. J Drugs Dermatol 2004;3:367-73.
9. Kircik L, Lebwohl MG, Del Rosso JQ, Bagel J, Stein Gold L, Weiss JS. Clinical study results of desoximetasone spray, 0.25% in moderate to severe plaque psoriasis. J Drugs Dermatol 2013;12:1404-10.
10. Cornell RC, Stoughton RB. Six-month controlled study of effect of desoximetasone and betamethasone 17-valerate on the pituitary-adrenal axis. Br J Dermatol 1981;105:91-95.
11. Kuokkanen K. Comparison of 0.25% desoxymethasone ointment with 0.05% fluocinonide ointment in psoriasis. Curr Med Res Opin 1976;4:703-5.
12. Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis? quantitative evaluation in a systematic review. J Invest Dermatol 2010;130:933-43.
13. Taheri A, Cantrell J, Feldman SR. Tachyphylaxis to topical glucocorticoids; what is the evidence? Dermatol Online J 2013; 19:18954.
14. Rathi SK, D'Souza P. Rational and ethical use of topical corticosteroids based on safety and efficacy. Indian J. Dermatol 2012;57:251-9.
15. Rajabi-Estarabadi A, Hasanzadeh H, Taheri A, Feldman SR, Firooz A. The efficacy of short-term clobetasol lotion in the treatment of scalp psoriasis. J Dermatolog Treat 2018;29:111-5.
16. Bagel J, Nelson E. An Open-label, Observational Study Evaluating Desoximetasone Topical Spray 0.25% in Patients with Scalp Psoriasis. J Clin Aesthet Dermatol 2018;11:27-9.

Evaluation of Hypotensive Prevention Effect of Intramuscular Glycopyrrolate in Spinal Anaesthesia of Elderly TURP Patients: A Randomized Control Trial

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ABSTRACT

Objective: Spinal anaesthesia is one of the options for patients who need transurethral resection of the prostate (TURP). However, due to typical patient age, risk factors, and the procedure itself, hemodynamic instability is common and hazardous. Glycopyrrolate, an anticholinergic drug, has been used in many indications, including in hypotensive prevention in caesarean section patients undergoing spinal anaesthesia. The study aims to evaluate the hypotensive prevention effect of the drug in elderly (> 60 years) spinal anaesthesia TURP patients.

Methods: A prospective randomized control trial of 62 elderly patients who needed TURP was conducted from December 2019 to January 2020. Exclusion criteria were an American Society of Anesthesiologists classification of more than three, contra-indication for glycopyrrolates, and an inability to take spinal anaesthesia. The primary testing process was administration of 0.2 milligram (mg) intramuscular glycopyrrolate 15 minutes before spinal anaesthesia. Data were collected concurrently with hemodynamic parameters, which were recorded as a baseline and every 5 minutes up to 60 minutes. The analysis was done with both single-measure and repeated-measures analysis.

Results: Hypotensive incidence was significantly reduced in the glycopyrrolate group (38.7 vs. 74.2%, p-value=0.01) and showed significantly decreased use of epinephrine [0.2 (±1.1) vs. 4.55 (±6.0) mg, p-value<0.01). Intravenous fluid and vasopressor requirements were also lower. All hemodynamic parameters were higher in the glycopyrrolate group, except heart rate.

Conclusion: Intramuscular glycopyrrolate could prevent spinal anaesthesia-related hypotension without a difference in heart rate in elderly TURP patients.

Keywords: Glycopyrrolate; hypotensive prevention; TURP; spinal anaesthesia; elderly (Siriraj Med J 2020; 72: 380-385)

INTRODUCTION

Transurethral resection of the prostate (TURP) is an effective therapeutic procedure for indication of benign prostatic hyperplasia (BPH).[1] Although TURP is technically a less invasive procedure, sometimes lethal events can occur either by the process itself or by patient risk factors. The latter is because BPH usually afflicts elderly patients.[2] Thus, the choice of anaesthesia is essential. Spinal anaesthesia is an attractive option due to the ability to monitor conscious patients directly. Nevertheless, vital sign instability is a troublesome procedure-related unwanted effect.

Hypotension is a frequent procedure-related hemodynamic change and can lead to many adverse

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consequences, even myocardial ischemia.[3] Sympathetic blockade after induction of spinal anaesthesia, which sequentially decreases systemic vascular resistance and cardiac output, is its pathophysiology.[4-6] Unintended and uncorrected hypotension can cause serious consequences, such as myocardial infarction and even death. Reported hypotensive incidence among ageing patients was 65-75%.[6-8] Several preventive strategies were intravenous fluid administration and vasopressors.[9] Nevertheless, TURP-related volume overload can occur and worsen the condition.[10]

Anticholinergic drugs have been proven to be able to prevent adverse cardiovascular effects and decrease secretion during induction of general anaesthesia.[11] The anticholinergic drug glycopyrrolate has reportedly high activity for these preventive effects.[12] Later studies also showed that giving glycopyrrolate before spinal anaesthesia could prevent hypotension and bradycardia in caesarean section[13,14] and in hip arthroplasty patients.[15] Regarding these beneficial effects, we decided to study this drug in elderly TURP patients to determine whether it can alleviate harmful hemodynamic effects. Previous studies reported increased hemodynamic stability using a combination of neostigmine and glycopyrrolate during the reversal of anaesthesia.[16,17] We, however, excluded patients with cardiovascular diseases because there were also some published arrhythmic consequences of the drug in this group of patients.[18]

MATERIALS AND METHODS

This study was registered with the Thai Clinical Trial Registry (Identification number: TCTR20191105001) and approved by the Sawanpracharak Hospital ethics committee.

BPH patients, who were indicated as needing TURP, were included if they were more than 60 years old and decided to do spinal anaesthesia on an elective basis between December 2019 and January 2020. Patients were excluded if they had an American Society of Anesthesiologists (ASA) classification of more than three, had glycopyrrolate contra-indications (glaucoma, hyperthyroid, morbid obesity, cardiovascular disease, pulmonary disease, renal or hepatic dysfunction, and neuromuscular disease), or were unable to take spinal anaesthesia.

Eligible patients were randomly allocated in parallel by computer-generated numbers and the allocations were sealed in envelopes after informed consent was obtained. Both actions were done by a non-clinically related official. The envelope content was revealed before the beginning of intervention by another non-clinically involved investigator. Before spinal anaesthesia was administered in the intervention group (Group G), 0.2 milligrams (mg) of glycopyrrolate was given intramuscularly. The same volume of normal saline was given as a placebo to the control group (Group C). Both sets of injections were prepared by the investigator who opened the envelopes. The anaesthesiologist team that gave and recorded outcomes were blind to the group identity during all of the procedures. The study flow is illustrated in Fig 1.

Collected outcomes were age, ASA classification, bupivacaine dosage, spinal blockage level, total ephedrine dosage, total intravenous (IV) volume, estimated blood loss (EBL), and hemodynamic outcomes. The hemodynamic outcomes included systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate. All hemodynamic parameters, which were primary outcomes, were recorded as the baseline, every minute after spinal anaesthesia for 10 minutes, and then every 5 minutes for up to 60 minutes. Hypotension was defined as decreased SBP at least 20% below the patient's baseline level, SBP less than 90 mmHg, or DBP less than 60 mmHg.

Sixty-two of the included participants were calculated to have experienced hypotension: 70% and 27.3% between drug and placebo groups,[15] respectively, with adjusted statistic power to 90% of the two-sided test. Statistical analysis for single-measure data was calculated with Fisher's exact test for categorical data and t-test or Mann-Whitney U test for continuous data. Repeated-measures data were analysed with a multilevel mixed-effects linear regression model. Statistical analysis was performed by statistical software. A p-value of <0.05 was considered to be significant statistically.

RESULTS

After application of the study design, no eligible patient was excluded, and no patient refused to provide informed consent. Thus, 31 patients were distributed equally in both groups. Table 1 presents the baseline data and the results of single-measure data. Hypotensive incidence was significantly lower in the glycopyrrolate group (38.7 vs. 74.2%, p-value=0.01). With less hypotension, epinephrine use and the IV volume was also lower in the glycopyrrolate group [0.2 (±1.1) vs. 4.55 (±6.0) mg, p-value<0.01, and 1.0 (±0.2) vs. 1.1 (±0.3) litre, p-value=0.03].

Regarding repeated-measures data, bar graphs with standard error are illustrated in Fig 2, and the summary of statistical analysis results is given in Table 2. The glycopyrrolate group had significantly higher values for all blood pressure parameters. SBP, DBP, and MAP were

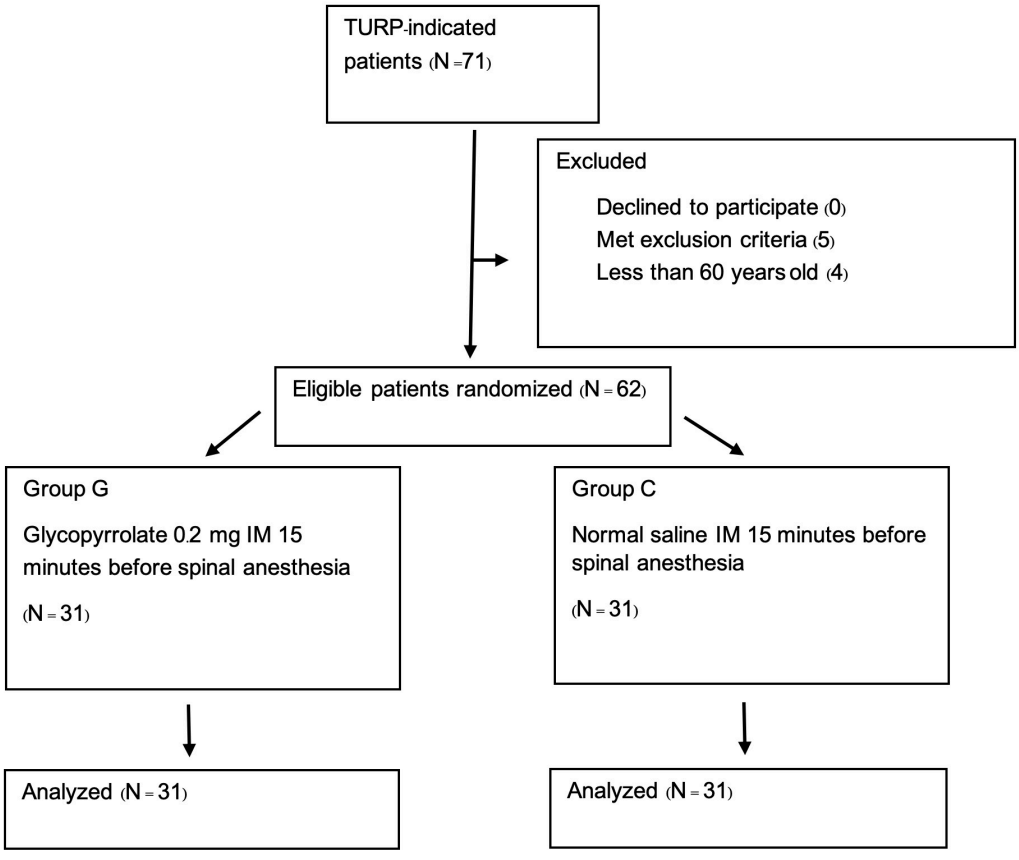

Fig 1. Study flow in which 62 patients were assessed for eligibility and eligible subjects were randomized.
Abbreviations: Group G = glycopyrrolate group; Group C = control group; IM = intramuscular

TABLE 1. Baseline data and single-measure outcomes according to study group.

Characteristic	Group C	Group G	*P*-value
Age (years), Mean (± SD)	69.68 (6.5)	70.9 (8.0)	0.97
Bupivacaine dosage (mg), Median (Range)	2.8 (2.6-3.2)	2.8 (2.6-4)	0.42
Anaesthesia level, N (%)			
T6	11 (35.5)	5 (16.1)	0.24
T8	9 (29.0)	10 (32.3)	
T10	11 (35.5)	16 (51.6)	
Operative time, Median (Range)	30 (25-55)	40 (25-85)	0.01
EBL (ml), Median (Range)	50 (20-150)	50 (20-100)	0.91
IV fluid volume (ml), Mean (± SD)	1,140.3 (297.9)	1,000.0 (204.9)	0.03
Total epinephrine dosage (mg), Mean (± SD)	4.55 (6.0)	0.2 (1.1)	<0.01
Hypotensive incidence, N (%)	23 (74.2)	12 (38.7)	0.01

Abbreviations: Group G = glycopyrrolate group; Group C = control group; SD = standard deviation; mg = milligram; T = thoracic level; EBL = estimated blood loss; ml = millilitre

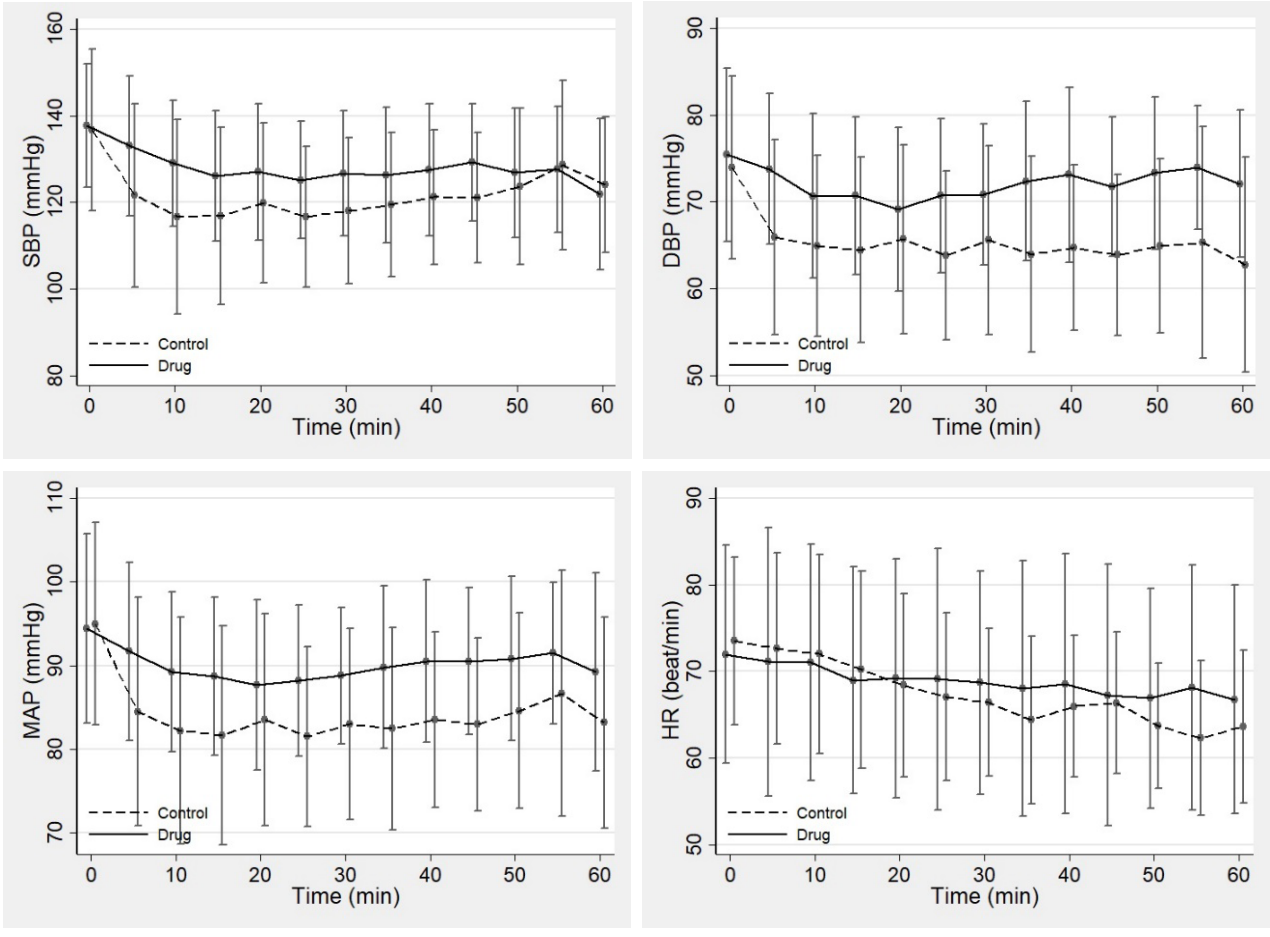

Fig 2. Bar charts with standard error for repeated-measures data.
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; mmHg = millimetre of mercury; beat/min = beats per minute

TABLE 2. Statistical analytic results of repeated-measures outcomes.

Outcome	Differences from control	95% Confidence interval	*P*-value
Systolic blood pressure	7.4 mmHg higher	3.1 to 11.8	<0.01
Diastolic blood pressure	4.3 mmHg higher	1.7 to 6.9	<0.01
Mean arterial pressure	5.4 mmHg higher	2.6 to 8.1	<0.01
Heat rate	1.5 beats/min	-3.8 to 6.7	0.59

higher, around 7.4 mmHg (95% CI: 3.1-11.8, p-value<0.01), 4.3 mmHg (95% CI: 1.7-6.9, p- value<0.01), and 5.4 mmHg (95% CI: 2.6-8.1, p-value<0.01), respectively. The graph also shows that the values were maintained for at least the entire 60-minute observation period. Heart rate, however, was no different between the two groups (p-value=0.59).

DISCUSSION

Spinal anaesthesia is the technique of choice for TURP. It is often preferred over general anaesthesia due to more hemodynamic stability during induction,[19] a lower post-operative analgesic requirement[20], and less blood loss.[21] This procedure also offers physicians the ability to monitor patient consciousness, which can indicate early

signs of TURP syndrome. These warning signs (such as dizziness, headache, and nausea)[22], if unaddressed, can lead to cyanosis, hypotension, or even cardiac arrest. TURP patients are also particularly vulnerable to volume overload, as most of them are elderly and have cardiopulmonary disorders. Excessive absorption of irrigation solution through open prostatic venous sinuses during the surgical procedure[10] is the unique cause of this condition. These pose a challenge to the procedure, especially with regard to hemodynamic parameters.

Glycopyrrolate, administered as glycopyrronium bromide, is an anticholinergic drug. It does not cross the blood-brain barrier,[23] has no central nervous system effect, and has fewer chronotropic properties compared to atropine.[12] In anaesthetic practice, glycopyrrolate is commonly used to reverse non-depolarizing muscle relaxants[17,24] or to reduce oral secretions.[25] Some studies have evaluated the effect of glycopyrrolate on hypotension following spinal anaesthesia induction during caesarean delivery.[26-28] According to the pharmacodynamics of glycopyrrolate, it will take effect at about 16.1 minutes and will be cleared about 75.4 minutes after injection. Thus, we decided to apply the drug 15 minutes before performing the procedure. The intramuscular application was chosen to avoid acute tachycardia from the drug's chronotropic effect.[12] Dosage was adjusted to be 0.2 mg to prevent hypertension.[29]

In Thailand, the incidence of spinal anaesthesia-associated hypotension was around 52.6% to 57.9%.[30,31] At age > 65 years, underlying hypertension and use of high doses of bupivacaine were risk factors for TURP patients.[32] Our patients were one of the high-risk groups. With our results, the drug could significantly suppress hypotension. The IV fluid requirement and vasopressor usage were even more reduced, which are attractive for this group of patients, who were vulnerable to fluid overload. Nevertheless, heart rate parameters were not different between the two groups in our study. This finding was partly compatible with the finding from a meta-analysis of glycopyrrolate use in caesarean delivery, that although the drug could maintain a higher heart rate, bradycardia incidence was not different statistically.[26]

There were, however, limitations in our study. Patients with cardiovascular disease and ASA status of more than three were excluded. Further studies are required to evaluate the effectiveness and safety of the drug in patients high ASA status, especially those with cardiovascular disease.

CONCLUSION

In summary, intramuscular glycopyrrolate may be able to prevent hypotension while decreasing vasopressor and IV fluid usage in elderly spinal anaesthesia TURP patients. Heart rate, however, was not affected.

Disclosure: The authors declare that they have no competing interests in this work.

REFERENCES

1. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol 2013;64:118-40.
2. Vuichoud C, Loughlin KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can J Urol 2015;22 Suppl 1: 1-6.
3. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. JAMA 1978;239:2566-70.
4. Hartmann B, Junger A, Klasen J, Benson M, Jost A, Banzhaf A, et al. The incidence and risk factors for hypotension after spinal anesthesia induction: an analysis with automated data collection. Anesth Analg 2002;94:1521-9.
5. Messina A, Frassanito L, Catalano A, Castellana A, Santoprete S. Haemodynamic effects of spinal anesthesia in elderly patients undergoing hip fracture surgery: 18AP1–4. Eur J Anaesth 2010;27:241-2.
6. Critchley LA, Stuart JC, Short TG, Gin T. Haemodynamic effects of subarachnoid block in elderly patients. Br J Anaesth 1994;73:464-70.
7. Buggy DJ, Power CK, Meeke R, O'Callaghan S, Moran C, O'Brien GT. Prevention of spinal anaesthesia-induced hypotension in the elderly: IM methoxamine or combined hetastarch and crystalloid. Br J Anaesth 1998;80:199-203.
8. Nishikawa K, Yamakage M, Omote K, Namiki A. Prophylactic IM small-dose phenylephrine blunts spinal anesthesia-induced hypotensive response during surgical repair of hip fracture in the elderly. Anesth Analg 2002;95:751-6.
9. Critchley LA. Hypotension, subarachnoid block and the elderly patient. Anaesthesia 1996;51:1139-43.
10. Okeke AA, Lodge R, Hinchliffe A, Walker A, Dickerson D, Gillatt DA. Ethanol-glycine irrigating fluid for transurethral resection of the prostate in practice. BJU Int 2000;86:43-6.
11. Sneyd JR, Mayall R. The effect of pre-induction glycopyrronium on the haemodynamic response of elderly patients to anaesthesia with propofol. Anaesthesia 1992;47:620-1.
12. Mirakhur RK, Dundee JW. Cardiovascular changes during induction of anaesthesia. Influence of three anticholinergic premedicants. Ann R Coll Surg Engl 1979;61:463-9.
13. Ure D, James KS, McNeill M, Booth JV. Glycopyrrolate reduces nausea during spinal anaesthesia for caesarean section without affecting neonatal outcome. Br J Anaesth 1999;82:277-9.
14. Chamchad D, Horrow JC, Nakhamchik L, Sauter J, Roberts N, Aronzon B, et al. Prophylactic glycopyrrolate prevents bradycardia after spinal anesthesia for cesarean section: a randomized,

double-blinded, placebo-controlled prospective trial with heart rate variability correlation. J Clin Anesth 2011;23:361-6.
15. Hwang J, Min S, Kim C, Gil N, Kim E, Huh J. Prophylactic glycopyrrolate reduces hypotensive responses in elderly patients during spinal anesthesia: a randomized controlled trial. Can J Anaesth 2014;61:32-8.
16. Bali IM, Mirakhur RK. Comparison of glycopyrrolate, atropine and hyoscine in mixture with neostigmine for reversal of neuromuscular block following closed mitral valvotomy. Acta Anaesthesiol Scand 1980;24:331-5.
17. Cozanitis DA, Dundee JW, Merrett JD, Jones CJ, Mirakhur RK. Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation. Br J Anaesth 1980; 52:85-9.
18. Nkemngu NJ, Tochie JN. Atrio-ventricular block following neostigmine-glycopyrrolate reversal in non-heart transplant patients: case report. Anesth Prog 2018;65:187-91.
19. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012;117: 72-92.
20. Bowman GW, Hoerth JW, McGlothlen JS, Magee PJ, Mendenhall IE, Sonnenberg G, et al. Anesthesia for transurethral resection of the prostate: spinal or general? AANA J 1981;49:63-8.
21. Blake DW. The general versus regional anaesthesia debate: time to re-examine the goals. Aust N Z J Surg 1995;65:51-6.
22. McGowan-Smyth S, Vasdev N, Gowrie-Mohan S. Spinal anesthesia facilitates the early recognition of TUR Syndrome. Curr Urol 2016;9:57-61.
23. Proakis AG, Harris GB. Comparative penetration of glycopyrrolate and atropine across the blood--brain and placental barriers in anesthetized dogs. Anesthesiology 1978;48:339-44.
24. Klingenmaier CH, Bullard R, Thompson D, Watson R. Reversal of neuromuscular blockade with a mixture of neostigmine and glycopyrrolate. Anesth Analg 1972;51:468-72.
25. Bernstein CA, Waters JH, Torjman MC, Ritter D. Preoperative glycopyrrolate: oral, intramuscular, or intravenous administration. J Clin Anesth 1996;8:515-8.
26. Patel SD, Habib AS, Phillips S, Carvalho B, Sultan P. The effect of glycopyrrolate on the incidence of hypotension and vasopressor requirement during spinal anesthesia for cesarean delivery: a meta-analysis. Anesth Analg 2018;126:552-8.
27. Rucklidge MW, Durbridge J, Barnes PK, Yentis SM. Glycopyrronium and hypotension following combined spinal-epidural anaesthesia for elective caesarean section in women with relative bradycardia. Anaesthesia 2002;57:4-8.
28. Yentis SM, Jenkins CS, Lucas DN, Barnes PK. The effect of prophylactic glycopyrrolate on maternal haemodynamics following spinal anaesthesia for elective caesarean section. Int J Obstet Anesth 2000;9:156-9.
29. Ngan Kee WD, Lee SW, Khaw KS, Ng FF. Haemodynamic effects of glycopyrrolate pre-treatment before phenylephrine infusion during spinal anaesthesia for caesarean delivery. Int J Obstet Anesth 2013;22:179-87.
30. Sathanasaowaphak P. Hypotension after spinal anesthesia at Phrachomklao. Thai J Anesth 2011;37:18-26.
31. Vorrakitpokatorn P, Supajanyarach C, Limsittisiri S. Incidence and risk factors of spinal anesthesia induced hypotension for transurethral resection of prostate (TURP) in Siriraj hospital. Thai J Anesth 2009;35:58-64.
32. Chinachoti T, Tritrakarn T. Prospective study of hypotension and bradycardia during spinal anesthesia with bupivacaine: incidence and risk factors, part two. J Med Assoc Thai 2007;90: 492-501.

Incidence and Pattern of Nodal Metastasis in Colon and Rectal Cancer: a Study of 1012 Cases from Thailand

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ABSTRACT

Objective: Lymph node (LN) metastasis is a key to determine prognosis and adjuvant treatment for resectable colorectal cancer. This study aimed to determine and compare the incidence and pattern of LN metastasis between colon cancer and rectal cancer.

Methods: Medical and pathological reports of patients with stage I-III colorectal adenocarcinoma undergoing oncological resection between 2009 and 2013 at the Faculty of Medicine Siriraj Hospital were reviewed. The incidence and pattern of LN metastasis related to tumor staging between colon cancer and rectal cancer were analyzed.

Results: This study included 1012 cases (502 colon cancer and 510 rectal cancer). Compared with rectal specimens, colonic specimens had a larger tumor size (5.8 cm vs 5.0 cm; P<0.001), more T4 lesion (24% vs 6.3%; P<0.001) and more LNs harvested (24 vs 18; P<0.001). Nodal metastases were found in 552 specimens (54.5%). The rate of LN metastasis was 14.3% for T1 tumors, 25.6% for T2 tumors, 61.2% for T3 tumors, and 65.6% for T4 tumors. There was no significant difference in the overall rate of nodal metastasis between colon cancer and rectal cancer (52.6% vs 56.5%; P=0.22), but rectal cancer had more N2 staging (31% vs 22.5%; P=0.002). Rectal cancer yielded more median number of positive LN (4 vs 3; P=0.002) with a greater LN ratio (0.22 vs 0.12; P<0.001) than colon cancer. Based on the depth of tumor invasion, T3 rectal cancer had a significantly higher rate of LN metastasis (66.8% vs 55.7%; P=0.004) and a greater LN ratio (0.23 vs 0.10; P<0.001) than T3 colon cancer.

Conclusion: Although colon cancer had a larger tumor size and a higher percentage of deeper invasion, rectal cancer were associated with a higher number of positive LN, more N2 status and a greater LN ratio - especially T3 lesion.

Keywords: Colon cancer; rectal cancer; nodal metastasis; lymph node ratio; Thailand (Siriraj Med J 2020; 72: 386-390)

INTRODUCTION

The incidence of colorectal cancer (CRC) is rapidly increasing in Asia including Thailand. At present, CRC is the third common malignancy in Thai males and the fourth in Thai females, and accounts for 11% of cancer burden in Thailand.[1] Oncological resection remains a mainstay treatment of non-metastatic CRC. Meanwhile, the status of lymph node (LN) metastasis determines the prognosis of CRC and the need of adjuvant therapy. Negative resection margin and adequate LN harvested (more than 12 LNs) indicate the quality of surgical specimens. Therefore, many surgeons advocate extensive operations including complete mesocolic excision with central vascular ligation and D3 lymphadenectomy for

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colon cancer to achieve utmost removal of potentially cancer-harboring LN.[2] Apart from surgical extent, it was evident that the number of LN harvested was dependent on the length of surgical specimen, tumor size, depth of CRC invasion, and location of the tumor.[3]

Another interesting aspect of LN removal and nodal metastasis is that lymph nodes ratio (LNR), defined as the ratio of metastatic LN to the total number of LN harvested, is predictive of disease-free survival and overall survival in stage III CRC.[4] The LNR may provide an additional value to the N-stage of TMN classification for CRC. However, histopathology and nodal status of CRC could be various among tumor location and may be different among ethnics.[3,5] In Asian countries, most studies examining these subjects were based on the East Asia population.[6-10] It would be interesting to have this information form other regions of Asia including Southeast Asia. The objective of this study was to determine and compare the incidence and pattern of nodal metastasis between colon cancer and rectal cancer using a database from the largest hospital in Thailand.

MATERIALS AND METHODS

After obtaining ethics approval from the Institution's Ethics Committee (Si 122/2014), medical records and pathological reports of patients undergoing elective and emergency colectomy and/or proctectomy for stage I-III colorectal adenocarcinoma between 2009 and 2013in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, were reviewed. Our oncological principles of CRC resection included a resection margin at least 5 cm from colon cancer with the removal of node-baring mesentery and proximal ligation of the feeding vessels, and adequate or total mesorectal excision for rectal cancer.

The clinicopathological records were identified from the hospital's prospectively-collected database. Pathological reports were excluded from this review if patients had local excision or palliative resection, and those underwent an operation for recurrent CRC, carcinoma in situ, synchronous CRC, or familial adenomatous polyposis. Patients having neoadjuvant therapy were also excluded. Rectal cancer was defined as a tumor locating within 15 cm from the anal verge measured by an endoscopy. High-grade tumors were poorly differentiated adenocarcinoma, mucin-producing tumors, signet ring cells. Notably, pathologists would identify LNs by careful palpation a surgical specimen after proper formalin fixation. The seventh edition of UICC TNM staging system for colorectal cancer was used in this study. The primary outcomes measured were the incidence and pattern of nodal metastasis between colon cancer and rectal cancer. This study was performed in accordance with the Declaration of Helsinki.

All data were prepared and compiled using SPSS computer software (version 15.0 for Windows). Mean and standard deviation are presented for continuous data. The Kolmogorov-Smirnov test was used to test for the pattern of data distribution. Student unpaired *t*-tests were used to compare data between the two groups when they showed normal distribution. The Mann-Whitney *U* tests were used when data were not normally distributed. The Pearson χ 2 tests or Fisher's exact tests were used for categorical data. A P-value of less than 0.05 was considered statistically significant.

RESULTS

This study included 1012 cases (502 colon cancer and 510 rectal cancer). Patients with colon cancer was about 2-year older than those with rectal cancer (average age 64.7 years vs 62.6 years, P=0.011). Compared with rectal specimens, colonic specimens had a larger tumor size (5.8 cm vs 5.0 cm; P <0.001), more T4 lesion (24% vs 6.3%; P<0.001) and more harvested lymph nodes (24 vs 18; P<0.001) - but a comparable percentage of high-grade histology (5.4% vs 3.7%; P=0.21). Clinicopathological characteristics between colon cancer and rectal cancer are shown in Table 1.

Nodal metastases were found in 552 specimens (54.5%). The rate of nodal involvement was 14.3% for T1 tumors, 25.6% for T2 tumors, 61.2% for T3 tumors, and 65.6% for T4 tumors. There was no significant difference in the overall rate of nodal metastasis between colon cancer and rectal cancer (52.6% vs 56.5%; P=0.22), but rectal cancer had more N2 staging (31% vs 22.5%; P=0.002). Rectal cancer yielded more median number of positive LN (4 vs 3; P=0.002) with a greater LNR (0.22 vs 0.12; P<0.001) than colon cancer. Based on the depth of tumor invasion, T3 rectal cancer had a significantly higher rate of nodal metastasis (66.8% vs 55.7%; P=0.004) (Table 2) and a greater LNR (0.23 vs 0.10; P<0.001) than T3 colon cancer (Table 3).

DISCUSSION

This study examining 1012 surgical specimens of colorectal cancer in Thailand demonstrated that, although colon cancer had a larger tumor size and a higher percentage of deeper invasion, rectal cancer were associated with a higher number of LN metastasis, more N2 status and a greater lymph node ratio - especially T3 lesion. Rectal cancer appeared to be more aggressive than colon cancer.

TABLE 1. Clinicopathological characteristics between colon cancer and rectal cancer. Data are presented as mean ± standard deviation, median [interquartile range], or number (percentage).

Characteristics	Colon cancer (n=502)	Rectal cancer (n=510)	*P*-value
Age (years)	64.7 ± 13.3	62.6 ± 12.4	0.011
Male	265 (52.8)	278 (54.5)	0.58
Tumor size (cm)	5.8 ± 2.9	5.0 ± 1.8	<0.001*
High-grade tumor [a]	27 (5.4)	19 (3.7)	0.21
Tumor stage			<0.001*
T1	16 (3.2)	19 (3.7)	
T2	68 (13.5)	104 (20.4)	
T3	296 (59.0)	355 (69.6)	
T4	122 (24.3)	32 (6.3)	
Harvested lymph node	24 [17-36]	18 [13-25]	<0.001*
≥ 12 lymph node removal	453 (90.2)	424 (83.1)	0.001*
Node stage			0.008*
N0	238 (47.4)	222 (43.5)	
N1	151 (30.1)	130 (25.5)	
N2	113 (22.5)	158 (31.0)	
Of patients with nodal metastasis			
Positive lymph node	3 [1-6]	4 [2-7]	0.002*
Lymph node ratio (%)	0.12 [0.06-0.29]	0.22 [0.10-0.41]	<0.001*

*P-value <0.05

Note: [a] High-grade tumors were poorly differentiated adenocarcinoma, mucin-producing tumors, signet ring cells.

TABLE 2. Comparison between tumor stage and nodal stage in colon cancer and rectal cancer. Data are presented as number (percentage).

T stage	Proportion of nodal metastasis (%)			*P*-value
	Colorectal cancer (n=1012)	Colon cancer (n=502)	Rectal cancer (n=510)	
T1	5/35 (14.3)	4/16 (25.0)	1/19 (5.3)	0.16
T2	44/172 (25.6)	18/68 (26.5)	26/104 (25.0)	0.83
T3	402/651 (61.2)	165/296 (55.7)	237/355 (66.8)	0.004*
T4	101/154 (65.6)	77/122 (63.1)	24/32 (75.0)	0.21

*P-value <0.05

TABLE 3. Comparison between tumor stage and lymph node ratio (LNR) in colon cancer and rectal cancer. Data are presented as median [interquartile range].

T stage	Lymph node ratio		*P*-value
	Colon cancer (n=264)	Rectal cancer (n=288)	
T1	0.24 [0.08-0.84]	-	n/a
T2	0.10 [0.07-0.22]	0.17 [0.07-0.31]	0.54
T3	0.10 [0.05-0.25]	0.23 [0.10-0.44]	<0.001*
T4	0.16 [0.07-0.33]	0.20 [0.11-0.39]	0.19

*P-value <0.05

Abbreviation: n/a = not available

Surgical specimens of colon cancer in this study yielded more median number of LN harvested than those of rectal cancer (24 LNs vs 18 LNs). The number of colonic specimens containing adequate LN removal (at least 12 LNs) was also significantly higher than that of rectal specimens (90.2% vs 83.1%). These finding were consistent with those reported from Austria[3] and China[9] – where right-sided colon specimen had the highest number of LN harvested followed by left-sided colon and rectal specimens. Other factors influencing the number of LNs harvested included patient's age, tumor size, tumor staging, type of operation, and technique to identify LN in a surgical specimen.[11] The presence of at least 12 LNs in a CRC specimen is widely regarded as one of quality assurances for appropriate CRC operations. It is associated with proper staging, subsequent treatment, surveillance protocol and CRC prognosis.[8]

It is known that the possibility of nodal metastasis is related to the depth of tumor invasion. For example, using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, the rate of nodal involvement for CRC was approximately 10% for T1 tumors, 20% for T2 tumors, 40% for T3 tumors, and 50% for T4 tumors. Moreover, nodal metastasis was more prominent in rectal cancer and poorly differentiated cancer.[12] Our findings confirmed this correlation and were in line with the results of this US population-based study as we found that the proportion of nodal metastasis increased by advanced T-staging and rectal cancer had more percentage of LN involvement than colon cancer – especially T3 lesions. In addition, rectal cancer also had more median number of positive LN, more N2 staging and a greater LNR than colon cancer.

A higher rate of nodal metastasis and greater LNR in rectal cancer shown in our study was supported by a review of population-based studies[11] and hospital-based cohorts.[10] For instance, a study of 2340 Chinese surgical patients with stage I-III CRC found that patients with rectal cancer had significantly more LNs involved and higher LNR than those with colon cancer.[10] There is no clear rationale why rectal cancer has more nodal involvement than colon cancer, but some possible explanation includes their differences in anatomical and oncological characteristics. Although LNR could be a significant prognostic factor for stage III CRC, its optimal cut-off point remains debatable for determining the regimen of adjuvant treatment and CRC survival.

It is interesting that the rates of nodal metastasis based on T-staging in our study appeared to be slightly higher than those reported in other studies[11,12] – ours ranged from 14.3% for T1 tumors to 65.6% for T4 tumors. One possible explanation for these findings is that the average size of the tumor was quite large (about 5-6 cm) in our study and a tumor with large diameter (especially more than 4.5 cm) could increase the risk of nodal involvement.[13] Also, some T1 tumors in our institute were treated by endoscopic removal or transanal excision thus resulting in those with large tumor or high-risk for nodal metastasis underwent oncological resection with LN-bearing area. Moreover, 50% of our cases were rectal cancer which was more prone to have LN metastasis.[10]

Our study benefited from a review of a prospectively-collected database of the largest hospitality in Thailand – which could be a good representative of real-world practice and overall clinicopathological characteristics of CRC in Thailand. However, there are some limitations of this observational study. First, the number of patient with T1 tumor was small - which represented a real picture of CRC in Thailand where the incidence of stage I CRC was less than 10% due to the lack of CRC screening and cancer awareness.[1] Therefore the incidence of LN metastasis in T1 lesion may be difficult to interpretate especially for T1 colon cancer. Specifically, there were 4 cases with LN metastasis out of 16 cases with T1 colon cancer (accounting for 25%). This should not be perceived as a true incidence of nodal involvement for T1 lesion because a majority of malignant colonic polyps were removed endoscopically in our institute thus leaving only high-risk T1 lesions for oncological resection. Second, the comparison of LNR in T1 tumors between colon cancer and rectal cancer cannot be performed because the rectal cancer group had only one case with LN metastasis. Hence, future studies with large sample size especially for early CRC are needed from Thailand. Third, the correlation between nodal status including LNR and oncological outcomes was beyond the scope of this study. However, several population-based prospective studies have shown a strong correlation between a high number of LNs harvested and better survival, and a prognostic indicator of LNR for stage III CRC.[11]

In summary, this single-center study demonstrated that the incidence of LN metastasis in CRC increased by the depth of tumor invasion. Although the overall rate of nodal metastasis between colon cancer and rectal cancer was comparable, rectal cancer had more median number of positive LN, more N2 staging and a greater LNR – especially T3 rectal cancer.

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REFERENCES

1. Lohsiriwat V, Chaisomboon N, Pattana-arun J, for the Society of Colorectal Surgeons of Thailand. Current Colorectal Cancer in Thailand. Ann Coloproctol 2020;36:78-82.
2. West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 2012;30:1763-9.
3. Betge J, Harbaum L, Pollheimer MJ, Lindtner RA, Kornprat P, Ebert MP, et al. Lymph node retrieval in colorectal cancer: determining factors and prognostic significance. Int J Colorectal Dis 2017;32:991-8.
4. Ceelen W, Van Nieuwenhove Y, Pattyn P. Prognostic value of the lymph node ratio in stage III colorectal cancer: a systematic review. Ann Surg Oncol 2010;17:2847-55.
5. Maajani K, Khodadost M, Fattahi A, Shahrestanaki E, Pirouzi A, Khalili F, et al. Survival Rate of Colorectal Cancer in Iran: A Systematic Review and Meta-Analysis. Asian Pac J Cancer Prev 2019;20:13-21.
6. Ren JQ, Liu JW, Chen ZT, Liu SJ, Huang SJ, Huang Y, et al. Prognostic value of the lymph node ratio in stage III colorectal cancer. Chin J Cancer 2012;31:241-7.
7. Shimomura M, Ikeda S, Takakura Y, Kawaguchi Y, Tokunaga M, Egi H, et al. Adequate lymph node examination is essential to ensure the prognostic value of the lymph node ratio in patients with stage III colorectal cancer. Surg Today 2011;41:1370-9.
8. Wong KP, Poon JT, Fan JK, Law WL. Prognostic value of lymph node ratio in stage III colorectal cancer. Colorectal Dis 2011;13:1116-22.
9. Yang L, Xiong Z, Xie Q, He W, Liu S, Kong P, et al. Prognostic value of total number of lymph nodes retrieved differs between left-sided colon cancer and right-sided colon cancer in stage III patients with colon cancer. BMC Cancer 2018;18:558.
10. Wang H, Wei XZ, Fu CG, Zhao RH, Cao FA. Patterns of lymph node metastasis are different in colon and rectal carcinomas. World J Gastroenterol 2010;16:5375-9.
11. Akagi Y, Adachi Y, Kinugasa T, Oka Y, Mizobe T, Shirouzu K. Lymph node evaluation and survival in colorectal cancer: review of population-based, prospective studies. Anticancer Res 2013;33:2839-47.
12. Ricciardi R, Madoff RD, Rothenberger DA, Baxter NN. Population-based analyses of lymph node metastases in colorectal cancer. Clin Gastroenterol Hepatol 2006;4:1522-7.
13. Balta AZ, Ozdemir Y, Sucullu I, Derici ST, Bagci M, Demirel D, et al. Can horizontal diameter of colorectal tumor help predict prognosis? Ulus Cerrahi Derg. 2014;30:115-9.

Effect of Ultrafiltration Rate in Long Interdialytic Interval Hemodialysis Session versus Average Weekly Ultrafiltration Rate on Mortality Rate and Adverse Cardiovascular Outcomes in Maintenance Hemodialysis Patients

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ABSTRACT

Objective: Cardiovascular events are more commonly observed during hemodialysis sessions after a long interdialytic interval compared to average weekly hemodialysis sessions, and ultrafiltration rate (UFR) was reported to be associated with cardiovascular outcomes. Whether the UFR during hemodialysis sessions after a long interdialytic interval is a better predictor of cardiovascular outcome than the average weekly UFR is unknown.

Methods: The charts of patients aged >18 years with end-stage renal disease that received hemodialysis treatment Siriraj Hospital during January 2008 to December 2017 were retrospectively reviewed.

Results: Two hundred and forty-one patients (52.8% females) were included. During the median time follow-up of 54 months, the rate of adverse cardiovascular outcomes was 7.26 events/100-patient-years, and the mortality rate was 8.40 deaths/100-patient-years. Mean UFR was significantly higher in the long interdialytic interval hemodialysis sessions than in the average weekly UFR sessions (14.07±5.29 *vs.* 13.13±5.14 ml/h/kg, $p<0.001$). Compared with UFR of ≤10 ml/h/kg, the adjusted hazard ratio (HR) for mortality in the UFR >13 ml/h/kg subgroup was 1.29 (95% CI: 0.65-2.56) and 1.05 (95% CI: 0.55-2.03) in the long interdialytic interval hemodialysis sessions and the average weekly UFR, respectively. The adjusted HR for adverse cardiovascular outcome in the UFR >13 ml/h/kg subgroup was 1.32 (95% CI: 0.64-2.80) and 0.72 (95% CI: 0.36-1.35) in the long interdialytic interval hemodialysis sessions and the average weekly UFR, respectively.

Conclusion: This study revealed that the UFR in long interdialytic hemodialysis sessions has the trend to be associated with more adverse cardiovascular outcomes and all-cause mortality than the average weekly UFR. A larger population is needed to further elucidate the relationship between UFR and outcomes in Thai hemodialysis population.

Keywords: Ultrafiltration rate; cardiovascular outcomes; mortality, maintenance hemodialysis patients; long interdialytic interval hemodialysis; weekly hemodialysis (Siriraj Med J 2020; 72: 391-398)

INTRODUCTION

Volume management in maintenance hemodialysis (HD) patients is challenging. An increasing body of evidence points to association between fluid-related factors and treatment outcomes in these patients. Moreover, fluid retention or excessive interdialytic weight gain (IDWG) was found to be associated with adverse cardiovascular outcomes.[1-3] Experts suggest that

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normalization of extracellular fluid volume should be added to the traditional goals of dialysis that include molecule clearance and patient well-being.[4] Rapid fluid removal was also found to be associated with adverse cardiovascular outcomes and mortality in maintenance hemodialysis patients.[5-8] In addition, long interdialytic interval was found to be associated with cardiovascular morbidity, mortality, and higher risk of sudden death[9,10], which further suggests that volume abnormalities may be complicit. IDWG is commonly observed to be higher during dialysis after long interdialytic intervals compared to midweek dialysis, and this leads to a need for a higher ultrafiltration rate (UFR). Whether the UFR used during a long interdialytic interval hemodialysis session is a better predictor of patient outcomes compared to the UFR used during average weekly HD is still unclear. Accordingly, the aim of this study was to investigate the effect of ultrafiltration rate in long interdialytic interval hemodialysis session versus average weekly ultrafiltration rate on mortality rate and adverse cardiovascular outcomes in maintenance hemodialysis patients.

MATERIALS AND METHODS

Study design

The electronic medical charts of patients aged greater than 18 years with end-stage renal disease (ESRD) that received hemodialysis treatment at the Division of Nephrology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 1 January 2008 to 31 December 2017 were retrospectively reviewed. Patients were enrolled in the following phases: phase 1 – starting on 1 January 2008; phase 2 – starting on 1 January 2010; phase 3 – starting on 1 January 2012; and, phase 4 – starting on 1 January 2014. Each patient's baseline characteristics were considered at the time of enrollment. Baseline demographic characteristics and comorbidity data were collected. Baseline laboratory measurements were collected and calculated for difference in predialysis serum sodium (pre-HD SNa) and dialysate sodium (DNa), urea reduction ratio (URR), dialysis adequacy (single pool Kt/V), and normalized protein catabolic rate (nPCR). Hemodialysis data, including access type [arteriovenous fistula (AVF), arteriovenous graft (AVG), permanent catheter (PC), or double lumen catheter (DLC)], DNa, dry weight, IDWG, UFR, pre-hemodialysis (pre-HD) and post-hemodialysis (post-HD) blood pressures, were also collected at baseline. The estimation of baseline mean average weekly UFR was calculated from average UFR of the first 2 weeks of consecutive hemodialysis sessions at the time of enrollment for each phase. The UFR in the long interdialytic interval was calculated from the mean UFR in the beginning of week of hemodialysis sessions after the longest interdialytic period in the first 2 weeks at the time of enrollment. Pre-HD and post-HD blood pressure data were collected in the same way that average UFR data were collected. Patients were followed forward in the historical timeline until death or until the end of the study (31 December 2017). The protocol for this study was approved by the Siriraj Institutional Review Board (Si 043/2019). The requirement to obtain written informed consent was waived due to this study's retrospective design.

Data collection

All data were retrieved from an electronic medical records search of our hospital database. Demographic and comorbidity data were recorded at the time of admission to the dialysis unit, and that information was updated based on the patient's clinical status during the follow-up period. Laboratory data were measured monthly according to the standard protocol of the dialysis unit. Hemodialysis details were recorded during each dialysis session.

Exposures and outcomes

Prescribed UFR was calculated from net ultrafiltration estimated from IDWG (milliliters, ml) divided by duration of prescribed dialysis session in hours (h) of each hemodialysis session. UFR normalized for body weight is expressed as ml/h/kg. We assumed that the prescribed UFR was constant during the study period, and the HD sessions in the first 14 days of each phase was used for calculations.

The primary outcome was all-cause mortality. Patients were considered at risk for the study outcome during the exposure period until death or censoring for loss to follow-up or end of study (31 December 2017). The secondary outcomes were adverse cardiovascular outcomes (myocardial infarction, stroke or death from cardiovascular cause) and hospitalization rate. The effect of the average UFR and the UFR at the beginning of weekly hemodialysis sessions on mortality and adverse cardiovascular outcomes was also compared.

Statistical analysis

Cross-sectional data at baseline is presented as descriptive data using percentage for categorical variables, mean ± SD for continuous variables with normal distribution, and median and range (minimum, maximum) for continuous variables with non-normal distribution. Patients were categorized into 1 of the 3 following UFR subgroups: ≤10, 10-13, or >13 ml/h/kg.

The UFR of ≤10 ml/h/kg was used as a reference for comparison with the other 2 UFR subgroups relative to clinical outcomes. The UFR cutoff of 13 ml/h/kg, which was used in previous studies, is equivalent to 3 kg of IDWG in a post-HD body weight of 60 kg.[7,8,11] Association between UFR and outcomes was analyzed using log rank test and survival analysis, while overall survival was analyzed using Kaplan-Meier survival analysis. Cox proportional hazard analysis was used to identify association between different factors and survival. The results of that analysis are presented as hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using SPSS Statistics software version 18 (SPSS, Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

Baseline demographic, clinical, and laboratory data were stratified by UFR category, as shown in Tables 1 and 2. A total of 241 Thai patients (52.8% females) were included. The median time of follow-up was 54.05 months (min: 1.77, max: 118.77). The number of patients recruited in phase 1, 2, 3, and 4 was 121, 47, 37, and 43, respectively. The prescribed dialysis treatment was 2 sessions per week in 19%, and 3 sessions per week in 81% of all patients. Compared with the group of patients with UFR <10 ml/h/kg, patients in the higher UFR groups (10-13 and >13 ml/h/kg) were significantly younger and had a lower percentage of DM, hypertension, dyslipidemia, and cardiovascular disease; however, they had more IDWG, longer dialysis vintage, lower body weight, and a lower percentage of preserved residual renal function.

Association between average weekly UFR and outcomes

All-cause mortality and cardiovascular events in each UFR subgroup of average weekly UFR are presented in Table 3. Median time to all-cause mortality was 98.6 months, with a 5-year survival rate of 68.08%. Median time to adverse cardiovascular outcome was 108.33 months. Outcomes were adjusted for age, gender, history of cardiovascular disease (CVD), history of diabetes, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD blood pressure, post-HD blood pressure, Kt/V, and normalized protein catabolic rate (nPCR). Mean UFR in the long interdialytic interval hemodialysis group was significantly higher than in the average weekly UFR group (14.07±5.29

TABLE 1. Patient demographic and clinical characteristics.

Characteristics	UFR (ml/h/kg)			*P*-value
	≤10 (n=64)	10-13 (n=69)	>13 (n=108)	
Age (years)	68.3±12.7	60.2±14.1	50.9±14.5	***<0.001***
Female gender	54.7%	50.7%	50.9%	0.87
Duration of follow-up (months)	45.67 (1.77, 118.77)	59.97 (1.87, 118.73)	58.98 (3.73, 118.77)	***0.04***
Residual urine	36.0%	15.9%	12.0%	***<0.001***
No. of anti-HT drugs	1 (0, 5)	1 (0, 5)	1 (0, 6)	0.37
Underlying disease				
Coronary artery disease	25.0%	17.4%	11.1%	***0.06***
Stroke	7.8%	5.8%	3.7%	0.51
Peripheral artery disease	3.1%	1.4%	0.0%	0.21
Hypertension	54.7%	49.3%	35.2%	0.11
Diabetes mellitus	37.5%	20.3%	14.8%	***0.02***
Dyslipidemia	43.8%	39.1%	25.0%	***0.02***

Data presented as mean ± standard deviation, percentage, or median (minimum, maximum)

A *p*-value<0.05 indicates statistical significance

Abbreviations: UFR, ultrafiltration rate; HT, hypertension

TABLE 2. Hemodialysis factors at baseline.

Factors	UFR (ml/hr/kg)			*P*-value
	≤10 (n=64)	10-13 (n=69)	>13 (n=108)	
Dialysis vintage (months)	20.7 (0.2, 139.6)	39.7 (0.2, 255.5)	60.7 (0.2, 282.7)	***0.001***
HD sessions				0.14
2 per week	15.6%	27.5%	16.7%	
3 per week	84.4%	72.5%	83.3%	
Access				0.28
AVF	55.2%	63.0%	67.9%	
AVBG	5.2%	9.3%	9.0%	
Permanent catheter	32.8%	20.4%	15.4%	
Double lumen catheter	6.9%	7.4%	7.7%	
Dry weight (kg)	60.63±13.22	59.46±11.22	52.80±10.83	***<0.001***
Dry weight				***0.001***
≤50 kg	25.0%	18.8%	41.7%	
50-60 kg	26.6%	39.1%	33.3%	
>60 kg	48.4%	42.0%	25.0%	
UF (L)	1.78±0.66	2.71±0.54	3.67±0.76	***<0.001***
UFR (ml/h/kg)	7.33±2.09	11.4±0.77	17.67±3.67	***<0.001***
IDWG (%DW)	2.93±0.84	4.56±0.31	7.07±1.47	***<0.001***
Pre-HD SBP (mmHg)	148.0±20.0	149.0±18.0	152.0±16.0	0.34
Pre-HD DBP (mmHg)	76.0±11.0	78.0±9.0	80.0±11.0	0.07
Post-HD SBP (mmHg)	150.0±23.0	145.0±18.0	150.0±17.0	0.18
Post-HD DBP (mmHg)	77.0±9.0	78.0±9.0	80.0±9.0	0.20
Pre-HD SNa (mmol/L)	139.0±4.0	139.0±3.0	138.0±3.0	0.20
Delta SNa - DNa (mmol/L)	1 (-10, 8)	1 (-8, 5)	0 (-7, 5)	0.78
Serum albumin (g/dl)	3.84±0.36	3.98±0.36	4.00±0.30	0.06
Pre-HD BUN (mg/dl)	64.12±22.80	71.01±19.08	76.79±20.17	0.06
URR	70.4±29.8	74.9±22.7	79.7±15.5	0.11
Kt/V				
HD 2 times per week	2.12±0.45	2.05±0.48	2.08±0.28	0.89
HD 3 times per week	2.05±0.40	2.12±0.39	2.22±0.38	0.53
nPCR (g/kg/day)	1.0±0.25	1.05±0.27	1.11±0.32	0.06

Data presented as median (minimum, maximum), percentage, or mean ± standard deviation

A *p*-value <0.05 indicates statistical significance

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; AVF, arteriovenous fistula; AVBG, arterioveneous bridge graft; UF, ultrafiltration; UFR, ultrafiltration rate; IDWG, interdialytic weight gain; DW, dry weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; SNa, serum sodium; DNa, dialysate sodium; BUN, blood urea nitrogen; URR, urea reduction ratio; Kt/V, dialysis adequacy

TABLE 3. Association between UFR and all-cause mortality and cardiovascular events in each UFR subgroup of patients that received average weekly UFR.

Factors	Number of patients (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality			
UFR >13 ml/h/kg	41 (38.0%)	0.62 (0.39-1.01)	1.05 (0.55-2.03)
UFR 10-13 ml/h/kg	28 (40.6%)	0.77 (0.46-1.29)	0.97 (0.53-1.79)
UFR ≤10 ml/h/kg	29 (45.3%)	Reference	Reference
Cardiovascular events			
UFR >13 ml/h/kg	33 (30.6%)	0.67 (0.39-1.15)	0.72 (0.36-1.35)
UFR 10-13 ml/h/kg	24 (34.8%)	1.14 (0.64-2.02)	0.72 (0.38-1.35)
UFR ≤10 ml/h/kg	31 (48.4%)	Reference	Reference

[a]Adjusted for age, gender, history of CVD, DM, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD BP, post-HD BP, Kt/V, nPCR

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; HR, hazard ratio; CI, confidence interval

vs. 13.13±5.14 ml/h/kg, $p<0.001$). The median unadjusted HR for all-cause mortality and adverse cardiovascular outcome for patients in the average weekly UFR >13 ml/h/kg subgroup was 0.62 (0.39-1.01) and 0.67 (0.39-1.15), respectively. After adjusting for relevant factors, the higher average weekly UFR subgroups (UFR 10-13 and >13 ml/h/kg) were not found to be associated with increased all-cause mortality or adverse cardiovascular outcomes.

Association between UFR in long interdialytic hemodialysis session and outcomes

All-cause mortality and adverse cardiovascular events in each subgroup of UFR in the long interdialytic interval hemodialysis group are presented in Table 4. The mean IDWG of the hemodialysis sessions after the longest interval was 3.08±1.04 kg, and the mean UFR was 14.07±5.29 ml/h/kg. The two higher UFR (10-13 and >13 ml/h/kg) subgroups showed an increasing trend in all-cause mortality and adverse cardiovascular outcomes after adjustment for all relevant factors. A subgroup analysis in patients with 3 hemodialysis sessions per week was also performed, and a similar result was observed.

DISCUSSION

Previous studies have examined the association between mean UFR and mortality. Kim, *et al.* examined a US cohort of 110,800 patients who started hemodialysis and found a linear association between UFR and both all-cause and CV mortality, and UFR of more than 10 ml/h/kg was found to have the highest risk.[8] From the international Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort of 21,919 participants, Wong, *et al.* reported an elevated risk of mortality with relative IDWG of greater than 5.7%.[12] Using DOPPS cohort data, Saran, *et al.* found longer treatment time and slower UFR to be associated with lower mortality rate, and that UFR of >10 ml/h/kg was associated with more episodes of hypotension and higher mortality.[13] Assimon, *et al.* reported higher mortality in hemodialysis patients with higher UFR after being normalized for body weight, body mass index, and body surface area.[7]

In the present study, unadjusted HR for mortality and adverse cardiovascular outcomes tended to be higher in the UFR ≤10 ml/min group. This may be due to several confounding factors, including older age and more underlying diseases (diabetes, CAD, and

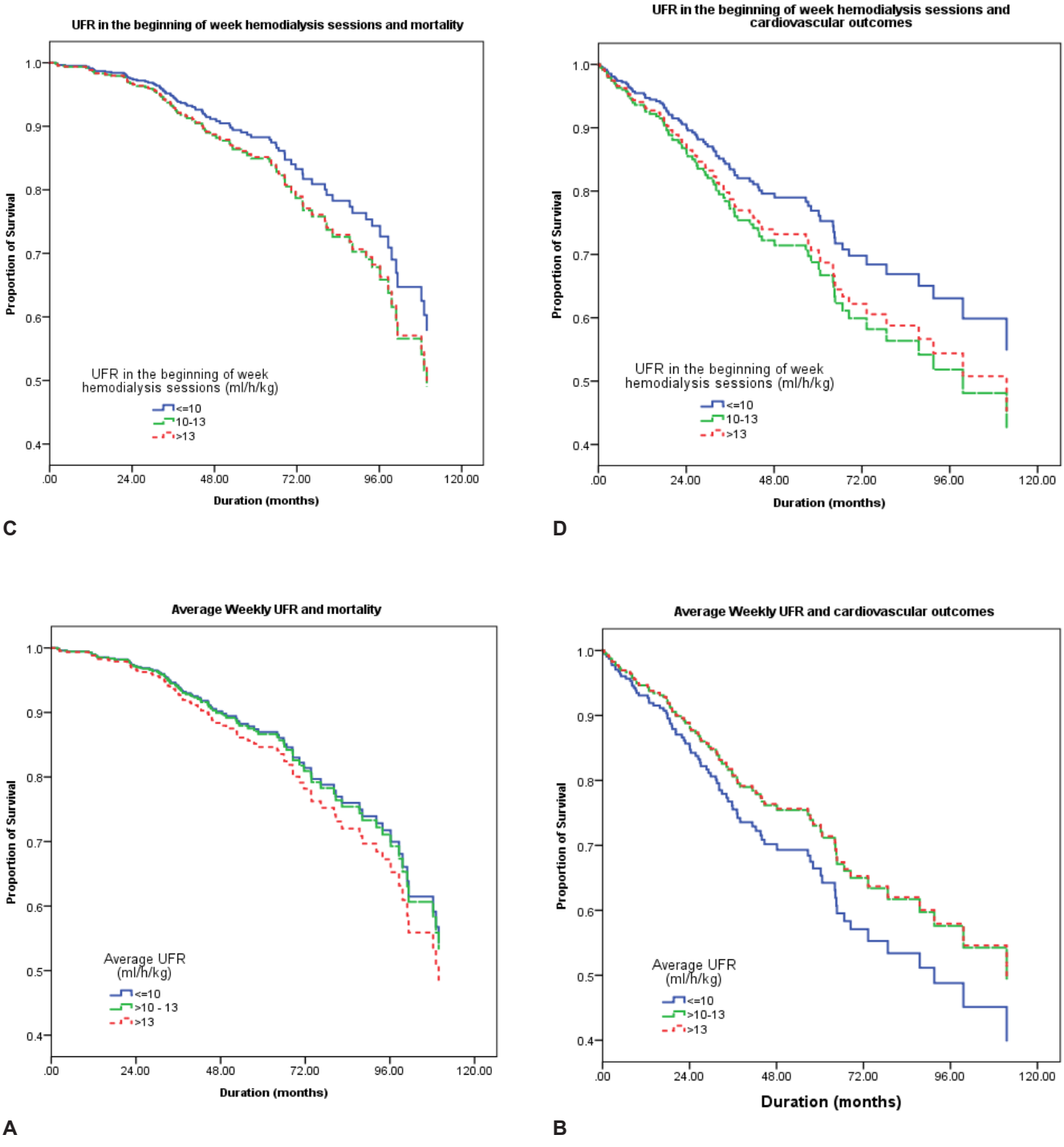

Fig 1. Kaplan-Meier survival analysis. UFR was categorized into 3 groups, as follows: ≤10 ml/h/kg shown in blue, 10-13 ml/h/kg shown in green, and >13 ml/h/kg shown in red. The associations between subgroup of UFR and outcomes are shown. Association between UFR after the longest interval and mortality **(A)**, and between UFR after the longest interval and adverse cardiovascular outcomes **(B)**. Association between average weekly UFR and mortality **(C)**, and adverse cardiovascular outcomes **(D)**.

TABLE 4. Association between UFR and all-cause mortality and cardiovascular events in each UFR subgroup of long interdialytic interval HD.

Factors	Number of patients (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality			
UFR >13 ml/h/kg	47 (37.0%)	0.76 (0.45-1.27)	1.29 (0.65-2.56)
UFR 10-13 ml/h/kg	30 (48.4%)	1.05 (0.60-1.83)	1.31 (0.66-2.59)
UFR ≤10 ml/h/kg	21 (40.4%)	Reference	Reference
Cardiovascular events			
UFR >13 ml/h/kg	39 (30.7%)	0.47 (0.28-0.78)	1.32 (0.64-2.80)
UFR 10-13 ml/h/kg	29 (46.8%)	0.62 (0.37-1.03)	1.43 (0.70-2.89)
UFR ≤10 ml/h/kg	20 (38.5%)	Reference	Reference

[a]Adjusted for age, gender, history of CVD, DM, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD BP, post-HD BP, Kt/V, nPCR

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; HR, hazard ratio; CI, confidence interval

dyslipidemia), whereas patients in the UFR >10 ml/hr/kg group were significantly younger. After adjusting for the relevant confounding factors, high average weekly UFR was not found to be associated with increased all-cause mortality (HR: 1.05) or adverse cardiovascular outcomes (HR: 0.97). In contrast, high UFR in the long interval hemodialysis sessions showed a trend of increasing risk for both all-cause mortality (HR: 1.29-1.31) and adverse cardiovascular outcomes (HR: 1.32-1.43). Our study found that higher UFR in long interdialytic hemodialysis session is a better predictor of all-cause mortality and adverse cardiovascular outcomes than average weekly UFR.

Limitations

The limitations of this study include its retrospective design and the small size of the study population. Moreover, we only observed the UFR over a short period, so it is possible that all UFRs that were prescribed in these patients were not included in our analysis, and this could mean that all statistical differences and associations between UFR and outcomes were not identified. To our knowledge, no previous study has compared the effects of UFR between long interdialytic hemodialysis sessions and average weekly UFR relative to all-cause mortality and cardiovascular outcome.

CONCLUSION

The results of this study showed that the UFR in long interdialytic hemodialysis sessions has the trend to be more strongly associated with adverse cardiovascular outcomes and all-cause mortality than the average weekly UFR. A larger study population is needed to confirm these findings, and to further elucidate the relationship between UFR and outcomes in Thai hemodialysis population.

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REFERENCES

1. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, Van Wyck D, Bunnapradist S, Horwich TB, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation 2009;119:671-9.
2. Lee MJ, Doh FM, Kim CH, Koo HM, Oh HJ, Park JT, et al. Interdialytic weight gain and cardiovascular outcome in incident hemodialysis patients. Am J Nephrol 2014;39:427-35.
3. Cabrera C, Brunelli SM, Rosenbaum D, Anum E, Ramakrishnan K, Jensen DE, et al. A retrospective, longitudinal study estimating the association between interdialytic weight gain and cardiovascular events and death in hemodialysis patients. BMC Nephrol 2015;16:113.
4. Weiner DE, Brunelli SM, Hunt A, Schiller B, Glassock R, Maddux FW, et al. Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. Am J Kidney Dis 2014;64:685-95.
5. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int 2011;79(2):250-7.
6. Assimon MM, Flythe JE. Rapid ultrafiltration rates and outcomes among hemodialysis patients: re-examining the evidence base. Curr Opin Nephrol Hypertens 2015;24:525-30.
7. Assimon MM, Wenger JB, Wang L, Flythe JE. Ultrafiltration Rate and Mortality in Maintenance Hemodialysis Patients. Am J Kidney Dis 2016;68:911-22.
8. Kim TW, Chang TI, Kim TH, Chou JA, Soohoo M, Ravel VA, et al. Association of Ultrafiltration Rate with Mortality in Incident Hemodialysis Patients. Nephron 2018;139:13-22.
9. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 2011;365:1099-107.
10. Agarwal R. Patients on three times-weekly haemodialysis have increased mortality during the long, 2-day interdialytic interval. Evid Based Med 2012;17:161-2.
11. Flythe JE, Assimon MM, Overman RA. Target weight achievement and ultrafiltration rate thresholds: potential patient implications. BMC Nephrol 2017;18:185.
12. Wong MM, McCullough KP, Bieber BA, Bommer J, Hecking M, Levin NW, et al. Interdialytic Weight Gain: Trends, Predictors, and Associated Outcomes in the International Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2017;69:367-79.
13. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006;69:1222-8.

Mortality and Prevalence of Falls, and Their Association with Psychiatric Diagnoses and Psychotropic Medications

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ABSTRACT

Objective: Falls are a significant health problem that can affect the quality of life of older adults. This study was undertaken to study the mortality and prevalence of falls, and their associations with psychiatric diagnoses and psychotropic medications.

Methods: The study was a retrospective 10-year data analysis of a general hospital database from 2006-2015. The prevalence, odds ratio, hazard ratio, and survival analysis were analyzed to study the association with falls.

Results: The overall prevalence of falls was 3.6%. Subjects with a psychiatric diagnosis had a 3.28 times greater chance of falls. Subjects taking prescribed psychotropic medication had a 1.76 times greater chance of falls. Survival analysis revealed a mean survival of 6.84 years after falls. The average survival years after falls was age-related. Subjects with a history of falls and carrying a psychiatric diagnosis had a mean survival of 6.55 years and a hazard ratio of 0.84. Subjects with a history of falls and taking prescribed psychotropic medication had a mean survival of 6.15 years and a hazard ratio of 1.27.

Conclusion: A psychiatric diagnosis and psychotropic medication prescriptions were associated with a greater chance of falls. Subjects with a history of taking prescribed psychotropic medication had a higher risk of mortality from falls.

Keywords: Falls; prevalence; psychiatric diagnosis; psychotropic medication; survival (Siriraj Med J 2020; 72: 399-406)

INTRODUCTION

Falls are a very significant health problem for the elderly. Falls are associated with disability, death, increased medical resources utilization,[1,2] and a limited sense of well-being and reduced quality of life in the elderly.[3,4] In Thailand, from the Annual Epidemiological Surveillance Report 2015, falls, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): W00–W19, were the second most common cause of injury, second only to traffic accidents, with an increasing risk of mortality associated with falls.[5]

In falls studies, the causes of falls are mainly divided into two major categories: internal and external. One of the most significant internal causes of falls is related to the medication prescribed by physicians. Although with different methodologies, populations of study, and definitions of falls, the research findings in this field indicate

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that prescribed medications are associated with a higher risk of falls, especially psychotropic medications. The most common psychotropic medications reported to be associated with falls are antipsychotics, antidepressants, antimanics, and anxiolytic-hypnotics.[6-9] Centrally-acting psychotropic medications have been reported to have side-effects of drowsiness, dizziness, orthostatic hypotension, blurred vision, gait and balance difficulties, and also abnormal movements, which are all associated with falls.[10]

Besides the studies of the association between falls and psychotropic medications, a psychiatric diagnosis has also been reported to be related with a history of injuries, falls, and accidents more than physical diagnoses,[11] which might be explained by the nature of psychiatric illnesses. Psychiatric disorders can affect a person's behavior and judgment and might cause injuries unable to be explained only from the side-effects of psychotropic medications. In addition, mental disorders, psychotropic medications, polypharmacy, and multiple psychotropic drug use have also been reported to be associated with accidental death and all-cause mortality.[12-14]

Many newer psychotropic medications have been launched on the market over the past 20 years. In Thailand, there has been an increasing evaluation of new psychiatric cases yearly, and the trend in prescribing psychotropic medication has also been escalating. This study aimed to look into the current situation of falls in a psychiatric context; in particular, to study the prevalence of falls in a general hospital setting, the association between falls and psychotropic medications and psychiatric diagnoses, and also the survival in subjects with a history of falls.

MATERIALS AND METHODS

Study design and population

The study involved a retrospective 10-year data analysis. The protocol was approved by Siriraj Hospital IRB (Si 375/2015). The study population consisted of all subjects included in Siriraj Hospital's database during the 10-year period from 2006 to 2015 as well as cases in the Siriraj Hospital Death Registry, which was updated and matched with the Thai National Death Registry (Fig 1).

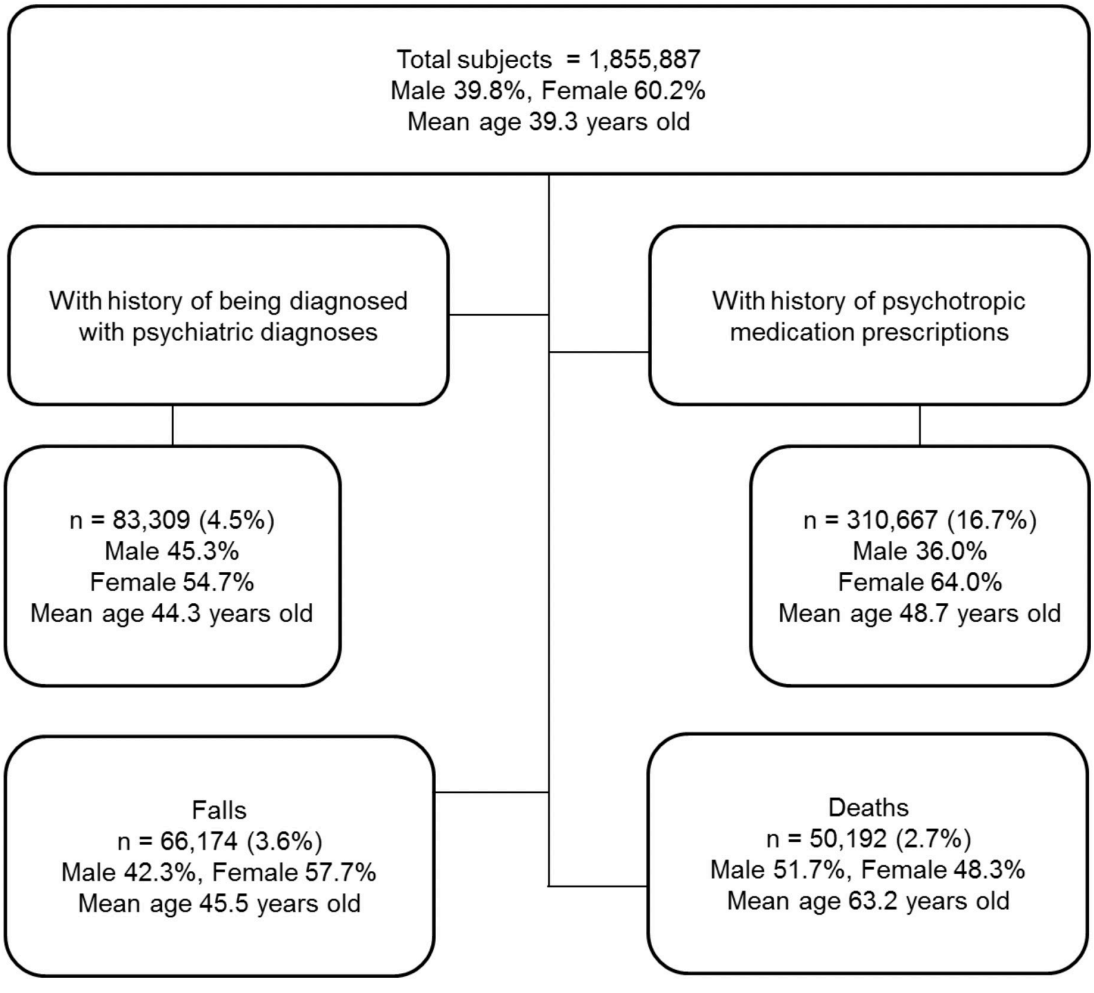

Fig 1. Diagram of the study process.

Procedure and data

The authors retrieved and classified data into four main groups: (1) subjects with and without a history of falls (ICD 10 codes: W00-W19), (2) subjects with and without a history of psychiatric diagnoses (ICD 10 codes: F00-F99), (3) subjects with and without a history of receiving any psychotropic medication before falls, including antidepressants, mood stabilizers, antipsychotics, hypnotics-anxiolytics, and cognitive enhancing agents groups, and 4) subjects with and without hospital death registration (Fig 1). We studied the association by comparing the data in each group.

Statistical analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS; version 18.0). We compared dependent variables, subjects with/without a history of falls, and independent variables, such as age, sex, psychiatric diagnosis, and psychotropic medications, by using chi-square tests. Multiple logistic regression analysis, adjusted for age, was performed to assess the associations of falls with psychiatric diagnoses and psychotropic medications. Kaplan–Meier (K-M) survival curves were calculated to determine survival years after falls for subjects with a history of psychiatric diagnoses and subjects with a history of taking psychotropic medication. Significances of the log-rank tests were interpreted at a two-sided alpha value of 0.05. Multivariate comparisons were performed with the adjusted Cox proportional hazards (PH) model. Significances of the hazard ratios (HR) estimates were based on a two-sided alpha value of 0.05, and confidence intervals at 95% were obtained for the estimations. Unadjusted and adjusted-for-age Cox PH models were tested for differences in survival years after falls in subjects with a psychiatric diagnosis and taking psychotropic medication.

RESULTS

Study population

The number and gender of the population in the study are shown in Fig. 1. There was a total of 1,855,887 subjects in the hospital database from 2006 to 2015. The mean age was 39.21±21.419 years. Their age ranged from 0-117 years. 39.8% were male. There were 66,174 falls, and 50,192 deaths recorded.

Association between falls and psychiatric diagnoses and psychotropic medications

Regarding subjects with a history of psychiatric diagnoses, there were 9,326 cases (11.2%) with a history of falls, whereas this figure was only 3.2% in subjects with no psychiatric diagnosis. Falls were age-related and more common in males. Subjects with a psychiatric diagnosis had a 3.28 (adjusted OR, 95%CI 3.20-3.37) greater chance of falls. The chances of falls, after adjusting for age, sex, marital status, and employment status, were the greatest in patients with organic mental disorders (F00-F09) and mental and behavioral disorders due to psychoactive substance use (F10-F19) (Table 1).

Regarding subjects with a history of previous psychotropic medication prescriptions, there were 14,850 cases (4.9%) with a history of falls, whereas this figure was only 2.6% in subjects without a history of receiving psychotropic medication prescriptions. Subjects with psychotropic medication prescriptions had a 1.76 (adjusted OR, 95%CI 1.73-1.80) times greater chance of falls. The strongest association between psychotropic medications and falls, after adjusting for age, sex, marital status, and employment status, was found in patients taking hypnotics-anxiolytics, mood stabilizers, cognitive enhancing agents, antidepressants, and antipsychotics, respectively (Table 1).

Survival in subjects with a history of falls and a history of psychiatric diagnoses and psychotropic medication use

There was a total of 66,174 recorded cases of falls, and a total of 50,192 deaths recorded in the 10-year hospital database, of which 6,537 deaths (9.9%) were patients with a history of falls.

There were 2,082 (22.3%) deaths recorded of subjects with a history of falls and having a psychiatric diagnosis, whereas 7.8% of deaths recorded were in subjects with a history of falls but who had no psychiatric diagnosis. Psychiatric diagnoses were predictive of decreased survival in subjects with a history of falls (HR 1.15; 95%CI 1.10-1.22). However, when adjusted for age, sex, marital status, and employment status, psychiatric diagnoses were not predictive of decreased survival (adjusted HR 0.84; 95%CI 0.79-0.89). The only decrease in survival chances was found in subjects with mental and behavioral disorders due to psychoactive substance use (adjusted HR 1.43; 95%CI 1.26-1.63) (Table 1).

There were 2,300 (15.5%) deaths recorded in subjects with a history of falls after receiving psychotropic medications, whereas 8.3% of deaths were recorded in subjects with a history of falls but who had no previous history of psychotropic medication prescriptions. Psychotropic medication prescriptions were predictive factors for decreased survival in subjects with a history of falls (adjusted HR 1.27; 95%CI 1.20-1.34). The largest decrease in survival was found in subjects with antipsychotics (adjusted HR 1.49; 95%CI 1.35-1.65), cognitive enhancing agents

TABLE 1. Logistic regression assessing the risk and Cox proportional hazards analysis of falls.

Variables	Total N	Fall N (%)	Risk of falls		Death after falls N (%)	Risk of Death	
			Unadjusted OR (95%CI)	Adjusted OR[b] (95%CI)		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)
Total	1,855,887	66,174 (3.6)			6,537 (9.9)		
Male	739,344	27,987 (3.8)	1.11 (1.09-1.13)[a]	1.13 (1.11-1.15)[a]	3,063 (10.9)	1.50 (1.43-1.57)[a]	2.01 (1.95-2.19)[a]
Age 60-79 years	307,491	16,592 (5.4)	1.91 (1.87-1.94)[a]	2.03 (1.99-2.08)[a]	3,009 (18.1)	3.53 (3.31-3.76)[a]	2.94 (2.71-3.19)[a]
Age ≥80 years	44,129	5,858 (13.3)	5.11 (4.97-5.26)[a]	4.95 (4.77-5.14)[a]	2,106 (36.0)	6.35 (5.94-6.79)[a]	4.87 (4.44-5.34)[a]
Employment status							
Employed	941,806	30,805 (3.3)	1	1	2,101 (6.8)	1	1
Non-employed	402,876	21,755 (5.4)	1.69 (1.66-1.72)[a]	1.43 (1.41-1.46)[a]	3,381 (15.5)	1.91 (1.81-2.01)[a]	1.06 (0.99-1.13)
Marital status							
Never married	799,037	28,157 (3.5)	1	1	987 (3.5)	1	1
Married	832,049	27,290 (3.3)	0.93 (0.91-0.94)[a]	0.58 (0.57-0.60)[a]	3,588 (13.1)	2.61 (2.44-2.80)[a]	1.44 (1.32-1.57)[a]
Divorced/Widowed	153,031	7,979 (5.2)	1.51 (1.47-1.54)[a]	0.73 (0.71-0.76)[a]	1,779 (22.3)	4.03 (3.73-4.35)[a]	2.03 (1.83-2.24)[a]
Psychiatric diagnoses							
F00-F09: Organic, including symptomatic, mental disorders	19,706	4,403 (22.3)	8.27 (7.98-8.56)[a]	5.17 (4.96-5.38)[a]	1,593 (36.2)	1.86 (1.75-1.96)[a]	0.92 (0.86-0.98)[a]
F10-F19: Mental and behavioral disorders due to psychoactive substance use	9,196	1,247 (13.6)	4.31 (4.05-4.57)[a]	3.98 (3.72-4.26)[a]	283 (22.7)	1.29 (1.14-1.45)[a]	1.43 (1.26-1.63)[a]
F20-F29: Schizophrenia, schizotypal, and delusional disorders	6,357	630 (9.9)	2.99 (2.76-3.25)[a]	2.40 (2.19-2.64)[a]	102 (16.2)	0.76 (0.62-0.92)[a]	0.81 (0.65-1.01)
F30-F39: Mood [affective] disorders	22,009	2,692 (12.2)	3.89 (3.73-4.05)[a]	3.20 (3.06-3.36)[a]	441 (16.4)	0.72 (0.65-0.79)[a]	0.64 (0.58-0.71)[a]
F40-F48: Neurotic, stress-related, and	24,452	2,161 (8.8)	2.68 (2.56-2.80)[a]	2.52 (2.40-2.65)[a]	190 (8.8)	0.40 (0.35-0.46)[a]	0.48 (0.41-0.56)[a]

[a] Statistically significant at $p < 0.05$, [b] Adjusted for age, sex, marital status, and employment status

Abbreviations: OR = Odds Ratio; HR = Hazard Ratio; CI = Confidence Interval

TABLE 1. Logistic regression assessing the risk and Cox proportional hazards analysis of falls. (continued)

Variables	Total N	Fall N (%)	Risk of falls		Death after falls N (%)	Risk of Death	
			Unadjusted OR (95%CI)	Adjusted OR[b] (95%CI)		Unadjusted HR (95%CI)	Adjusted HR[b] (95%CI)
F50-F59: Behavioral syndromes associated with physiological disturbances and physical factors	4,499	605 (13.4)	4.23 (3.88-4.61)[a]	3.54 (3.22-3.89)[a]	88 (14.5)	0.63 (0.51-0.78)[a]	0.52 (0.42-0.66)[a]
F60-F69: Disorders of adult personality and behavior	2,466	255 (10.3)	3.13 (2.75-3.56)[a]	3.06 (2.63-3.55)[a]	32 (12.5)	0.54 (0.38-0.77)[a]	0.77 (0.53-1.12)
F70-F79: Mental retardation	3,602	280 (7.8)	2.29 (2.02-2.58)[a]	2.68 (2.33-3.08)[a]	21 (7.5)	0.32 (0.21-0.49)[a]	1.12 (0.72-1.74)
F80-F89: Disorders of psychological development	9,571	550 (5.7)	1.65 (1.52-1.80)[a]	2.32 (2.10-2.56)[a]	14 (2.5)	0.12 (0.07-0.21)[a]	0.41 (0.23-0.71)[a]
F90-F98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	8,356	541 (6.5)	1.88 (1.72-2.05)[a]	2.53 (2.28-2.81)[a]	10 (1.8)	0.08 (0.04-0.14)[a]	0.40 (0.21-0.77)[a]
All psychiatric diagnoses	83,309	9,326 (11.2)	3.80 (3.72-3.89)[a]	3.28 (3.20-3.37)[a]	2,082 (22.3)	1.15 (1.10-1.22)[a]	0.84 (0.79-0.89)[a]
Psychotropic medications							
Antidepressants	127,249	5,662 (4.4)	1.51 (1.47-1.56)[a]	1.36 (1.31-1.40)[a]	753 (13.3)	1.24 (1.15-1.34)[a]	1.12 (1.03-1.21)[a]
Mood stabilizers	14,036	819 (5.8)	1.83 (1.71-1.97)[a]	1.60 (1.48-1.73)[a]	134 (16.4)	1.19 (1.01-1.42)[a]	1.09 (0.91-1.31)
Antipsychotics	42,751	2,111 (4.9)	1.62 (1.55-1.70)[a]	1.30 (1.23-1.36)[a]	461 (21.8)	1.83 (1.66-2.01)[a]	1.49 (1.35-1.65)[a]
Central nervous system stimulants	5,322	135 (2.5)	0.73 (0.62-0.87)[a]	0.97 (0.79-1.19)	3 (2.2)	0.17 (0.06-0.54)[a]	0.64 (0.20-1.97)
Cognitive enhancing agents	7,048	516 (7.3)	2.56 (2.34-2.80)[a]	1.45 (1.32-1.61)[a]	180 (34.9)	2.55 (2.19-2.95)[a]	1.43 (1.22-1.67)[a]
Drugs used in substance dependence	26,319	1,029 (3.9)	1.19 (1.12-1.27)[a]	1.06 (0.99-1.14)	98 (9.5)	1.05 (0.86-1.28)	0.99 (0.80-1.23)
Hypnotics and anxiolytics	225,234	11,280 (5.0)	1.93 (1.89-1.97)[a]	1.71 (1.67-1.76)[a]	1,774 (15.7)	1.52 (1.44-1.61)[a]	1.32 (1.25-1.40)[a]
All psychotropic medications	310,667	14,850 (4.8)	1.92 (1.89-1.96)[a]	1.76 (1.73-1.80)[a]	2,300 (15.5)	1.48 (1.41-1.56)[a]	1.27 (1.20-1.34)[a]

[a] Statistically significant at $p < 0.05$, [b] Adjusted for age, sex, marital status, and employment status

Abbreviations: OR = Odds Ratio; HR = Hazard Ratio; CI = Confidence Interval

(adjusted HR 1.36; 95%CI 1.17-1.58), and hypnotics-anxiolytics prescriptions (adjusted HR 1.24; 95%CI 1.17-1.31) (Table 1).

Survival analysis revealed an average mean survival of 6.84 (SE = 0.03; 95%CI 6.77–6.90) years after falls. The average survival years after falls was age related, whereby the survival was 8.53 (SE = 0.04; 95%CI 8.45–8.61) years in subjects aged under 60 years old, 5.92 (SE = 0.05; 95%CI 5.82–6.02) years in subjects aged 60–79 years old, and 3.88 (SE = 0.06; 95%CI 3.75–4.00) years in subjects aged 80 years old or more. Survival years were significantly shorter in subjects with a history of falls and having psychiatric diagnoses (mean survival = 6.55; SE = 0.06; $p < 0.0001$), and in subjects with a history of falls and having psychotropic medication prescriptions (mean survival = 6.15; SE = 0.07; $p =< 0.0001$) (Fig 2).

DISCUSSION

The prevalence of falls was higher in subjects with psychiatric diagnoses, 11.2%, with a 3.28-times greater chance of falls compared to subjects without a psychiatric diagnosis. The highest psychiatric diagnoses associated with falls were organic mental disorders (F00-09) (adjusted OR 5.17), and mental and behavioral disorders due to psychoactive substance use (F10-19) (adjusted OR 3.98). Subjects with a history of psychotropic medication prescriptions had a 1.76 greater chance of falls. The most common psychotropic medication associated with falls was hypnotics-anxiolytics (adjusted OR 1.71). After adjusting for age, sex, marital status, and employment status, the only psychiatric diagnosis associated with death after falls was mental and behavioral disorders due to psychoactive substance use (F10-19) (adjusted HR 1.43). The psychotropic medications associated with an increased risk of death after falls were antipsychotics, cognitive enhancing agents, hypnotics-anxiolytics, and antidepressants. Survival analysis revealed an average mean survival of 6.84 years after falls. The average survival years after falls was age related.

Mental disorders were reported to be associated with accidental death in a Swedish national cohort study,[12] with the three highest disorders stated as alcohol use disorder, other substance use disorders, and dementia. The hazard ratios of accidental death due to falls (ICD 10 W00-19) in subjects with a history of any psychiatric disorders were associated more with the male gender, 6.2 in men versus 4.6 in women.[12] The present study showed that the male gender (adjusted HR 2.01) and subjects with a history of falls and having mental and behavioral disorders due to psychoactive substance use had an increased risk of death (adjusted HR 1.43). However, psychiatric diagnoses were not associated with an increased risk of death after adjusting for age, sex, marital status, and employment status. This difference might be explained by the differences in population studied and the definition of fall-related deaths.[12]

From the results of this study, psychotropic medication prescriptions; hypnotics-anxiolytics, mood stabilizers, cognitive enhancing agents, antidepressants, and antipsychotics were significantly associated with falls, which was in line with meta-analyses showing that psychotropic medications and falls in the elderly are significantly correlated.[15,16] Benzodiazepines, antidepressants, and antipsychotics have all been shown to be significantly associated with falls injuries and hospitalization.[14-16] In the present study, hypnotics-anxiolytics showed the

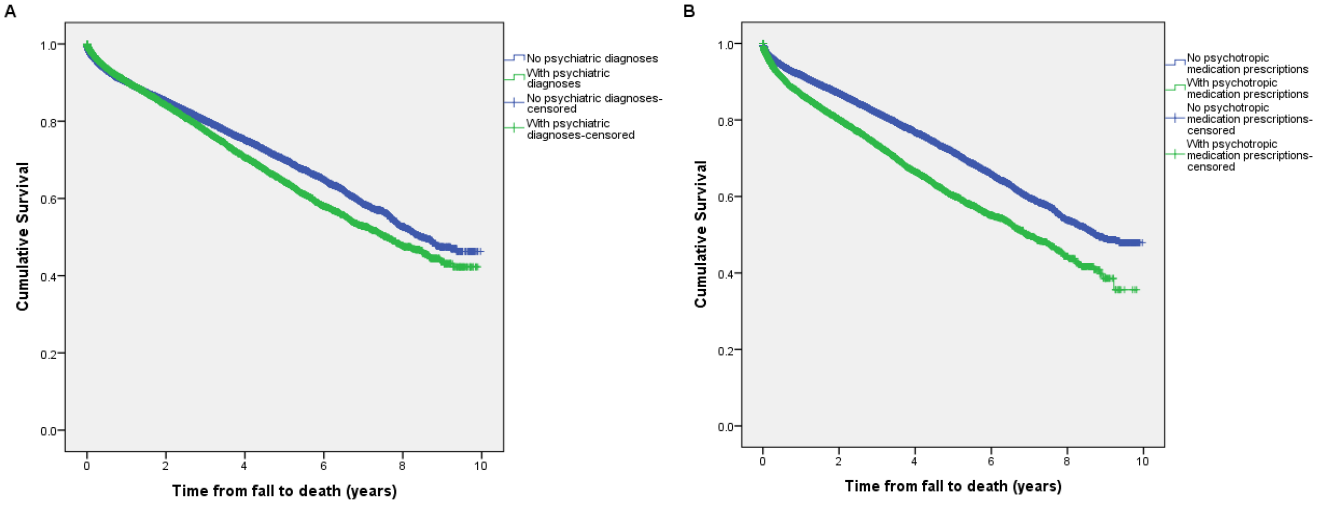

Fig 2. Time from fall to death **(A)** subjects with psychiatric diagnoses, and **(B)** subjects with history of psychotropic medication prescriptions

highest risk associated with falls, which is similar to the results from the meta-analyses.[16] Benzodiazepines are one of the most widely prescribed psychotropic medications and hypnotics-anxiolytics.[17] Benzodiazepines have been reported to increase postural sway and a loss of balance.[18] Besides the side-effects of benzodiazepines, differences in the duration of the half-life and the dosage of benzodiazepines are also related with a greater chance of falls.[19]

The association between mood stabilizers and falls is not well established. Since some anti-epileptics are classified as mood stabilizers and as most fall-related studies have been done on the elderly, their subjects were less likely to be prescribed anti-epileptics. However, in the present study, mood stabilizers were the psychotropic medications second most associated with falls. Anti-epileptics were reported to be associated with falls in emergency room visits by the elderly.[20] Further studies of falls and mood stabilizers might be needed.

In the present study, cognitive enhancing agents were the other psychotropic medications associated with falls. The detrimental effects of dementia medications may outweigh the benefits of dementia treatment in the elderly; for instance, side-effects, including syncope, dizziness, vertigo, nausea, and fatigue, were 2–5 times more common in patients who received dementia medications compared to a placebo.[21] Moreover, falls in the elderly were multifactorial. Besides psychiatric diagnoses and cognitive enhancing agent prescriptions, other causes, such as physiological changes, autonomic nervous system function, visibility, hearing, muscle strength, reaction time, a change in pharmacokinetics and pharmacodynamics,[22] multiple medical diagnoses,[23] and polypharmacy,[24] were also associated with falls.

This study showed that psychotropic medication prescriptions, antipsychotics, cognitive enhancing agents, hypnotics-anxiolytics, and antidepressants, after adjusting for age, sex, marital status, and employment status, were associated with falls and death, which was consistent with the study of mortality in a population-based cohort of older hip fracture patients.[13] Antipsychotics prescriptions had the highest association with death after falls, followed by cognitive enhancing agents, and hypnotics-anxiolytics, which was consistent with a nationwide study among older adults in Sweden.[14] A retrospective study and a meta-analysis from randomized controlled trials revealed that dementia medications might increase the risk of syncope; however, with no effects on falls, fracture, or accidental injury in dementia treatment in the elderly,[25,26] which was in contrast with the present study, which showed that after adjusting for age, cognitive enhancing agents were significantly associated with both falls and death after falls, but not the diagnosis of organic mental disorders. The dose, total number of medications, and the co-administration of medications for other physical disorders were also related with a risk of falls in the elderly,[27-29] but the data were not available in this study. In a study of falls after spinal cord injury, the mean survival was 7.4 years.[30] In the present study, subjects with a history of falls and having a psychiatric diagnosis had a shorter mean survival of 6.55 years.

Psychiatric diagnoses and psychotropic medication prescriptions were clearly associated with falls in the present study. Subjects with a history of being prescribed psychotropic medications were associated with a higher risk of mortality. Patients with psychiatric diagnoses and patients with a history of psychotropic medication prescriptions should benefit from fall-prevention measures.

The key strengths of this study were the use of a 10-year hospital database of all subjects, including outpatients, inpatients, and a death registry that was updated with the National Death Registry, and the fact all age groups were included. The limitations of this study were that the data were obtained only from one big university general hospital in Bangkok, Thailand, the retrospective nature of the study, and the fact that other clinical- and medication-related factors were not included in the study. Physical disorders, disease severity, medication adherence, use of over-the-counter drugs as well as non-psychotropic medications and total number of medications merit studying in future researches.

Our study may be confounded by other physical diagnoses and other medications besides psychotropic medications and central nervous system-acting medications. Furthermore, an ascertainment of falls diagnosis was obtained from computerized coding in the hospital database, not directly from a review of the medical records, and might possibly underrepresent the exact prevalence of falls.

In conclusion, our study demonstrates that psychiatric diagnoses and psychotropic medication prescriptions were significantly associated with 3.28-times and 1.76-times increased risks of falls, respectively. Furthermore, patients with a history of being prescribed psychotropic drugs were associated with a 1.92-times higher risk of mortality. Fall monitoring should be considered for patients with psychiatric diagnoses and for patients with a history of psychotropic medication prescriptions. In addition, physicians should consider prescribing psychotropic medication according to individuals' clinical needs and obviates unnecessary psychotropic drug use, especially in the elderly.

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Conflicts of Interest: None

REFERENCES

1. Vu T, Day L, Finch CF. The burden of hospitalised fall-related injury in community-dwelling older people in Victoria: a database study. Aust N Z Publ Health 2014;38:128-33.
2. Sartini M, Cristina ML, Spagnolo AM, Cremonesi P, Costaguta C, Monacelli F, et al. The epidemiology of domestic injurious falls in a community dwelling elderly population: an outgrowing economic burden. Eur J Public Health 2010;20:604-6.
3. Lach HW, Parsons JL. Impact of fear of falling in long term care: an integrative review. J Am Med Dir Assoc 2013;14:573-7.
4. Hartholt KA, van Beeck EF, Polinder S, van der Velde N, van Lieshout EM, Panneman MJ, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. J Trauma-Injury Infect Crit Care 2011;71:748-53.
5. Department of Disease Control. Severe injury due to accidental falls. In: Palipatna T, editor. Annual epidemiological surveillance report 2015. Nonthaburi, Thailand: Department of Disease Control, Minister of Public Health; 2016. p. 193-6.
6. Hill KD, Wee R. Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem. Drugs Aging 2012;29:15-30.
7. Heckenbach K, Ostermann T, Schad F, Kroz M, Matthes H. Medication and falls in elderly outpatients: an epidemiological study from a German Pharmacovigilance Network. SpringerPlus 2014;3:483.
8. Bozat-Emre S, Doupe M, Kozyrskyj AL, Grymonpre R, Mahmud SM. Atypical antipsychotic drug use and falls among nursing home residents in Winnipeg, Canada. Int J Geriatr Psychiatr 2015;30: 842-50
9. Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, et al. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. J Gerontol Ser A-Biol Sci Med Sci 2013;68:1575-81.
10. Kallin K, Lundin-Olsson L, Jensen J, Nyberg L, Gustafson Y. Predisposing and precipitating factors for falls among older people in residential care. Public Health 2002;116:263-71.
11. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PloS One 2015;10:e0116820.
12. Crump C, Sundquist K, Winkleby MA, Sundquist J. Mental disorders and risk of accidental death. Br J Psychiatry 2013;203:297-302.
13. Kragh Ekstam A, Elmstahl S. Do fall-risk-increasing drugs have an impact on mortality in older hip fracture patients? A population-based cohort study. Clin Interv Aging 2016;11:489-96.
14. Johnell K, Jonasdottir Bergman G, Fastbom J, Danielsson B, Borg N, Salmi P. Psychotropic drugs and the risk of fall injuries, hospitalisations and mortality among older adults. Int J Geriatr Psychiatry 2017;32:414-20.
15. Bloch F, Thibaud M, Dugue B, Breque C, Rigaud AS, Kemoun G. Psychotropic drugs and falls in the elderly people: updated literature review and meta-analysis. J Aging Health 2011;23:329-46.
16. Bloch F, Thibaud M, Tournoux-Facon C, Breque C, Rigaud AS, Dugue B, et al. Estimation of the risk factors for falls in the elderly: can meta-analysis provide a valid answer? Geriatr Gerontol Int 2013;13:250-63.
17. Griffin CE, 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J 2013;13:214-23.
18. Robin DW, Hasan SS, Edeki T, Lichtenstein MJ, Shiavi RG, Wood AJ. Increased baseline sway contributes to increased losses of balance in older people following triazolam. J Am Geriatr Soc 1996;44:300-4.
19. Passaro A, Volpato S, Romagnoni F, Manzoli N, Zuliani G, Fellin R. Benzodiazepines with different half-life and falling in a hospitalized population: The GIFA study. Gruppo Italiano di Farmacovigilanza nell'Anziano. J Clin Epidemiol 2000;53:1222-9.
20. Kelly KD, Pickett W, Yiannakoulias N, Rowe BH, Schopflocher DP, Svenson L, et al. Medication use and falls in community-dwelling older persons. Age Ageing 2003;32:503-9.
21. Buckley JS, Salpeter SR. A Risk-Benefit Assessment of Dementia Medications: Systematic Review of the Evidence. Drugs Aging 2015;32:453-67.
22. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp gerontol 2003;38:843-53.
23. Crentsil V, Ricks MO, Xue QL, Fried LP. A pharmacoepidemiologic study of community-dwelling, disabled older women: Factors associated with medication use. Am J Geriatr Pharmacother 2010;8:215-24.
24. Laflamme L, Monarrez-Espino J, Johnell K, Elling B, Moller J. Type, number or both? A population-based matched case-control study on the risk of fall injuries among older people and number of medications beyond fall-inducing drugs. PloS One 2015; 10:e0123390.
25. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc 2011;59:1019-31.
26. van Strien AM, Koek HL, van Marum RJ, Emmelot-Vonk MH. Psychotropic medications, including short acting benzodiazepines, strongly increase the frequency of falls in elderly. Maturitas 2013; 74:357-62.
27. Blachman NL, Leipzig RM, Mazumdar M, Poeran J. High-Risk Medications in Hospitalized Elderly Adults: Are We Making It Easy to Do the Wrong Thing? J Am Geriatr Soc 2017;65:603-7.
28. Sterke CS, van Beeck EF, van der Velde N, Ziere G, Petrovic M, Looman CW, et al. New insights: dose-response relationship between psychotropic drugs and falls: a study in nursing home residents with dementia. J Clin Pharmacol 2012;52:947-55.
29. Pan HH, Li CY, Chen TJ, Su TP, Wang KY. Association of polypharmacy with fall-related fractures in older Taiwanese people: age- and gender-specific analyses. BMJ Open 2014;4:e004428.
30. Hatch BB, Wood-Wentz CM, Therneau TM, Walker MG, Payne JM, Reeves RK. Factors predictive of survival and estimated years of life lost in the decade following nontraumatic and traumatic spinal cord injury. Spinal Cord 2017;55:540-4.

Retrospective Cohort Study on Effect of Frenulotomy Techniques on Breastfeeding

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ABSTRACT

Objective: The primary objective of this study was to compare the outcomes between frenulotomy by bedside technique and surgery under general anesthesia to successful breastfeeding in ankyloglossia infants. The secondary objective was to compare the differences in the infants' body weight, length of hospital stay and overall maternal satisfaction.

Methods: A quantitative research of retrospective cohort study was conducted in Naresuan University Hospital, Thailand between July 2012 and June 2017. We enrolled all infants born and identified the infants diagnosed with ankyloglossia. The severity of ankyloglossia was assessed at birth. Age of infants at the time of frenulotomy was on the second day of life. The outcomes of two types of frenulotomy were compared.

Results: Ankyloglossia was diagnosed in 187 (6.3%) of 2,968 infants born. The main breastfeeding problems in both groups were maternal sore nipples, cracked nipples and poor latch on. The infants in the bedside technique group had more successful rate of exclusive breastfeeding at day 7 when compared with the surgical group (87.3% and 39% respectively, $p<0.001$). More percent increment of infant's body weight at day 7 in the bedside technique group than the surgical group (60% and 20.8% respectively, $p<0.001$). Overall maternal satisfaction in the bedside technique group was notably higher than that in the surgical group (96.4% and 59.7% respectively, $p< 0.001$). The length of hospital stay was less in the bedside group for 1.2 days. More weight gain was found in the bedside group.

Conclusion: Frenulotomy is the procedure that should be performed in indicated ankyloglossia infants. This study found that bedside technique frenulotmy had association to a more satisfactory outcome than surgery under general anesthesia to successful breastfeeding.

Keywords: Ankyloglossia; tongue-tie; frenulotomy; breastfeeding (Siriraj Med J 2020; 72: 407-414)

INTRODUCTION

Breastfeeding benefits include immunity, decreased risk of allergy, greater intellectual quotient than formula-fed infants especially in exclusive breastfeeding for over 6 months.[1,2] Generally, mother and newborn are evaluated immediately during the postnatal period concerning breastfeeding position, latching technique, and sucking efficiency of the newborn. The correct latch-on technique displays peristaltic tongue movements. Infants with ankyloglossia or tongue-tie limit the range of motion of the tongue due to the tight lingual frenulum.[3] This causes severe discomfort to the mother having sore and cracked nipples and eventually fails to exclusively breastfeed.[4-7]

A frenulotomy is a surgical intervention usually done when the indications include latch-on problems, maternal sore nipples and substantial weight loss in infants.[8-16] The benefits after frenulotomy such as better latching, maternal nipple pain reduction, and maintenance of breastfeeding practices have been reported.[11,15,17,18] The conventional technique is the surgical frenulotomy

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done by the surgeons in the operating room under general anesthesia. An alternative way is the frenulotomy performed on the bedside by experienced neonatologists. This technique eliminates risks of general anesthesia and the infants are able to latch on immediately after the procedure.[14,19]

The primary objective of this study was to compare the outcome of two frenulotomy procedures for successful breastfeeding in ankyloglossia infants. In addition, the secondary objective was to compare the differences in the infants' body weight, length of hospital stay and overall maternal satisfaction.

MATERIALS AND METHODS

A quantitative research of retrospective cohort study was conducted. Data were collected from all infants born in Naresuan University Hospital, Phitsanulok, Thailand, whom were diagnosed with ankyloglossia and undergone frenulotomy between July 2012 and June 2017. The medical records of all included infants were reviewed. This study was approved by the Institutional Review Board of Naresuan University (COA No.539/2016). The assessment for a severity of ankyloglossia was done by using a quantitative tool. The inclusion criteria were the infants with ankyloglossia and undergone frenulotomy. The exclusion criteria were the infants with ankyloglossia who had a conservative treatment, incomplete follow up, missing data records or ankyloglossic infants who were unable to breastfed since birth according to any infant or maternal reason. The contents of all enrolled medical records included the assessment of ankyloglossia by using a quantitative tool, called "Siriraj Tongue Tie score; STT score"[20-22] (Fig 1), which scores both the appearance of tongue tie and the function of the tongue in attaching the maternal nipples. The indication for frenulotomy was the STT score of less than 8.[20,21]

The included infants were divided into 2 groups of frenulotomy types according to attending physician's consideration. The first group comprised infants with ankyloglossia who underwent frenulotomy by a bedside technique done by one neonatologist. The technical procedures[5,10,23,24] were as follows: First, the neonatologist applied a 2% Xylocaine Viscous topical anesthetic at the frenulum. The arterial clamps were used to stop the blood supply and hold the frenulum in place. Then, the frenulum was immediately snipped using the Metzenbaum scissors. Next, cotton buds were utilized to divide any attached residual frenulum at the base of tongue. Lastly, pressure was applied at the incision site using sterile-gauze in order to stop the bleeding.

The second group consisted of those who underwent frenulotomy by one surgeon.[25,26] The infants with ankyloglossia were transported to the operating room. After administering the general anesthesia, the surgeon used the electrocautery to cut the frenulum to prevent bleeding. The infants had to stay in the recovery room before sending them back to their mothers.

Data records collected contains birth weight, sex, gestational age, LATCH score[9,10,14,27-29] before frenulotomy, maternal nipple pain score (visual analog scale : VAS for nipple pain severity)[28,30-32] before frenulotomy, overall maternal satisfaction after each frenulotomy procedure, complications after frenulotomy and the length of hospital stay.

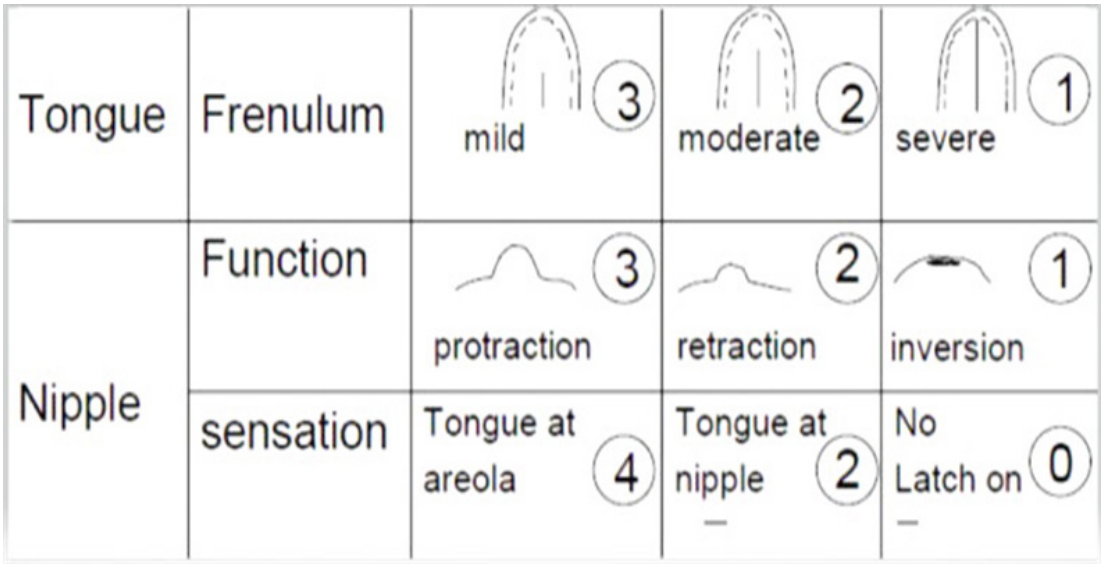

Fig 1. Siriraj Tongue Tie score (STT score)[20,21]

After hospital discharge, the information of follow up data records at 7 days and 6 months were reviewed and statistically analyzed as for the results of the increment of body weight in 7 days and exclusive breastfeeding success rate in 7 days and 6 months.

Statistical analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY). Continuous data were shown as mean+standard deviation (SD). Categorical data were shown as frequency and percentage. Independent T-test and Chi-square test were used to compare continuous and categorical data, respectively. The absolute differences between the two types of frenulotomy procedure with the p-values of <0.05 are considered to be statistically significant.

RESULTS

Of 2,968 infants born between July 2012 and June 2017, 187 infants were identified and diagnosed as having a significant ankyloglossia and met the inclusion criteria. Of these, 110 ankyloglossia infants were identified as to be in the first group of whom underwent bedside frenulotomy and 77 in the second group of whom underwent surgical frenulotomy under general anesthesia. Table 1 provides the demographic details and information of each frenulotomy group. The main breastfeeding problems in the first group were maternal nipple sore (76 from 110, 69.1%), cracked nipple (47 from 110, 42.7%) and poor latch on (20 from 110, 18.2%). The LATCH score was less than 7 (78.2%, mean+SD 6.2+1.5). The average maternal nipple pain score was 1.2±0.7. In the second group, there were similar breastfeeding problems as in the first group. There were maternal nipple sore (58 from 77, 75.3%), cracked nipple (53 from 77, 68.8%) and poor latch on (17 from 77, 22.1%). The LATCH score was less than 7 (90.9%, mean+SD 5.9±1.3). The average maternal nipple pain score was 1.5±0.7.

Although the indication for frenulotomy was the STT score less than 8, there were 6 infants that undergone frenulotomy despite the STT score more than 8. The reasons were parental concern about feeding problems, speech articulation problems. Therefore, the doctor had to do the frenulotomy after their discussion.[33]

Data shown in Table 2 are follow-up records in each frenulotomy group. The infants in the first group had the mean body weight of 3,083.5±358.9 grams on day 7. Their increment of body weight was 60%, 39.6±14.4 grams. The mean percentage of body weight difference at birth and on day 7 was1.4±0.5 grams. The success rate of exclusive breastfeeding on day 7 and 6 months were 87.3%and 70.0%, respectively. On the contrary, the infants in the second group had the mean body weight of 3,028.2±361.3 grams on day 7. The increase of body weight was 20.8%, -24.6±13.7 grams. The mean percentage of body weight difference at birth and on day 7 was -0.7±0.5 grams. The success rate of exclusive breastfeeding on day 7 and 6 month were 39.0% and1.3%, respectively.

Analysis between the two types of frenulotomy procedures showed that infants who had the bedside technique (the first group) of frenulotomy had a significantly higher success rate of exclusive breastfeeding on day 7 than those who had surgery under general anesthesia (the second group)(87.3% and 39.0%, respectively, p < 0.001).When using Risk ratio, the infants in the first group had greater chances of successful exclusive breastfeeding on day 7 when compared with the second group. (RR =2.23; 95%CI: 1.68 to 2.99) as shown in Table 3.

In addition, the types of frenulotomy procedures were associated with overall maternal satisfaction (p<0.001). The satisfaction rate in the first group was 96.4% while the second group was 59.7%. When using Risk ratio, the first group had greater chances (1.62) of overall maternal satisfaction after frenulotomy (RR=1.62; 95%CI: 1.34 to 1.94).The types of frenulotomy procedures were also associated with the increment of infant's body weight on day 7 (p<0.001). Increase of infant's body weight on day 7 for the first and second groups was recorded at 60.0%and 20.8%, respectively. The Risk ratio result was 2.89 higher in the first group (RR=2.89; 95%CI:1.82 to 4.58) as shown in Table 3.

The mean nipple pain scores for the groups undergoing bedside technique and surgical technique were 1.2±0.1 and 1.5±0.1, respectively. This was not statistically significant (p = 0.012). The mean difference was -0.3 (95%CI: -0.5 to -0.1).

The infants in the first group had a significant shorter length of hospital stay than the infants in the second group (4.4±0.2 vs 5.6±0.2, p< 0.001). The first group had lesser length of hospital stay than the second group with the mean difference of 1.2 days (95%CI: -1.8 to -0.7).

The infants in the first group had the average mean difference in infant's body weight of 39.6 ±14.4 grams while in the second group had the average mean difference of -24.6±13.7 grams. When compared, there was a statistical significance (p =0.002) in the weight difference between the two groups.The results also found that infants in the first group had more weight gain (64.3 grams) when compared to the second group (95%CI: 23.5-105.1) as shown in Table 4.

TABLE 1. Participant Demographics.

Characteristics	Bedside technique (n=110) (%)	Surgical technique (n=77) (%)	*P*-value
Sex			
Male	63 (57.3)	48 (62.3)	0.488
Gestational age (weeks)			
> 37	106 (96.4)	74 (96.1)	
Birth weight (grams)			
< 3,000	45 (40.9)	34 (44.2)	0.658
Mode of delivery			
Vaginal	47 (42.7)	34 (44.2)	0.464
Cesarean section	58 (52.7)	42 (54.5)	
Vacuum extraction	5 (4.6)	1 (1.3)	
STT score (Siriraj Tongue tie score)			
> 8	4 (3.6)	2 (2.6)	
Mean (± S.D.)	6.4 (0.9)	6.5 (0.8)	
Breast feeding problems (may be >1 problems)			
Cracked nipple	47 (42.7)	53 (68.8)	<0.001
Sore nipple	76 (69.1)	58 (75.3)	0.352
Inadequate milk flow	35 (31.8)	17 (22.1)	0.143
Short nipple	14 (12.7)	9 (11.7)	0.831
Poor latch on	20 (18.2)	17 (22.1)	0.510
Significant infant's weight loss	2 (1.8)	2 (2.6)	0.717
LATCH score			0.021
< 7	86 (78.2)	70 (90.9)	
>7	24 (21.8)	7 (9.1)	
Mean (± SD)	6.16 (1.5)	5.9 (1.3)	
Nipple pain score (VAS)			0.012
Mean (±SD)	1.2 (0.7)	1.5 (0.7)	

TABLE 2. Outcome after Frenulotomy.

Outcome	Bedside technique (n=110) (%)	Surgical technique (n=77) (%)	*P*-value
Body weight on day 7 (grams)			0.303
Mean (± SD)	3,083.5 (358.9)	3,028.2 (361.3)	
Body weight difference (grams)			<0.001
Increase	66 (60.0)	16 (20.8)	
Decrease	44 (40.0)	61 (79.2)	
Mean (± SD)	39.6 (14.4)	-24.6 (13.7)	
Percentage of body weight difference			0.003
Mean (± SD)	1.4 (0.5)	-0.7 (0.5)	
Exclusive breastfeeding on day 7			<0.001
Yes	96 (87.3)	30 (39.0)	
Exclusive breastfeeding on the 6th month			<0.001
Yes	77 (70.0)	1 (1.3)	

TABLE 3. Outcome Comparison between two types after frenulotomy.

Outcome	Bedside technique (n=110) (%)	Surgical technique (n=77) (%)	Risk ratio (RR) (95 % CI)	*P*-value
Successful rate of exclusive breastfeeding on day 7				
Success	96 (87.3)	30 (39.0)	2.23 (1.68-2.99)	<0.001
Not success	14 (2.7)	47 (61.0)		
Overall maternal satisfaction				
Satisfy	106 (96.4)	46 (59.7)	1.62 (1.34-1.94)	<0.001
Unsatisfied	4 (3.6)	31 (40.3)		
Increment of infant's body weight on day 7				
Increase	66 (60.0)	16 (20.8)	2.89 (1.82-4.58)	<0.001
Decrease	44 (40.0)	61 (79.2)		

TABLE 4. Comparison of nipple pain score, length of hospital stay and the difference of infant's body weight.

Procedure	N	Mean	S.D.	Mean Difference	95 %CI	*P*-value
Nipple pain score						0.012
Bedside technique	110	1.2	0.1			
Surgical technique	77	1.5	0.1	-0.3	-0.5 to -0.1	
Length of hospital stay (days)						<0.001
Bedside technique	110	4.4	0.2			
Surgical technique	77	5.6	0.2	-1.2	-1.8 to -0.7	
Difference of infant's body weight						0.002
Bedside technique	110	39.6	14.4			
Surgical technique	77	-24.6	13.7	64.3	23.5 to 105.1	

DISCUSSION

Ankyloglossia is the condition that leads to limitation of tongue movement by the attachment of lingual frenulum to floor of mouth. This can lead to maternal sore and cracked nipples, and eventually a failure of exclusive breastfeeding.[1,6] Several studies have shown the association between ankyloglossia and unsuccessful breastfeeding. They found that predominant cause that brings the mothers to the hospitals is sore nipples but after the surgical release, the nipple pain score has considerably improved with a significant correlation of the average score point of the nipple pain before and after the surgery.[5,9,13,34,35] However, the nipple sore that occurs in the first 3 weeks of breastfeeding causes 10-26% of the mothers to stop breastfeeding.[36] Schlomer et al. have reported that 64-84% of infants are diagnosed with ankyloglossia. In fact, difficult latch on can be found in 25% of infants with ankyloglossia compared with only 3% in normal infants. In their study, using an infant breastfeeding assessment tool, significant difference in scores between pre and post frenulectomy has been found among ankyloglossia infants.[37]

The definition of ankyloglossia in our current study was based on Siriraj Tongue Tie Score (STT Score), which is a standard quantitative assessment tool for ankyloglossia evaluation in Thailand.[20,21] The STT score is used to evaluate the appearance of frenulum, nipple function and sensation of tongue when infants was latching on. The benefit of this assessment tool is that physicians and nurses can accurately detect ankyloglossia and provide indication for treatment.[38] Surgical frenulotomy performed in the operating room with general anesthesia is a conventional treatment for ankyloglossia. In contrast, the bedside technique, which is currently used, is advantageous on both the mother and the infants. This method is conveniently performed at bedside or outpatient department without anesthesia complications and infants can be breastfed immediately after the procedure.[19,39,40] However, only few studies were conducted regarding the advantages of bedside technique and data on the comparison between the two types of procedures are insufficient.

Our study found that the incidence of ankyloglossia was 6.3%. The main breastfeeding problems are nipples sore, cracked nipple and poor latch on, which are similar to the previous studies.[5,13,34] After we analyzed the data from two groups of frenulotomy procedures, we found that infants who underwent bedside technique had a significant success rate of exclusive breastfeeding at day 7 as compared with the surgical procedure with general anesthesia. The types of frenulotomy procedures are associated with the increment of infant's body weight on day 7, with the bedside technique outperforming the surgical technique. The overall maternal satisfaction rate after frenulotomy is higher and the length of hospital stay is significantly shorter in the bedside technique than in the surgical technique. The factors that affected different outcomes between the two techniques were the mode of anesthesia. In bedside technique, we used the

local anesthesia so the infants can immediately return to breast fed. While we were using the general anesthesia in surgical technique that need longer time to return to breastfeeding after surgery. The types of equipment we used for frenulotomy also affected different outcomes. The electrocauterization that we used in surgical technique can cause the complication such as wound swelling more than the scissor in bedside technique. Therefore, the infants had more length of hospital stay and the overall successful in breastfeeding was less in the surgical technique. In our study, we did not found the complication such as massive blood loss, wound infection or any damage to the tongue or salivary glands after each procedures. The limitation of this study is its retrospectivity where the randomization between groups could not be done and there is a lack of control group without undergoing frenulotomy.

The expected benefit of our research is to encourage the physicians charge with the care of breastfeeding mothers of infants with ankyloglossia on how to effectively select the appropriate frenulotomy procedures. However, the characteristics of ankyloglossia such as the thickness and the muscular type ankyloglossia, the surgical technique with electrocautery should be considered to minimize the risk of active bleeding.

CONCLUSION

Ankyloglossia is one of the major issues affecting breastfeeding of infants. The significant problems associated with ankyloglossia are maternal nipple sore, cracked nipples and poor infant latch on which may cause early cessation of breastfeeding. Frenulotomy is the procedure that should be performed in indicated ankyloglossia infants. This study found that bedside technique frenulotmy had association to a more satisfactory outcome to successful breastfeeding, more increment of infant's body weight, higher maternal satisfaction and also shorten duration of hospitalization than surgical technique. Further randomized, prospective, and long-term follow-up studies are also needed to determine whether the types of frenulotomy is appropriate to any infants.

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REFERENCES

1. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al. Breastfeeding and the use of human milk. Pediatrics 2005;115:496-506.
2. Edmunds J, Miles SC, Fulbrook P. Tongue-tie and breastfeeding: a review of the literature. Breastfeed Rev 2011;19:19-26.
3. Mills N, Keough N, Geddes DT, Pransky SM, Mirjalili SA. Defining the anatomy of the neonatal lingual frenulum. Clin Anat 2019;32:824-35.
4. Ricke LA, Baker NJ, Madlon-Kay DJ, DeFor TA. Newborn tongue-tie: prevalence and effect on breast-feeding. J Am Board Fam Pract 2005;18:1-7.
5. Hong P, Lago D, Seargeant J, Pellman L, Magit AE, Pransky SM. Defining ankyloglossia: a case series of anterior and posterior tongue ties. Int J Pediatr Otorhinolaryngol 2010;74:1003-6.
6. Messner AH, Lalakea ML, Aby J, Macmahon J, Bair E. Ankyloglossia: incidence and associated feeding difficulties. Arch Otolaryngol Head Neck Surg 2000;126:36-9.
7. Edmunds JE, Fulbrook P, Miles S. Understanding the experiences of mothers who are breastfeeding an infant with tongue-tie: a phenomenological study. J Hum Lact 2013;29:190-5.
8. Kumar M, Kalke E. Tongue-tie, breastfeeding difficulties and the role of Frenotomy. Acta Paediatr 2012;101:687-9.
9. Srinivasan A, Dobrich C, Mitnick H, Feldman P. Ankyloglossia in breastfeeding infants: the effect of frenotomy on maternal nipple pain and latch. Breastfeed Med 2006;1:216-24.
10. Dollberg S, Botzer E, Grunis E, Mimouni FB. Immediate nipple pain relief after frenotomy in breast-fed infants with ankyloglossia: a randomized, prospective study. J Pediatr Surg 2006;41:1598-600.
11. Buryk M, Bloom D, Shope T. Efficacy of neonatal release of ankyloglossia: a randomized trial. Pediatrics 2011;128:280-8.
12. Geddes DT, Langton DB, Gollow I, Jacobs LA, Hartmann PE, Simmer K. Frenulotomy for breastfeeding infants with ankyloglossia: effect on milk removal and sucking mechanism as imaged by ultrasound. Pediatrics 2008;122:e188-94.
13. Ballard JL, Auer CE, Khoury JC. Ankyloglossia: assessment, incidence, and effect of frenuloplasty on the breastfeeding dyad. Pediatrics 2002;110:e63.
14. Surijamorn S, Laohapensang M, Wongvisuthi T. The comparison of frenulotomy with conventional frenuloplasty in the management of breastfeeding difficulty: A randomized controlled trial. Thai J Surg 2004;25:79-83.
15. Muldoon K, Gallagher L, McGuinness D, Smith V. Effect of frenotomy on breastfeeding variables in infants with ankyloglossia (tongue-tie): a prospective before and after cohort study. BMC Pregnancy Childbirth 2017;17:373.
16. Walsh J, Links A, Boss E, Tunkel D. Ankyloglossia and Lingual Frenotomy: National Trends in Inpatient Diagnosis and Management in the United States, 1997-2012. Otolaryngol Head Neck Surg 2017;156:735-40.
17. Berry J, Griffiths M, Westcott C. A double-blind, randomized, controlled trial of tongue-tie division and its immediate effect on breastfeeding. Breastfeed Med 2012;7:189-93.
18. Power RF, Murphy JF. Tongue-tie and frenotomy in infants with breastfeeding difficulties: achieving a balance. Arch Dis Child 2015;100:489-94.
19. Yeh ML. Outpatient division of tongue-tie without anesthesia in infants and children. World J Pediatr 2008;4:106-8.

20. Srisasalux J, Tantaviwong A. Proceedings of R2R (Routine to Research); 2008 Jul 2-3; Miracle Grand Hotel. Bangkok, Thailand: Health Systems Research Institute; 2008. p. 101-22.
21. Sawasdivorn S, editors. Proceedings of the 6th National Breastfeeding Conference: "Sustaining Breastfeeding Together" [Internet]. Bangkok: Thai Breastfeeding Center Foundation; 2017. [cited 2020 Jun 4]. Available from: https://library.thaibf.com/bitstream/handle/023548404.11/451/TBC-TNBC-2017-Proceeding.pdf?sequence=1&isAllowed=y
22. Laohapensang M. Tongue tie [Internet]. Bangkok. [cited 2020 Jun 4]. Available from: https://www.si.mahidol.ac.th/th/department/surgery/surgery%20new/file/division/ped.html
23. Lalakea ML, Messner AH. Ankyloglossia: does it matter? Pediatr Clin North Am 2003;50:381-97.
24. Chaubal TV, Dixit MB. Ankyloglossia and its management. J Indian Soc Periodontol 2011;15:270-2.
25. Manfro AR, Manfro R, Bortoluzzi MC. Surgical treatment of ankyloglossia in babies--case report. Int J Oral Maxillofac Surg 2010;39:1130-2.
26. Junqueira MA, Cunha NN, Costa e Silva LL, Araujo LB, Moretti AB, Couto Filho CE, et al. Surgical techniques for the treatment of ankyloglossia in children: a case series. J Appl Oral Sci. 2014;22(3):241-8.
27. Jensen D, Wallace S, Kelsay P. LATCH: a breastfeeding charting system and documentation tool. J Obstet Gynecol Neonatal Nurs 1994;23:27-32.
28. McGuire W, Soll R. Commentary on "Frenotomy for Tongue-Tie in Newborn Infants". Neonatology 2020;117:1-3.
29. Puapornpong P, Raungrongmorakot K, Mahasitthiwat V, Ketsuwan S. Comparisons of the latching on between newborns with tongue-tie and normal newborns. J Med Assoc Thai 2014;97:255-9.
30. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;18:205-7.
31. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217-26.
32. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45-56.
33. Chinnadurai S, Francis DO, Epstein RA, Morad A, Kohanim S, McPheeters M. Treatment of ankyloglossia for reasons other than breastfeeding: a systematic review. Pediatrics 2015;135:e1467-74.
34. Puapornpong P, Paritakul P, Suksamarnwong M, Srisuwan S, Ketsuwan S. Nipple Pain Incidence, the Predisposing Factors, the Recovery Period After Care Management, and the Exclusive Breastfeeding Outcome. Breastfeed Med 2017;12:169-73.
35. O'Shea JE, Foster JP, O'Donnell CP, Breathnach D, Jacobs SE, Todd DA, et al. Frenotomy for tongue-tie in newborn infants. Cochrane Database Syst Rev 2017;3:CD011065.
36. Hogan M, Westcott C, Griffiths M. Randomized, controlled trial of division of tongue-tie in infants with feeding problems. J Paediatr Child Health 2005;41:246-50.
37. Schlomer JA, Kemmerer J, Twiss JJ. Evaluating the association of two breastfeeding assessment tools with breastfeeding problems and breastfeeding satisfaction. J Hum Lact 1999;15:35-9.
38. Ngerncham S, Laohapensang M, Wongvisutdhi T, Ritjaroen Y, Painpichan N, Hakularb P, et al. Lingual frenulum and effect on breastfeeding in Thai newborn infants. Paediatr Int Child Health 2013;33:86-90.
39. Wallace H, Clarke S. Tongue tie division in infants with breast feeding difficulties. Int J Pediatr Otorhinolaryngol 2006;70:1257-61.
40. Griffiths DM. Do tongue ties affect breastfeeding? J Hum Lact 2004;20:409-14.

Active Learning Classes in a Preclinical Year May Help Improving Some Soft Skills of Medical Students

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ABSTRACT

Objective: Active learning methods are an effective way to improve essential soft skills, such as critical thinking and social skills, and so medical educators frequently implement active learning approaches as a means to improve the soft skills of medical students. This study reports an improvement in the soft skills of medical students after the implementation of an active learning curriculum.

Methods: More active learning activities were implemented in 2016 in the 3rd year medical class, involving 330 students. Overall, the number of hours devoted to active learning classes was increased from 340 hours (38.2%) in 2015 to 481 hours (59.98%) in 2016. To evaluate whether this led to any improvements in the soft skills of medical students, students undertaking the 3rd year course in the 2015 and 2016 academic years were asked to complete questionnaires to evaluate themselves (self-evaluation) as well as four other students in their same study group (peer-evaluation) at the end of the academic year. The questionnaire responses from the 2015 and the 2016 groups were compared.

Results: Most students believed there was no improvement in most of the evaluated soft skills during the year. However, students in the 2016 class showed improvements in eleven outcomes in the peer-evaluation: presentation, information, technology, creativity, communication, leadership, life planning, adaptability, self-sufficiency, courtesy, and punctuality ($p < 0.05$). The differences were not due to the students' different background skills as the initial scores of most outcomes were identical between the two student groups ($p > 0.05$).

Conclusion: Even without a proper design for teaching soft skills, active learning classes in a preclinical year of the medical curriculum may help improve some of the essential soft skills that medical practitioners need and, therefore, should be implemented in the medical curriculum.

Keywords: Active learning; small group discussion; medical curriculum; preclinical teaching; soft skills (Siriraj Med J 2020; 72: 415-423)

INTRODUCTION

In order to be fully prepared for the medical profession, medical students must acquire knowledge in medicine and master essential procedural skills, for which they must engage in a long period of extensive higher level learning.[1] But besides medical knowledge and procedural skills, medical students also need to possess other essential skills to function as medical professionals, including critical thinking and communication skills, teamwork and collaboration skills, information assessment skills, and other life skills.[2] These skills are collectively termed 'soft skills.' However, in contrast to medical knowledge

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and procedural skills, soft skills are hardly directly taught or evaluated in the 6-year medical curriculum taught in Thai medical schools.[3]

The preclinical curriculum comprises the second and third year of the medical curriculum. Traditionally, the preclinical curriculum in Thailand is based on large-group teaching with occasional laboratory classes. Large-group teaching, such as lectures, are considered appropriate for the delivery of a large amount of knowledge from the lecturer to the students in a limited time.[4,5] However, in this approach students passively take in knowledge with little or no class participation, and as such, they hardly develop any high-level learning or essential soft skills during the process.[1,6] In order for high-level learning to be achieved and soft skills to be taught, other teaching methods are needed. We hypothesized that active learning classes might have some effects on soft skills development or improvement in medical students.

Active learning is defined as "a teaching method that involves students' active participation in class." In this approach, instead of receiving one-way information from lecturers, the students contribute and gain knowledge through taking part in various activities, such as group discussions, debates, and presentations.[7] Active learning has been proven to improve students' academic performance and satisfaction.[8,9] Also, as students get to communicate in class and express their ideas, active learning also improves students' team cooperation, critical thinking, and presentation skills, all of which are essential soft skills.[10]

This study tested whether there was an improvement in the soft skills outcomes of medical students after the implementation of an active learning curriculum, using self- and peer-evaluation questionnaires to gather the research data.[11,12] Although the number of hours devoted to active learning activities was increased, the activities were not specifically designed to teach such skills. We evaluated improvements in 14 expected soft skills outcomes based on 4 essential skills, namely medical professionalism, learning and innovation skills, life and career skills, and information literacy. We gathered data from students in the modified class in 2016, which included a higher number of hours devoted to active learning, and from students who took the traditional class in 2015 before the curriculum changes, and compared their results.

MATERIALS AND METHODS

Structure of the medical curriculum

Our medical curriculum structure has been described previously in the literature.[13] Briefly, Thai medical students enter medical school promptly after finishing high school and then follow a 6-year medical curriculum. The second and third years of the curriculum, termed the "preclinical years," focus on the teaching of basic medical sciences related to the normality and abnormality of human bodies, respectively. Both preclinical years are divided into two parts: 'general concepts' and 'organ systems.' The general concepts and organ system parts focus on introductory subjects and the applications of those introductory subjects to human organ systems, respectively. No real patients are involved in these preclinical years. The expected knowledge outcomes of both parts of the training are based on the Medical Competency Assessment Criteria for National License 2012 established by the Medical Council of Thailand.[14]

Implementation of more active learning hours in the medical curriculum

In 2016, a change was made to the third-year medical curriculum structure taught at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, to include various active learning methods in the medical curriculum, including both large- and small-group teaching, as shown in Table 1. Team-based learning[15], flipped classrooms[16], and formative evaluations were also introduced.

Creation of a tool for evaluating the soft skills outcomes

As part of the new curriculum evaluation and development, an online questionnaire was created to assess selected soft skills outcomes based on the "21st-century skills" needed by modern medical practitioners[17], including medical professionalism, learning and innovation skills, life and career skills, and information literacy. The online questionnaire was critically amended and finally approved by the medical education expert committee of the Undergraduate Education Division, Faculty of Medicine Siriraj Hospital. Table 2 presents an example of the questionnaire used to evaluate 14 soft skills outcomes of the medical students in 4 main categories: (1) information literacy (presentation, information, and technology), (2) learning and innovation skills (creativity and communication), (3) life and career skills (leadership, life planning, adaptability, and self-sufficiency) and (4) medical professionalism (courtesy, responsibility, punctuality, kindness, and honesty).

Comparison of soft skills outcomes

A total of 234 third-year medical students in the class of 2015 (before the curriculum change, thus representing a traditional learning group) and 294 third-year medical students in the class of 2016 (first year of the change,

TABLE 1. Comparison of the teaching hours in the traditional (2015) and active (2016) learning curricula.

Teaching methods	Description	Teaching hours (%) 2015	2016
Total number of classes		**890 (100)**	**802 (100)**
Large-group teaching (330 students per class with 1–5 instructors per class)		**550 (61.80)**	**409 (51.00)**
Traditional lectures	- Passive one-way lectures - Giving basic knowledge of the designated knowledge outcomes	430 (48.31)	170 (21.20)
Case-based lectures	- Passive one-way lectures - Giving applications of basic knowledge based on simple clinical cases	120 (13.48)	151 (18.83)
Large active-learning*	- Interactive lectures with quizzes and instructors' feedback - Giving applications of basic knowledge based on simple clinical cases	0 (0.00)	88 (10.97)
Small-group teaching (5 small-groups of 5-6 students per room facilitated by 1–3 instructors and a total of 12 rooms were run simultaneously)		**340 (38.20)**	**393 (49.00)**
Traditional group discussions*	- Group discussions based on assigned worksheets of selected topics - Giving basic knowledge of the designated knowledge outcomes - Students' reflections and instructors' feedback	24 (2.70)	14 (1.75)
Case-based group discussions*	- Group discussions based on assigned worksheets of clinical cases - Giving applications of basic knowledge based on simple clinical cases - Students' reflections and instructors' feedback	180 (20.22)	223 (27.81)
Laboratory skills*	- Hands-on laboratory practice - Students' reflections and instructors' feedback	45 (5.06)	28 (3.49)
Demonstrative laboratory*	- Demonstration of laboratory results, followed by - Students' reflections and instructor feedback	91 (10.22)	46 (5.74)
Flipped classroom*	- Pre-class assignments given 1 week in advance, followed by - In-class students' reflections and instructor feedback	0 (0.00)	26 (3.24)
Team-based learning*	- Individual readiness assurance test (iRAT), followed by - Group RAT (gRAT), then instructor feedback, followed by - Application exercises on clinical cases, followed by - Students' reflections and instructors' feedback	0 (0.00)	26 (3.24)
Formative evaluations*	- MCQs or short answer questions at the end of each study section - Students' reflections and instructors' feedback	0 (0.00)	27 (3.37)
Project-based learning*	- A project is chosen based on student–instructor discussions - Students conduct the project over a period of 1–2 months - Students' reflections and instructors' feedback during the activity	0 (0.00)	3 (0.37)

*Active learning classes

TABLE 2. Example of the questionnaire used to evaluate the 14 soft skill outcomes.

Give scores representing your ability or behavior in the following aspects **5 = very good; 4 = good; 3 = neutral; 2 = bad; 1 = very bad**										
Soft skills outcomes	**Yourself**		**Lab Partner 1**		**Lab partner 2**		**Lab partner 3**		**Lab partner 4**	
	At present	**1st day of year 3**	**At present**	**1st day of year 3**	**At present**	**1st day of year 3**	**At present**	**1st day of year 3**	**At present**	**1st day of year 3**
Information literacy										
1. Presentation										
2. Information										
3. Technology										
Learning and innovation skills										
4. Creativity										
5. Communication										
Life and career skills										
6. Leadership										
7. Life planning										
8. Adaptability										
9. Self-sufficiency										
Medical professionalism										
10. Courtesy										
11. Responsibility										
12. Punctuality										
13. Kindness										
14. Honesty										

thus representing an active learning group) were asked to complete the web-based questionnaire at the end of their respective academic year. Briefly, each student received a username and password to log in to the questionnaire. Each student was then asked to score him or herself (self-evaluation) and to score other four members of his/her study group (peer-evaluation) according to the list of soft skills (Table 2). The students were asked to score by using a Likert scale ranging from 1 (very bad) to 5 (very good) at two time points: at the beginning of the academic year and at the end of the academic year. After excluding controversial results, including partially filled questionnaires and questionnaires with the same scores for all the responses, the results for each question scored at the beginning and at the end of the academic year were compared. To eliminate response bias in the use of the Likert scale, the results were only categorized as either an improvement (positive change) or no improvement (no change). It was noteworthy, however, that a negative change was not found in this study.

Statistical analysis

The improvement rate of each outcome was evaluated using the chi-square test. Scores at the beginning of the academic year were compared between the two groups using the Mann–Whitney U test. All the analyses were performed using Statistical Package for the Social Sciences (SPSS®) for Windows 18.0. Statistical significance was achieved at $p < 0.05$.

RESULTS

The number of hours involving active learning was markedly increased in the active learning group (2016)

All the active learning classes were mainly designed for teaching medical knowledge or procedural skills. None of them were specifically designed for teaching soft skills. Overall, the number of hours devoted to active learning was increased in the active learning group (2016; 481 hours, 59.98%) compared to the traditional learning group (2015; 340 hours, 38.2%). Also, the amount of hours devoted to large-group teaching decreased (550 hours to 409 hours) while small-group teaching increased (340 hours to 393 hours). For the large-group teaching, the traditional lecture classes decreased (430 hours to 170 hours) while the time devoted to case-based lecture classes increased (120 hours to 151 hours) and more large active-learning-activities classes were introduced (88 hours). For the small-group teaching, the number of hours devoted to traditional group discussion classes decreased (24 hours to 14 hours) while case-based group discussion classes increased (180 hours to 223 hours). However, the time devoted to both hands-on and demonstrative laboratory classes decreased (45 and 91 hours to 28 and 46 hours, respectively).

Students in the 2016 group reported more improvement in most soft skills outcomes in the peer-evaluation

After excluding the controversial results, there were 119 and 187 self-evaluation responses and 527 and 820 peer-evaluation responses returned from the 2015 and 2016 groups, respectively. According to the self-evaluation results (Table 3), most students (58-100%) in both 2015 and 2016 groups believed there was no improvement in each of their soft skill outcomes. The number of those who believed there was an improvement of these skills were not statistically different comparing between the two groups. Similarly found in the peer-evaluation results (Table 4), as most students in both groups (65-100%) believed there was no improvement in each soft skill outcomes of their peers. However, there were significantly higher numbers of the students in the 2016 group who believed there was an improvement in these skills of their peers. Specifically, the improvement was detected in 11 outcomes (presentation, information, technology, creativity, communication, leadership, life planning, adaptability, self-sufficiency, courtesy, and punctuality). Both student groups had similar improvement rates in terms of responsibility and kindness. There was no improvement in the honesty outcome in both groups.

Students in both the traditional (2015) and active learning groups (2016) had similar initial scores in most outcomes

One possible reason for the higher improvements of the students in the 2016 group in 11 out of the 14 soft skills outcomes evaluated may be that the 2016 class might have started with lower rating scores at the beginning of the academic year, or initial scores, which would then have allowed more room for improvement when compared to the 2015 group. Therefore, we tested if this was such a case. The initial scores of the 11 soft skills outcomes between the two academic years were compared. The initial scores of nine outcomes were similar in both academic years (Table 5). The initial score for punctuality of the 2016 class was not lower, but the initial scores for the presentation skills of the 2016 class were significantly lower. Interestingly, the initial scores of the three outcomes with similar improvements between the two groups (namely, responsibility, kindness, and honesty) of the 2016 class were significantly higher in both the self- and peer-evaluations.

TABLE 3. Number of students showing improvements in soft skills outcomes as evaluated by self-evaluation.

Outcomes	Groups	No improvement (%)	Improvement (%)	*P*-value
Presentation	2015	69 (58%)	50 (42%)	0.740
	2016	112 (60%)	75 (40%)	
Information	2015	80 (67%)	39 (33%)	0.196
	2016	111 (60%)	75 (40%)	
Technology	2015	84 (71%)	35 (29%)	0.150
	2016	117 (63%)	70 (37%)	
Creativity	2015	82 (69%)	37 (31%)	0.448
	2016	121 (65%)	66 (35%)	
Communication	2015	78 (66%)	41 (34%)	0.597
	2016	117 (63%)	70 (37%)	
Leadership	2015	79 (66%)	40 (34%)	0.338
	2016	114 (61%)	73 (39%)	
Life planning	2015	86 (72%)	33 (28%)	0.168
	2016	121 (65%)	66 (35%)	
Adaptability	2015	91 (76%)	28 (24%)	0.088
	2016	126 (67%)	61 (33%)	
Self-sufficiency	2015	99 (83%)	20 (17%)	0.325
	2016	147 (79%)	40 (21%)	
Courtesy	2015	89 (75%)	30 (25%)	0.198
	2016	127 (68%)	60 (32%)	
Responsibility	2015	82 (69%)	37 (31%)	0.344
	2016	119 (63%)	68 (37%)	
Punctuality	2015	94 (79%)	25 (21%)	0.125
	2016	133 (71%)	54 (29%)	
Kindness	2015	92 (77%)	27 (23%)	0.789
	2016	147 (79%)	40 (21%)	
Honesty	2015	119 (100%)	0 (0%)	U
	2016	187 (100%)	0 (0%)	

Note: U = incalculable by Chi-square test; p-value calculated by Chi-square test.

TABLE 4. Number of students showing improvements in soft skills outcomes as evaluated by peer-evaluation.

Outcomes	Groups	No improvement (%)	Improvement (%)	*P*-value
Presentation*	2015	383 (73%)	144 (27%)	0.004
	2016	534 (65%)	286 (35%)	
Information*	2015	421 (80%)	106 (20%)	< 0.001
	2016	530 (65%)	290 (35%)	
Technology*	2015	421 (80%)	106 (20%)	< 0.001
	2016	574 (70%)	246 (30%)	
Creativity*	2015	415 (79%)	112 (21%)	0.02
	2016	600 (73%)	220 (27%)	
Communication*	2015	417 (79%)	110 (21%)	0.004
	2016	592 (72%)	228 (28%)	
Leadership*	2015	424 (80%)	103 (20%)	< 0.001
	2016	546 (67%)	274 (33%)	
Life planning*	2015	413 (78%)	114 (22%)	0.002
	2016	579 (71%)	241 (29%)	
Adaptability*	2015	429 (81%)	98 (19%)	< 0.001
	2016	591 (72%)	229 (28%)	
Self-sufficiency*	2015	452 (86%)	75 (14%)	0.045
	2016	669 (82%)	151 (18%)	
Courtesy*	2015	418 (79%)	109 (21%)	0.001
	2016	587 (72%)	233 (28%)	
Responsibility	2015	401 (76%)	126 (24%)	0.251
	2016	601 (73%)	219 (27%)	
Punctuality*	2015	431 (82%)	96 (18%)	< 0.001
	2016	588 (72%)	232 (28%)	
Kindness	2015	438 (83%)	89 (17%)	0.702
	2016	688 (84%)	132 (16%)	
Honesty	2015	527 (100%)	0 (0%)	U
	2016	820 (100%)	0 (0%)	

*Statistically significant; U = incalculable by Chi-square test; p values were calculated by Chi-square test.

TABLE 5. Comparison of the average initial scores between the traditional (2015) and active learning (2016) groups.

Outcomes	Self-evaluation			Peer-evaluation		
	2015	2016	*P*-value	2015	2016	*P*-value
Presentation*	3.96	3.88	0.268	4.19	4.12	0.030
Information	4.18	4.18	0.751	4.35	4.29	0.053
Technology	4.21	4.26	0.692	4.41	4.43	0.381
Creativity	4.04	4.12	0.469	4.26	4.25	0.511
Communication	4.15	4.19	0.760	4.36	4.37	0.550
Leadership	3.90	3.87	0.656	4.06	4.02	0.199
Life planning	4.18	4.22	0.977	4.38	4.37	0.832
Adaptability	4.24	4.36	0.236	4.39	4.39	0.909
Self-sufficiency	4.31	4.42	0.263	4.49	4.50	0.547
Courtesy	4.08	4.21	0.177	4.27	4.35	0.052
Responsibility**	3.98	4.26	0.001	4.30	4.48	< 0.001
Punctuality*	4.34	4.43	0.169	4.34	4.41	0.029
Kindness**	4.38	4.60	0.014	4.49	4.68	< 0.001
Honesty**	4.75	4.84	0.031	4.72	4.83	< 0.001

*Statistical significance for the peer evaluation; **Statistical significance for both the self- and peer-evaluation; p-values were calculated by Mann–Whitney U test.

DISCUSSION

The active learning method was implemented in the third-year medical curriculum in 2016 for teaching medical students at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, as it has been proven to enhance academic performance and independent learning.[8,9] It has also been reported to improve many essential soft skills.[10] Despite the lack of a specific design for teaching soft skills, students in the active learning group (the 2016 group) had higher improvement rates in 11 out of the 14 soft skills outcomes evaluated based on peer-evaluation compared to the traditional group, namely students in the 2015 class prior to the curriculum change. This implies that the active learning method is potentially superior to the traditional learning method in developing some soft skill outcomes. This result is similar to that reported in a recent systematic review of problem-based learning in China, which reported that such improvement came from the nature of group discussion, where students need to express their ideas and exchange their opinions with their peers.[10]

It should be first noted that despite some statistical difference in the peer-evaluation outcomes, most of the students in both groups believe there was no difference in the performances both of themselves and of their peers. This is likely due to the short study duration as these soft skills need to be developed over a longer period of time. A follow-up study at the end of the 6-year curriculum may be useful to clarify this point.

The similar initial scores of nine of the outcomes in both groups justified the higher improvement rates of those soft skills. The 2016 class even had a higher initial score for punctuality, in which they also showed greater improvements. The lower initial score for presentation skills was very minimal (4.19 vs. 4.12). However, whether the higher initial scores in the 2016 group for responsibility and kindness would result in the no difference in improvement between the two groups is controversial and requires further study. Finally, no improvement was detected in the honesty outcome. Among the tested outcomes, the honesty outcome had the highest initial scores in both student groups (4.72 and

4.84 in the 2015 and 2016 classes, respectively), leaving only a small gap for improvement. To further evaluate the honesty outcome, a study with higher discriminatory power is needed.

It should be noted that there was no significant difference in improvement rates of any of the tested outcomes observed in the self-evaluation responses. It is possible that the small sample size could account for the insignificant results from the self-evaluation questionnaires. However, other possible factors should also be considered. For instance, self-evaluation questionnaires are potentially subject to bias, which may lead to obscure data, especially in non-grade-associated outcomes, such as soft skills.[18] Moreover, one study reported that only peer-evaluation had a significant correlation with educator evaluation.[19]

There were two major limitations to this study. Firstly, there were higher proportions of relevant responses from both self- and peer- evaluation in the 2016 group which might have skewed the results. Secondly, all students were asked to complete the questionnaire at the end of their academic years and, therefore, had to recall their performances at the beginning of the year. This might lead to somewhat over- or underestimate of the performances. However, as the two groups were treated in the same manner, we believe these biases would be minimal.

CONCLUSION

In conclusion, even without applying a specific design for teaching soft skill outcomes, the active learning classes in a preclinical year of the medical curriculum may help improve some of the soft skills of medical students. However, as self- and peer-evaluation could be subject to bias and the Hawthorne effect, a standard in-depth method for the measurement of the quality of each soft skill is needed. Additionally, further study may include the study of number of time comsuming (in hours) outside the classroom in order to prepare for the active learning classes.

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REFERENCES

1. Krathwohl DR. A revision of Bloom's taxonomy: an overview. Theory into Practice 2002;41:212-8.
2. Häkkinen P, Järvelä S, Makitalo-Siegl K, Ahonen A, Näykki P, Valtonen T. Preparing teacher-students for twenty-first-century learning practices (PREP 21): a framework for enhancing collaborative problem-solving and strategic learning skills. Teach Teach 2017;23:25-41.
3. Dede C. Comparing Frameworks for "21st Century Skills". In: Bellanca J, Brandt R, editors. 21st century skills. Bloomington, IN: Solution Tree Press; 2009.p.51-76.
4. Charlton BG. Lectures are such an effective teaching method because they exploit evolved human psychology to improve learning. Med Hypotheses 2006;67:1261-5.
5. Cantillon P. ABC of learning and teaching in medicine - Teaching large groups. Bmj-Brit Med J 2003;326:437-40.
6. Lujan HL, DiCarlo SE. Too much teaching, not enough learning: what is the solution? Adv Physiol Educ 2006;30:17-22.
7. Felder RM, Brent R. Active learning: An introduction. ASQ Higher Education Brief 2009;2:1-5.
8. Azer SA, Hasanato R, Al-Nassar S, Somily A, AlSaadi MM. Introducing integrated laboratory classes in a PBL curriculum: impact on student's learning and satisfaction. BMC Med Educ 2013;13:71.
9. Freeman S, Eddy SL, McDonough M, Smith MK, Okoroafor N, Jordt H, et al. Active learning increases student performance in science, engineering, and mathematics. Proc Natl Acad Sci U S A 2014;111:8410-5.
10. Zhang S, Xu JC, Wang HW, Zhang D, Zhang QC, Zou LG. Effects of problem-based learning in Chinese radiology education: A systematic review and meta-analysis. Medicine 2018;97.
11. Zhang A. Peer Assessment of Soft Skills and Hard Skills. Journal of Information Technology Education: Research 2012;11:115-68.
12. Cimatti B. Definition, Development, Assessment of Soft Skills and Their Role for the Quality of Organizations and Enterprises. Int J Qual Res 2016;10:97-129.
13. Imwattana K, Kiratisin P, Techasintana P, Ngamskulrungroj P. An impact on medical student knowledge outcomes after replacing peer lectures with small group discussions. MedEdPublish 2018.
14. Medical Competency Assessment Criteria for National License 2012: The Medical Council of Thailand; 2012 [Available from: http://www.tmc.or.th/download/medical2555.pdf.
15. Parmelee D, Michaelsen LK, Cook S, Hudes PD. Team-based learning: A practical guide: AMEE Guide No. 65. Med Teach 2012;34:E275-E87.
16. Abeysekera L, Dawson P. Motivation and cognitive load in the flipped classroom: definition, rationale and a call for research. High Educ Res Dev 2015;34:1-14.
17. Wilson JI. Twenty-first century learning for teachers: helping educators bring new skills into the classroom. New Dir Youth Dev 2006;2006:149-54.
18. Mays KA, Branch-Mays GL. A Systematic Review of the Use of Self-Assessment in Preclinical and Clinical Dental Education. J Dent Educ 2016;80:902-13.
19. Avsar UZ, Cansever Z, Acemoglu H, Avsar U, Ithan AS, Cayir Y. Self-Assessment through Videotaping Compared with Peer and Trainer Feedback. Jcpsp-J Coll Physici 2015;25:41-5.

Public Awareness and Attitude toward Palliative Care in Thailand

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ABSTRACT

Objective: This study aims to examine the Thai public's awareness and attitude toward the end of life and palliative care.

Methods: We surveyed between February and April 2018. The sampling was framed by the Thailand National Statistical Office and used a stratified four-stage sampling. A total of 2,394 adults aged 20 to 80 years who had lived in one of nine provinces across all of Thailand for at least 3 months were interviewed with a questionnaire, which consisted of four parts.

Results: Thai culture and tradition were the main barriers to discuss the end of life preparation. Only 43% of the respondents, most of whom were elderly with chronic diseases, had concerned about the end of life. Most elderly respondents preferred to receive end-of-life care at home. Only 24% of respondents knew of palliative care. Most respondents believed that palliative care was provided in public hospitals. Most respondents (92%) were familiar with section 12 of the National Health Act., B.E. 2550, which states that a person has the right to refuse medical treatment; however, majority (79%) had never heard of a living will and only 14% had experience of advance care planning.

Conclusion: Public awareness on the end of life preparation of Thai people was challenged and limited. The main barriers to concerns about it are attitude and knowledge. Promoting and educating palliative care is necessary as well as improve the availability of palliative care, both institutional and home-based care.

Keywords: End of life; palliative care; advance care planning; living will (Siriraj Med J 2020; 72: 424-430)

INTRODUCTION

Many countries are experiencing rapid population ageing. Because of age-related increases in cancer and non-communicable diseases (NCDs), the need for palliative care is also increasing. According to the World Health Organization (WHO) Global Health Estimates, there were approximately 54.6 million deaths in 2011, the majority of which were caused by NCDs (66%). Moreover, over 29 million deaths were the result of diseases requiring palliative care, and approximately 20.4 million patients, most of whom were adults aged over 60 years (69%), were reportedly in need of palliative care at the end of life.[1]

As people age, they live and die with increasingly complex medical conditions, which in turn leads to an increasing demand for palliative care. The WHO has advocated that palliative care be made a public health service because it can substantially improve the quality of life of patients and families.[2] Moreover, the Worldwide Palliative Care Alliance (WPCA) recommends in 2014 that palliative care be integrated into health systems alongside curative care. In fact, palliative care should be provided even when curative care is unavailable.[1]

Unfortunately, the World Health Assembly has noted that the availability of palliative care services is limited worldwide-more than 40 million people globally

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were in need of palliative care in 2016, most of whom live in low and middle income countries; only 14% of these individuals, however, actually received palliative care.[1,3,4,5] Most of the developing countries are facing challenges of resourcing, availability of morphine, number of hospice-palliative care services.

Many countries are aware of the increasing need for palliative care and thus have begun concentrating on the development of palliative care services. The first step to this end is understanding public awareness of the end of life and palliative care. International studies on public awareness of palliative care have been used as evidence in support of the development of palliative care systems suitable to a given context. These studies revealed that the main barriers to use of palliative care were attitudes based in the culture and traditions of the country, along with knowledge of palliative care, especially among the developing countries.[6,7,8,9] Furthermore, most people were found to experience an end of life that fit with their way of life and culture and preferred home as the place of death.[10,11,12] Overall, palliative care services are facing many challenges, especially in developing countries, where there is need to change the traditionally negative attitudes toward the end of life and palliative care, as well as increase knowledge and health care system resources for the same.[13,14] Table 1 shows a summary of the literature review public awareness of palliative care and the end of life.

TABLE 1. Summary of literature review on public awareness of palliative care.

Author	Country	Sample	Methodology	Findings
Australian Department of Health and Ageing 2003[18]	Australia	• 750 members of the general population • 100 patients and family members	• Focus group	• 75% heard about PC • 41% able to explain PC • 37% had experience with PC • 51% were informed of PC by doctors
McIlfatrick et al. 2011[10]	Northern Ireland	• 600 members of the Patient and Client Council for Northern Ireland, all aged 18 years or older	• Postal and online survey	• 56% unaware of PC • Culture and traditions were the main barriers • Lack of resources for promoting PC
MacLeod et al 2012[11]	New Zealand	• 1,011 adults aged 18 years or older	• Online survey	• 65% aware of PC • 82% agree that PC is an important service • Aged was related to awareness of PC
Harris/Decima Inc. 2013[8]	Canada	• 2,976 adults aged 18 years or older	• Online survey	• > 50% aware of PC • Home was the preferred place of death of the majority • Culture and traditions were the main barrier
Hospis Malaysia 2016[9]	Malaysia	• 600 adults aged over 20 years	• Three levels of study (national level, provider level, and community level) • Interview survey	• National study: 56,384 patients needed palliative care (96.1% were adults and 3.9% were youth) in 2012 • Provider study: lack of health professionals on PC • Community study: >50% unaware of PC and 72.4% reported that PC services should be covered by public health

Abbreviation: PC = palliative care

According to a 2011 WPCA report on the level of palliative care development, Thailand is designated as level 3a, which means "isolated palliative care provision". More specifically, it means *"development of palliative care activism that is patchy in scope and not well-supported; source of funding that is often heavily donor dependent; limited availability of morphine; and a small number of hospice-palliative care services that are often home-based in nature and limited in relation to the size of the population"*.[15] Like other countries, Thailand is experiencing changing demographics due to an ageing society, which has led to an increasing demand for palliative care services. In 2015, more than 23% of deaths were due to cancer, of which 61% were elderly deaths which related to the number of palliative care needs.[16] However, health care costs are comparatively higher at the end of life than during other periods of life, and can lead to catastrophic health expenditure especially among poor households.[14]

The Thai government adopted the National Health Act, B.E. 2550 in 2007, Section 12 of the National Health Act endorsed the right of terminally ill patients to refuse futile medical interventions to prolong natural death or to end the severe suffering from that illness by writing a living will as a part of advance care planning of palliative care. The National Health Act provides a legal tool for society to respect patient's right to self-determination, and it is not to hasten death or active euthanasia or mercy killing.[17]

The research aims to explore public awareness, attitudes, and knowledge regarding palliative care in Thailand.

MATERIALS AND METHODS

We conducted a questionnaire survey using the Thailand NSO's sampling frame and a four-stage stratified sampling method. In the first stage, nine provinces were randomly selected to represent each part of the country. These provinces included Chiang-Rai and Sukhothai from the north, Khon-Kean and Buri-Rum from the northeast, Ayutthaya and Rayong from the center, Trang and Surat-Thani from the south, and Bangkok. In the second stage, 24 enumeration areas in each province were randomly selected. In the third stage, 20 households in each enumeration area were randomly selected. Finally, people aged 20–80 years who had lived in each of the households for a minimum of 3 months were randomly selected.

In total, 2,394 adults were interviewed face to face using a structured questionnaire during February and April 2018. This questionnaire was adopted from similar studies in other countries, translating into Thai language and develop some questions to be more suitable with Thai context.[6,7,18] The questionnaire was divided into four parts: 1) respondent demographic characteristics consisted of 12 questions; 2) information on the respondent's attitude toward end of life consisted of 6 questions; 3) information on the respondent's knowledge, attitudes and expectations toward palliative care and related legislation consisted of 9 questions; and 4) information on advance care planning consisted of 4 questions.

The interview took approximately 20 minutes. At the beginning of interview, each respondent was informed the objective and the steps of interview in the research, then was asked to sign on consent form to participate in the research. At the end of the interview, respondents received an umbrella costing about 100 THB as a gift of appreciation.

This research is approved by Khon-Kaen University Ethics Committee in Human Research (HE 603032). The institutional review board number was IRB00008614.

The project is approved by ethics committee and the preserve respondent' anonymity was concern by the researchers, the personal information of the respondents was recoded, and the results were shown as overall population. The data were analyzed by using Microsoft Excel 2016, Tableau Software version 10.5 and IBM SPSS Statistics 24.

RESULTS

Of the 2,394 respondents, 60% were female, 47% were aged 40–59 years, 74% were married or in a couple, 74% were covered under the universal health insurance scheme, 73% were employed, and half had education level at secondary school and below. The average family size was 4.2 persons and the average household annual income was 9,692.52 USD.[11] Nearly all respondents (95%) had a good health status and thought that their health would worsen as they aged.

Public Awareness of End of Life

Less than half (43%) of respondents were concerned about the end of life, and this proportion was higher among respondents older than 60 years of age (60%) and respondents with poor health (66%) as well as had education at secondary and below (53%).

Furthermore, only 37% of respondents had ever had a discussion about the end of life, with 33% holding discussions with family members and 2% with doctors. The main barriers to holding discussions about the end of life were culture and tradition, the perceived difficulty of beginning such a discussion, and the knowledge that talking about the end of life cause family members to become upset.

TABLE 2. Characteristics of respondents.

		Number	%
Gender	Male	954	39.85
	Female	1,440	60.15
Age (years)	20–29	228	9.52
	30–39	349	14.58
	40–49	550	22.97
	50–59	578	24.14
	60–69	483	20.18
	70–80	206	8.60
Marital status	Single	356	14.87
	Marriage	1,774	74.10
	Widow	205	8.56
	Divorce	59	2.46
Education	Secondary school and below	1,215	50.75
	High school	737	30.79
	University	442	18.46
Current health status	Good health	2,260	94.40
	Poor health	134	5.60
Employment	Civil servant	46	1.92
	Public employee	59	2.46
	Private employee	371	15.50
	Employer/owner	920	38.43
	Unemployed	658	27.49
	Other	340	14.20
Public health insurance	Civil Servant Medical Benefits	108	4.51
	Universal Health Coverage	1,770	73.93
	Social Security Scheme	472	19.72
	Other	44	1.84
Household annual income		**Average (USD)**	
	Total	9,692.52	
	Bangkok	11,552.66	
	Central	13,275.37	
	Northeast	4,159.94	
	Southern	1,4301.45	
	Northern	5,142.61	

Remark: 1 USD = 32.669 THB (Bank of Thailand 18.09.2018)

The majority of respondents preferred receiving palliative care at home (59%), with a minority opting to receive care at the hospital (40%). The preference was related to the age of respondents, with older respondents being more likely to prefer care at home. The chi-square test showed that the age of respondents who prefer care at home significantly differ from those prefer care at hospital. (Chi-square = 73.493, df = 4, P-value = 0.000).

Knowledge, Attitudes, and Expectations towards Palliative Care

Only about one fourth of the respondents knew of palliative care. However, 88% of respondents reported that palliative care is provided to all patients at the end of life, regardless of their illness; only about 5% of respondents reported that palliative care services were for only patients dying of life-threatening disease such as cancer or HIV/AIDS. Furthermore, most respondents (87%) believed that palliative care was mainly provided in public hospitals, while 33% believed that it was provided at home and 24% believed that it was provided at private hospital.

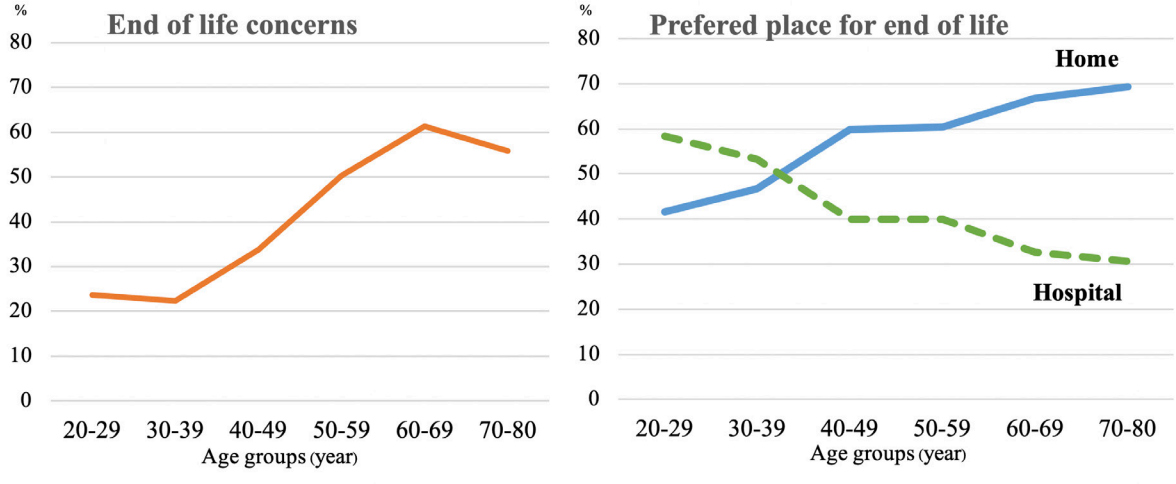
Most respondents expected that palliative care involved medical services, medical equipment, and psychological support (with 97%, 97% and 95% respectively), while fewer expected it to involve spiritual and social care or homemaking (41% and 37%, respectively). Nevertheless, 98% of respondents strongly agreed that palliative care should be integrated into care for anyone with chronic or life-limiting conditions that palliative care should be provided in a setting chosen by patients, that palliative care improves quality of life of patients, and that palliative care greatly reduces stress and burden placed on a patient's family.

Eighty percent of respondents indicated that palliative care should be a service provided by a public institution affiliated with a central or local government, and importantly palliative care services should be provided as one of benefit package under the public health insurance scheme. About 17% of respondents mentioned that family members had the responsibility of looking after patients receiving palliative care. Only a few respondents (4%) suggested including palliative care into private insurance schemes. The doctor was the main source of information for people seeking for information on palliative or end-of-life care (56%), followed by health center or community health volunteers (14%), and web pages or other media (8%).

Advance Care Planning

Advance care planning refers to the process of reflecting and communicating a written desire to let other know the needs of patients as well as pre-treatment planning. Advance care planning can include communication of patient preferences, advance decisions, and proxy nominations.

Thailand enacted National Health Act, B.E. 2550 on March 3, 2007. As noted earlier, section 12 of this act concerns end of life and advance care planning. About 92% of respondents seem to understand legally context as situations related to section 12. Despite this, only 21% of respondents had heard of advance care planning, with a greater proportion of female respondents than male respondents being aware of such care planning (23% and 17% respectively). The proportions of respondents who knew of advance care planning were higher among those aged 40–59 years (24%) and those living in Bangkok (44%).



[i] There are three main public health insurance schemes in Thailand: the Civil Servant Medical Benefit scheme (CSMBS), Social Security Scheme (SSS) and Universal Healthcare Coverage Scheme (UCS). The UCS covers the majority of Thais.
[ii] 1 USD = 32.669 THB (Bank of Thailand 18.09.2018)

Fig 1: End of life concerns and preferred place of death by age group (shown as %).

Only 14% of respondents had experience of advance care planning or a living will. After respondents received information about advance care planning, 72% of respondents planned to perform advance care planning and living will. However, 13% insisted that they did not want such planning ahead of death.

Many patients desired to receive end-of-life care at home, but were admitted to the hospital anyways. The main reasons for the admissions were the recommendation of a physician or health care provider, agreement among family members, and the decision of a caregiver based on the belief that healthcare providers could manage the patient's pain and symptoms.

DISCUSSION

The main barrier was culturally determined negative attitudes and poor knowledge toward end-of-life care. The end of life remains an avoided topic of discussion among Thais, just as among citizens of developed countries such as Canada and Northern Ireland.[6,7,8] The second barrier was a lack of knowledge of palliative care. Most respondents reported that they were unaware of dying and palliative care. A higher proportion of older respondents had an awareness, likely because of their higher risk of health problems (especially chronic illness) and the fact that they are the population group with greatest need for palliative care.[1] However, the promoting and educating for all population is necessary to improve awareness and attitude toward palliative care such as adding palliative care in teaching program.

For the majority of Thais, the home was the preferred place of care and death, much the same the populations of other countries.[10,11,12] Some countries showed large variations in preferred place of death according to healthcare resources, availability of a hospital, availability of long-term care beds, and the number of health personals.[10,11] Obtaining sufficient healthcare resources is a challenge in the development of palliative care systems.[13] While home is the preferred place of care and death for the majority of individuals, the limited coverage of a health system can be a barrier to the provision of home-based palliative care. As a result, patients and families bear the brunt of home care costs. The cost of care has been found to differ according to place of care-at home, palliative care costs in the last month of life were 826.47 USD, while at the hospital, the costs were 1,377.45 USD.[19] Thus, home-based palliative care costs less than does hospital-based care for patients. Promoting home-based palliative care would be more cost-effective for patients, meaning that home care services should be improved to better serve patients' need for palliative care. Moreover, an effective referral system should be created to improve the linkage between institutional and home care.[20]

Palliative care has been promoted as an approach to improve the quality of life of patients and families, and covers prevention, treatment, and management of other problems, whether physical, mental, or spiritual.[20] We found that only one out of every five respondents knew of palliative care; however, most Thais knew that palliative care was meant for all end-stage patients, regardless of their illness, and perceived that it was primarily focused on medical care rather than social or spiritual care.

However, the concepts of advance care planning and euthanasia are much more widely debated. Thai law has granted people the right to choose to die in a passive manner.[17] Active euthanasia or mercy killing is not considered legally or ethically acceptable in Thailand, unlike in countries such as Switzerland, Belgium, the Netherlands, and the United States.[21,22] In addition, some developed countries have a longstanding practice of publicly discussing and empowering society to directly deliberate on euthanasia issues.[23]

As noted above, the World Health Assembly indicated that palliative care service has limited availability across the world, especially in low and middle income countries.[1,3,4,5] Palliative care can be further developed in these countries by managing its barriers and thereby raising public awareness, particularly by changing culture-bound attitudes and increasing available resources. Enhancing the knowledge and skills of health care providers involved in institutional and community-based palliative care is also necessary.[24] Increasing communication among health professionals or health care providers and the population may also be important, given that health care providers are the key information source of palliative care.

CONCLUSION

The ageing population is leading to an increasing need for palliative care. Despite this, the development of palliative care services continues to face challenges. In Thailand, end of life remains a topic of discussion to be avoided, and the main barriers to discussing the end of life are culture-bound attitudes and limited knowledge of palliative care. Promoting and educating palliative care for general population is necessary as well as improve availability of palliative care both institutional and home-based care as home was preferred place of death.

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List of abbreviations

WHO = World Health Organization, NCD = non-communicable disease, WPCA = Worldwide Palliative Care Alliance

REFERENCES

1. World Health Organization. Global atlas of palliative care at the end of life. [Online]; 2014 [cited 2016 July 28]. Available from: www.who.int/nmh/Global_Atlas_of_Palliative_Care.pdf.
2. Davies E, Higginson I. The solid fact: Palliative care. [Online]; 2004 [cited 2016 July 28]. Available from: www.euro.who.int/_data/assets/pdf_file/0003/98418/E82931.pdf?ua=1.
3. World Health Organization. Palliative care for non-communicable diseases: a global snapshot in 2015. [Online]; 2018 [cited 2018 October 19]. Available from: http://apps.who.int/iris/bitstream/handle/10665/206513/WHO_NMH_NVI_16.4_eng.pdf?sequence=1.
4. World Health Organization. Palliative care. [Online]; 2018 [cited 2018 October 19]. Available from: http://www.who.int/en/news-room/fact-sheets/detail/palliative-care.
5. World Health Organization. 10 facts on palliative care. [Online]; 2017 [cited 2018 October 19]. Available from: http://www.who.int/features/factfiles/palliative-care/en/.
6. Anderson R, Grant L. What is the value of palliative care provision in low-resource settings? BMJ Global Health 2017;2:1-3.
7. Groeneveld EI, Cassel JB, Bausewein C, Csikós A, Krajnik M, Ryan K, et al. Funding models in palliative care: lessons from international experience. Palliat Med 2017; 31:296-305.
8. Canadian Hospice Palliative Care Association, What Canadians say: The way forward survey report, for the way forward initiative. [Online]; 2013 [cited 2018 October 19]. Available from: http://www.hpcintegration.ca/resources/what-canadians-say.aspx
9. Malaysia H. Palliative care need assessment report. [Online]; 2016 [cited 2018 October 19]. Available from: https://www.hospismalaysia.org/wp-content/uploads/2016/10/Palliative-Care-Needs-Assessment-Malaysia-2016.pdf
10. McIlfatrick S, Hasson F, McLaughlin D, Johnston G, Roulston A, Rutherford L, et al. Public awareness and attitudes toward palliative care in Northern Ireland. BMC Palliative Care 2013;12:1-7.
11. MacLeod RD, Thompson R, Fisher JW, Mayo K, Newman NW, Wilson DM. New Zealanders' knowledge of palliative care and hospice services. N Z Med J 2012; 125:51-60.
12. Cohen J, Pivodic L, Miccinesi G, Onwuteaka-Philipsen BD, Naylor WA, Wilson DM, et al. International study of the place of death of people with cancer: a population-level comparison of 14 countries across 4 continents using death certificate data. Br J Cancer 2015;113:1397-404.
13. Neergaard MA, Jensen AB, Sondergaard J, Sokolowski I, Olesen F, Vedsted P. Preference for place-of-death among terminally ill cancer patients in Denmark. Scand J Caring Sci 2011;25:627-36.
14. Gauthier G, Bernard E, Darrieux JC. End of life at home and preference for a place of death: a literature review. Exercer 2015;118:52-60.
15. Lynch T, Connor S, Clark D. Mapping levels of palliative care development: a global update. J Pain Symptom Manage 2013; 45:1094-106.
16. Ministry of Public Health. Public Health Statistics 2015 Nonthaburi: Strategies and Planning Division; 2015.
17. The National Health Commission Office. National Health Act, B.E. 2550 (A.D. 2007). [Online]; 2017 [cited 2018 October 19]. Available from: https://en.nationalhealth.or.th/wp-content/uploads/2017/11/HealthAct07.pdf.
18. The Australian Institute of Health and Welfare. Palliative care services in Australia. Canberra: The Australian Institute of Health and Welfare; 2013.
19. Chandoevwit W, Vajragupta Y. Long term care insurance system: Long term care system for Thailand (in Thai). Bangkok: Thailand Development Research Institute (TDRI); 2017. Report No.978-616-92250-5-8.
20. World Health Organization. WHO definition of palliative care. [Online]; 2018 [cited 2018 October 17]. Available from: http://www.who.int/cancer/palliative/definition/en/.
21. The National Health Commission Office. Thai living will (in Thai). [Online]. [cited 2018 October 19]. Available from: http://www.thailivingwill.in.th/.
22. Bosshard G, Fischer S, Bar W. Open regulation and practice in assisted dying: How Switzerland compares with the Netherlands and Oregon. Swiss Medical Weekly 2002; 132:527-34.
23. Nunes R, Rego G. Euthanasia: A challenge to medical ethics. J Clin Res Bioeth 2016;7: 1000282.
24. Millintangkul U. National policy on palliative care in Thailand. [Online]; 2015 [cited 2019 June 2]. Available from: https://en.nationalhealth.or.th/wp-content/uploads/2017/11/NationalPolicyonPCare2015_09_17-1.pdf.

Announcement of the Royal College of Surgeons of Thailand on Guidance for Surgery in COVID-19 Patients

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ABSTRACT

COVID-19 has demonstrated significantly impact on healthcare professionals practice including surgeons. The Royal College of Surgeons of Thailand (RCST) has developed the "Guidance for Surgery in COVID-19 Patients" for surgeons and related medical personnel to handle surgical care during COVID-19 pandemic.

COVID-19 is the newly emerged outbreak, the understanding of its nature, also the prevention and control of this disease is limited. Since there are very few studies on this new coronavirus, some knowledge and assumption were drawn from the lesson learnt from the outbreak of SARs and MERs (both are also RNA coronavirus) in the past. Therefore, the recommendation, as stated in this manuscript, needs to be updated accordingly to the current situation. The medical practitioners need to cling on the new status of COVID-19 constantly. In case that anyone who has any relevant information and want to bring to our attention, please email to siriwittayakorn@gmail.com.

With no legal effect, this guidance should contemporarily conform to the *occurrence* (current situation or incident), *character* (internal factors of the patient), and *circumstances* (external factors of the patient, e.g. hospital resources, equipment, and capacity).

Keywords: COVID-19; Guidance for Surgery; RCST (Siriraj Med J 2020; 72: 431-435)

INTRODUCTION

COVID-19 is an RNA virus. Until now (April 2020), it is believed that the disease can be spread out via two modes of transmission, which are respiratory droplets (thus, a person should stay at least 2 meters away from a carrier, and a medical-grade mask/respirator is required for protection), and contact transmission, caused by contact with infectious secretions and then manipulate T-zone mucous membrane of face with contaminated hand. It is not clear confirmed that COVID-19 can be transmitted via respiratory aerosol or not, even though, WHO has warned about respiratory aerosol transmission. Also, there is no shown evidence to prove that the disease can be transmitted via blood transfusion, even the coronavirus has been reported found in lymphocyte. In RNA coronavirus family, SARS and MERs, both of them are not infected through blood transfusion. However, the patients infected by COVID-19 are not recommended to donate their blood for at least 28 days after being completely cured. As the evidence on the infection via blood infusion remains unclear, the surgeons should comply with the measurement for surgery in AIDS patients in those cases infected by COVID-19.

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Overall Disease Management in Hospital

Recommendations

1) Limit numbers of regular patients. Separate patients with acute respiratory illness from other patients.
2) Implement technology such as telemedicine to screen and to manage patients.
3) Limit numbers of medical personnel to contact patients.
4) Avoid face-to-face communication. Alternatively, communicate through divider screen or via telephone/ VDO conference system.
5) Limit numbers of accompany person of the patient.
6) Group patients with similar disease in the same zone.
7) All relevant staffs, including patient transfer staffs and cleaners, must be well-trained for putting on, removing, leakage testing, and disposing of PPE.
8) In case that there are limited N-95 respirator, give priority to the person/staff in need.
9) There should be divider curtains in the waiting area to separate patient individually. If the waiting area has enough space, each patient shall stay at least 2 meters away from others.
10) Zone the patients with infectious respiratory diseases separately. Infected cases must be isolated in AIIR that reserved only for COVID-19 cases.
11) Conduct the intensive training for emergency physicians to handle COVID-19 cases.
12) Set up a joint operation team to handle the COVID-19 cases. A team consists of a surgeon, an anesthesiologist, a pulmonologist, and an infectious disease specialist.
13) Avoid using a central air-conditioner.

Surgeons and Resource Management during the pandemic

During pandemics, the preserving of limited resources and workforce is mandatory. Surgeons need to manage available resources (including workforce, equipment, drug, and consumable) with efficiency to deal with the unpredictable situation.

Recommendations

1) Postpone all non-urgent operations indefinitely or until the situation returns to normal. All patients are officially informed with written notification.
2) Minimize the numbers of patients and the frequency of OPD visit. Use alternative channels such as phone call or social media for the patient follow-up. Advise the patients to receive medication from the hospital in the closed-by location instead.
3) Ban significant events and social gatherings, especially events of the same surgical specialty. Use teleconference as an alternative.
4) Allow only one accompanying person per patient.
5) Measure the hospital capacity (including the numbers of ORs, ICUs, ventilators, wards, beds, facilities, consumables, and workforce) to assess the readiness of each hospital and the country in overall.
6) The hospital should arrange laboratory testing with a high rate of speed, accuracy and efficiency. The delayed result leads to wastage of resource uses during the quarantine. Precise and expedited testing result help to downsize the preparation to handle potential COVID-19 cases. It keeps down the expense and workforce.
7) Start fundraising to cover the increasing expenses of necessary supplies, due to the lack of government funding.

Patient Transport

Recommendations

1) Patient transfer staffs must be well-trained for putting on and removing PPE.
2) Secure the route from ward/ICU to the OR (including elevator) and vice versa route with staffs in-charge. Use only a designated route that prevents contamination of other people. Not allow other people to access the designated route on the same day.
3) All non-intubated patients should wear their medical-grade mask.
4) Transport respiratory used for COVID-19 patients must be separated from those for other patients.

At Operating Room

Recommendations

1) The OR for COVID-19 patients should be with a negative pressure environment, located at a corner of the operating complex, and separated from the setting for non COVID-19 cases.
2) Crucially understand the airflow within the OR. It needs to flow from non-contaminated to contaminated area, to minimize the risk of infection.
3) Use the same OR and the same anesthesia machine only for COVID-19 cases. Place an additional HME with HEPA filter on the expiratory limb of the circuit. Both HME with HEPA filter and soda lime are changed after each case.
4) Before starting the case, the anesthesiologist prepares all required drugs and equipment onto a trolley, each trolley for each operating room. Try not to move the trolley between the rooms. In case that the additional drugs or equipment are needed during the case, glove changing and hand hygiene with 70% alcohol are required before handing the drugs trolley in the other room.

5) Provide enough amount of airway equipment. Use disposable airway equipment.
6) Handle a video-laryngoscope, if needed, concisely. Decontaminate the video-laryngoscope with an effective disinfectant agent after use. Avoid repeated instrumentation before decontaminate the instrument.
7) All machines/equipment in limited supply in OR setting such as monitors and infusion pumps need to be thoroughly wiped down after uses.

At Induction Room

Recommendations

1) Follow the "Practical Recommendations for Caring of COVID-19 or Suspected COVID-19 Patients", issued by The Royal College of Anesthesiologists of Thailand. Use this guidance as an additional guideline.
2) Minimize number of personnel in the induction room.
3) Designated staffs keep N-95 respirator or PAPR on during the procedure. In case of a patient with a tracheostomy, all staffs at induction room must wear N-95 respirator throughout.
4) Regional anesthesia is preferable.
5) If general anesthesia is required, aerosol-generating procedure (e.g. manual ventilation before intubation, tracheal intubation, non-invasive ventilation, tracheostomy, bronchoscopy, CPR, etc.) shall be conducted concisely. All aerosol-generating procedure shall be done in an adequate ventilation room (at least 160 L/sec/patient) or in a negative pressure room with at least 12 air changes/hr.
6) In order to reduce aerosol generation, intubation shall be conducted by a well-practiced anesthesiologist.
7) For induction, pre-oxygenation with 100% oxygen and the rapid sequence induction (RSI) are required. The manual ventilation is not recommended due to the spread of disease. In the significant cases, such as the patient with very high alveolar-arterial oxygen gradient, patients who cannot tolerate an about 30 second apnea, or those who cannot be administered succinylcholine, must comply with low tidal volume manual ventilation before intubation.
8) Avoid using awake fiber-optic intubation.
9) If need, tracheal intubation should be done. Do not perform ventilation support using laryngeal mask.
10) In the significant respiratory failure case outside OR, intubation is recommended instead of a non- invasive ventilator.
11) For CPR, do not perform chest compressions while conducting intubation. Administration of neuro-muscular blockade is required before intubation.

During the Operation

Recommendations

1) Follow transmission-based precautions, including
   - at least, standard respirator, such as: N-95 (US Standard) or FFP2 (European Standard). Updated respirator fit testing is required.
   - goggles, or face shield
   - fluid-resistant gown
   - gloves
   - cases which are required aerosol-generating procedure (AGPs) should be operated in AIIR.
   - orthopedic surgical cases need to proceed with extra caution to minimize the risk of aerosolized contaminants.
2) Get all necessary instruments/consumables prepared before the operation
3) Avoid some surgeries which have to be done under high pressure, such as Laparoscopic Surgery, Robotic Surgery, These may increase the risk of aerosolized contaminants.
4) Avoid taking unnecessary items into the OR (e.g. radiograph, medical record, mobile phone, etc.)
5) The circulating nurse shall be stationed outside the OR. If additional items are needed during the procedure, these items shall be placed onto a trolley that left in the ante room for the OR team to retrieve. This same process in reverse is used to send anything, such as specimen for frozen section, out of OR.
6) A minimum of ONE hour is planned between cases to allow OR staff to send the patient back to the ward, conduct thorough decontamination of all surfaces, screens, keyboard, cables, monitors, and anesthesia machine.
7) All unused drugs and consumables placed in the OR should be assumed to be contaminated and need to be decontaminated or discarded.

Post-Operation

Recommendations

1) Remove used gown and gloves in ante room. Touch-free disposal bin is needed for discarding PPE.
2) Perform hand hygiene before leaving ante room.
3) Remove respirator or PAPR outside ante room.
4) The patient who does not require ICU care postoperatively is fully recovered in the OR itself. Once ready for sending back, the patient is transferred via a designated route back to the isolation ward.
5) Take a shower, including washing your hair, immediately after case.

Disinfectant Agents

Recommendation

1) Conduct thorough decontamination of all surfaces in OR with Hydrogen peroxide vaporizer.
2) Clean and disinfect the contaminated area with soapy water or detergent, and re-clean with alcohol-based hand rub (70% ethyl or Isopropyl alcohol), Quaternary Ammonium Disinfectant, or Potent Oxidizer. The disinfection can be effective if the exposure time is within the range of 30 seconds to 10 minutes, depends on the type of disinfectant agent.
3) Faculty of Pharmacy, Ubon Ratchathani University (UBU) introduces the cleaning and disinfection guideline for non-hospital settings (Table 1). This guideline can be adapted for a hospital setting as well. (Announced in March 2020)

- Block off the contaminated area for clean-up
- Put on well-fitting personal protective equipment (PPE)
- Use cleaning equipment/tool that has a handle.
- Open doors and windows to increase airflow.
- Wash clothes on 70°C degrees for at least 25 minutes.
- Disinfect reusable cleaning equipment.
- Clean floor and other surfaces with disinfecting wipes. Do not use the pressure-washers to avoid aerosolization. (This recommendation is reinforced by Infectious Disease Association of Thailand on 10 April, 2020)
- Discard any infectious wastes properly.

TABLE 1. The cleaning and disinfection guideline for non-hospital settings by Faculty of Pharmacy, Ubon ratchathani Univesity (UBU).

Disinfectant Agents	Unit of Concentration	Recommended for	Caution
Bleach (Sodium hypochlorite)	0.05% (1 part : 99 parts water)	general surfaces	strong odors, corrosive, causes irritation to skin
Bleach (Sodium hypochlorite)	0.5% (1 part : 9 parts water)	surface contaminated with bodily fluids spills, toilet bowl (leave on surface for at least 15 min)	strong odors, corrosive, causes irritation to skin
Alcohol	70%	metal surfaces	causes irritation to skin, cause rust stains
4.8% Chloroxylenol (Dettol)	2.5% (1 part : 39 parts water)	cloth washing, cleaning surfaces (soak in or leave on surface for at least 5 min)	causes irritation to skin
4.8% Chloroxylenol (Dettol)	5% (1 part : 19 parts 70% alcohol)	household utensils (soak in for at least 5 min)	causes irritation to skin
Laundry detergent	mixed with 70°C degrees water	cloth washing	causes irritation to skin

Abbreviation

AIIR = Air borne Infection Isolation Room
HME = Heat + Moisture Exchange
PAPR = Powered Air-Purifying Respirator
PPE = Personal Protective Equipment i.e. well-fitted respirator/mask, safety goggles or face shield, splash-resistant gown, latex gloves, and boot covers
HEPA = High Efficiency Particle Air

REFERENCES

1. Guidance of National Health Service (NHS) 2020, UK.
2. Ti LK, Ang LS, Foong TW, Ng BSW. What we do when a COVID-19 patient needs an operation: operating room reparation and guidance. Can J Anaesth 2020 Mar 6. doi: 10.1007/s12630-020-01617-4. [Epub ahead of print]
3. Peng PWH, Ho PL, Hota SS. Outbreak of a new coronavirus : what anesthetists should know? Br J Anaesth. 2020 May;124(5): 497-501. doi: 10.1016/j.bja.2020.02.008. Epub 2020 Feb 27.
4. Seminar on Prevention & Treatment of COVID-19: Experience from China. Co-hosted by Medical Association of Thailand, teleconference on 07 April, 2020.

Performing Tracheostomy in Intensive Care Unit- A Challenge duringCOVID-19 Pandemic

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ABSTRACT

COVID-19 is a rapidly spreading infection caused by novel corona virus. It is a challenging to the medical community in an unprecedented degree. Clinicians and health care workers are at added risk for infection during the procedure performing at the intensive critical care unit (ICU). Tracheostomy is a common surgical procedure performed at ICU for prolonged ventilation of the patient. Performing tracheostomy is currently a challenging for otolaryngologist at the ICU because of high chance of spread of the virus to the surrounding health care workers and also to the other patients. The location for this procedure in ICU should be well ventilated and the pressure in the room must be maintained negative or neutral. The health care personnel particularly Otolaryngologists have a central role for managing this situations where they are assessing the patients, preventing the contamination to other assisting staff and other patients. As there is progressive rise of the COVID-19 patients worldwide, it is surely expected that several patients may need intubation and mechanical ventilation. So, in this condition, patient my require tracheostomy for prolonged ventilation. Because of the very minimum literature available regarding tracheostomy in the COVID-19 pandemic, so this review article will surely increase awareness among health care workers and surgical team for prevention of the transmission of the infection from tracheostomy to medical staffs and other patients.

Keywords: COVID-19 pandemic; tracheostomy; intensive care unit; aerosolization (Siriraj Med J 2020; 72: 436-442)

INTRODUCTION

Currently we are facing a devastating pandemic with a great impact on the whole world because of the rapid spread of a novel corona virus (COVID-19). The medical fraternity is on the process to know the behavior of the virus. This knowledge of the medical community is extremely dynamic as the behavior of this virus is still not established. COVID-19 is a contagious infection of the respiratory tract caused by a novel virus called acute respiratory syndrome corona virus 2(SARS-CoV-2).[1] This patient often presents with cough, sore that and fever. Indications for tracheostomy include emergent airway and prolonged mechanical ventilation. COVID-19 patients sometime require tracheostomy for prolonged ventilation in the ICU. Otolaryngologists, intensivist and nursing staffs in the ICU play an indispensable role for performing this procedure. Performing tracheostomy and post-tracheostomy care are usually considered as high chance for contamination of health care personnel during COVID-19 pandemic due to corona virus (SARS-CoV-2).[2] Anticipating the rapid spread of the infection in case of the tracheostomy, all patients should be considered

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as potential candidates for virus infection. Appropriate protective measures can be taken for preventing the transmission of this viral infection to the health care workers.

Method of literature search

We performed a literature review of tracheostomy during the SARS pandemic consisting data base of PubMed, Medline, SCOPUS and Google scholar search with the terms COVID-19, SARS and tracheostomy. We reviewed the different current articles and recommendations from national and international medical societies and decisions from several government medical councils. This manuscript reviews the details of tracheostomy along with preventive measures for transmission of infection. This review article presents a baseline from where further prospective trials for safe technique of tracheostomy could be designed and helps as a spur for further research in the COVID-19 pandemic and so prevent transmission of the infections to the health care professions and other patients during this procedure.

Epidemiology

COVID-19 is a highly infectious disease of the respiratory system due to novel virus SARS-CoV-2. The first patient of COVID-19 was reported in Wuhan, China in late December 2019 by novel corona virus now called as SARS-CoV-2 (severe acute respiratory syndrome corona virus 2) and now spreaded worldwide. By 27th February, 2020, more than 82,000 COVID-19 positive cases and more than 2800 deaths have been documented of which around 95% of the cases and 97% of deaths were in China.[3] By the march 26th, 2020, there were 462684 cases of the COVID-19 reported in 199 countries.[4] At the time of drafting the manuscript i.e. 25th April, more than 50000 persons were died due to COVID-19 in United States. In the hospital setting, critically patients with respiratory failure often require endotracheal intubation and changed to tracheostomy in case of prolonged ventilation. In one study, 6.30% patients need tracheostomy during the COVID-19 outbreak.[5] Study showing 7.3-32% of the patients with COVID-19 progress to severe respiratory failure or critical ill condition, where patient may subsequently need tracheostomy for different reasons.[6,7]

Transmission of the COVID-19 infection

Open or surgical tracheostomy is usually an aerosol producing procedure with a high risk for contamination by exposing the secretions from the airway to the health care personnels.[8] The novel SARS-CoV-2 virus is transmitted from one person to another by respiratory droplets or contact with infected person. The procedures which deals with nose, nasopharynx, oral cavity, pharynx, larynx and trachea which generate respiratory droplets lead to high risk for infections. The common clinical symptoms of the COVID-19 patients are cough, fever, fatigue and dyspnea. There are some patients those are asymptomatic and considered as silent carriers in this pandemic. Symptoms like an osmia and taste alterations are two important clinical features often associated with these patients. So health care workers should be aware about these symptoms and so can prevent them from transmission to other patients.

Suspecting the COVID-19 patients

The most commonly found symptoms in patient of the hospitalized patients are fever (77-98%), dry cough (46-82%), fatigue, myalgia (11-52%) and dyspnea (3-315) at the onset of the COVID-19 infections.[9] Another study shows fever in 44% at the time of hospitalized COVID-19 patients whereas it goes to 89% during the period of hospitalization.[10] Other less commonly found symptoms in COVID-19 infections are sore throat, headache, cough with sputum production with or without hemoptysis. Few cases present with gastrointestinal upsets like diarrhea and nausea before development of the fever and lower respiratory airway symptoms and signs. There is established symptom such as anosmia/hyposmia in COVID-19 infection. In German, it was documented that more than two thirds of positive patients of COVID-19 infections presented with an osmia whereas in South Korea, 30% patients with COVID-19 infections showed symptom of the anosmia.[11]

Indications of tracheostomy

The progressive rise of the COVID-19 patients will expect more requirements of the orotracheal intubation and prolonged ventilation. In this clinical scenario of ICU, tracheostomy can be considered by health care professionals. Performing tracheostomy on COVID-19 patients or suspected patients for COVID-19 impose challenges not only to Otorhinolaryngologists but also to the entire health care team. If the trachesotomy is not an emergency, this can be reviewed by a multidisciplinary team and risk versus benefits of this surgery and also the associated health care team should be assessed. Unlike the bacteriogenic pneumonia, cases of COVID-19 present with dry cough and produce little mucus secretions, so it makes tracheostomy for pulmonary toilet less critical.[12] Bedside tracheostomy at the ICU with negative pressure is ideal for performing this procedure for needy patients.

Bed side tracheostomy avoids unnecessary transport of the patients and frequent connections and disconnections of the ventilator circuits during transfer.[13] The bedside tracheostomy should be well planned at the ICU because of the limited space, below optimal positioning of the patient and limited transfer of the surgical instruments. In case of planning tracheostomy at the operating room (OR), it should be undertaken in negative pressure at well demarcated area inside the OR complex with proper route for transferring the patients. During tracheostomy, provide adequate sedation including paralysis which eliminates the chance of coughing during the time of the procedure. Ventilation should be paused (apnea) at the end-expiration when making the opening on the trachea where the ventilation circuit is disconnected. A non-fenestrated cuffed trachesotomy tube is better and it keeps the cuff inflated to stop the spread of the virus through the upper airway. Tracheostomy suctioning should be done by a closed suction system with a viral filter. Heat moisture exchanger device can be used instead of tracheostomy collar at the time of the weaning for preventing virus spread or re-infection of the patient. Tracheostomy tube changing should be avoided until the viral load is as low as possible.

Surgical steps

The COVID-19 pandemic is highly infectious and performing the tracheostomy in such pandemic is highly contagious to other patients and health care workers. The classical tracheostomy should not be done and it must be modified to minimize the chance of the viral transmission.[14] For successful tracheostomy, the whole procedure is divided into 5 steps (5Ts) such as theater set up/area in ICU, team briefing, transferring the patient, tracheostomy and team doffing and De-brief.[15] Tracheostomy should be done in dedicated COVID theatre or designated area in ICU. The OR should under negative pressure with reverse laminar flow around the operating table. In team briefing, all the team members should be explained about their role during the procedure. All the equipments including suction probe should be ready before performing the tracheostomy. The tracheostomy tube can be sprayed with 5% lidocaine then aspiration for a few minute later is helpful. If the ventilation is done with tracheostomy tube, then anesthesiologist should sedate the patient and perform the neuromuscular block for decreasing chance of the cough at the time of the tube change. The patient must be completely paralyzed for the period of the procedure and the closed suction is connected to the endotracheal tube before beginning of the procedure. Before starting the tracheostomy, anesthetist/intensivist should perform suctioning the endotracheal tube including the subglottic area. Before making a window over the trachea, anesthetist is to stop the ventilator and deflate the cuff of the endotracheal tube. Then the surgeon creates a window on the second or third ring of the trachea. Minimal suctioning can be done at the window site and the endotracheal tube is advanced further below the window and the cuff is re-inflated/over-inflated and so establish a closed circuit.[16] This is a very crucial step for preventing spread of the infection. In this stage, patient is a t risk of alveolar derecruitment and may need aggressive recruitment after inflation of the cuff. So two number of anesthetists or intensivist are useful to deal with endotracheal tube and one will manage the ventilator.

Tracheostomy tube

The tracheostomy tube should be non-fenstrated, cuffed and the smaller side to make the tracheostomy smaller opening on the trachea. Shiley size of 6 for male and female is often adequate. The cuff of the tracheostomy tube should be inflated for preventing the spread of the virus via the upper airway.

Operating place/ICU

The place for this high risk procedure should be properly designated with negative pressure.[17] Unprotected health care workers should not be allowed to the site of the tracheostomy because of the high aerosol generating procedure. Appropriate PPE should be worn by the Otolaryngologist and the assisting personnel. The team for tracheostomy includes a consultant surgeon and two experienced assistant along with a scrub nurse and a floor nurse. Different case series of Open tracheotomies were done at the time of COVID-19 pandemic showing techniques and preventing measures (Table1).[18,19,20]

Benefits versus risk of trachesotomy at the ICU

Study of non-COVID-19 infected patients of critically ill reveal that early tracheostomy (within ten days of intubation) is associated with longer ventilator free days, lesser ICU stays, lesser duration of sedation and lower long-term mortality rates, although other studies document that timing of the trachesotomy does not affect the clinical outcomes.[21,22] In another study, 66.7% of the patients those underwent tracheostomy did not achieve the clinical benefit after the tracheostomy.[23] Another report from China is also against the positive outcome for tracheostomy in COVID-19 patients.[24] There is also another report from SARS treatment suggests that tracheostomy was not related to the significant better

TABLE 1. Different case series of Open tracheostomies done at the time of COVID-19 pandemic.[18,19,20]

Parameters	Wei et al[18]	Chee et al[19]	Tien et al[20]
Hospital	Queen Mary Hospital, Hong Kong SAR,	Tan Tock Seng Hospital, Singapore	Sunnybrook and China Women's College Health Sciences Centre, Toronto, Ontario, Canada
Number of tracheostomies done	3	15	3
Barrier precautions at time of surgery	Standard PPE, shoecovers, faceshield, goggles	Standard PPE, Shoecovers, powered air-purifying respirator system	Standard PPE, Stryker T4 protection system
Setting	Negative pressure room in ICU or OR	Negative pressure room in ICU	Negative pressure room in ICU
Intraoperative steps to minimize aerosolization	Complete paralysis of patient, mechanical ventilation stopped before tracheostomy, no suction used during procedure, diathermy avoided as much possible	Complete paralysis of the patient, mechanical ventilation stopped before tracheostomy,limited suction used during procedure, no specific avoidance of diathermy other than during tracheostomy	Complete paralysis of the patient,mechanical ventilation stopped before tracheostomy,no suction used once trachea opened,diathermy avoided as much as possible
Surgical team	Single surgeon, one intensive care specialist, one standby medical or nursing staff	An experienced surgeon, an experienced anesthesiologist, one scrub nurse and one surgical assistant	Senior attending trauma surgeon, most senior surgical staff member available, attending ICU anesthesist and no circulating nurse or scrub nurse.

outcome.[18] Sometimes the trachesotomy is associated with potential complication such as tracheal bleeding. Without doing specific treatment for this infection, the mortality rate goes to severe or critical ARDS is very high as around 70%, which goes against for performing the tracheostomy on patients with COVID-19 related ARDS.[25] These clinical experiences from China suggest that prolonged intubation should not be alone an indication for doing tracheostomy in COVID-19 patients, as there are risk for patients and health care providers likely show any marginal benefits in this pandemic. Rather the procedure like tracheostomy should only be done in specific condition such as airway obstruction where the successful extubation is compromised or certain situation where tracheostomy placement has positive impact on patient's potential for successful weaning of the ventilatory support. So, it needs careful consideration when the health resources like ventilators are in limited supply in present COVID-10 pandemic. Agreement with current recommendations by ENT UK, clinicians should believe the situations and evaluations by multidisciplinary fashion like consensus among the specialists for clinical benefits after tracheostomy as weighed against the risk of this procedure.[26]

Post-tracheostomy care

Patient with tracheostomy tube should be covered by trach collar for preventing aerosol from trachea.[27] The tracheostomy patients at the ICU those are connected with a closed ventilator circuit, standard precautions should be used for an patient who endotracheally intubated with ventilator. This type of closed strategy has been also used in Hong Kong in this current outbreak.[11] The suctioning of the tracheostomy should be done by a closed suction system with presence of the viral filter. Tracheostomy tube change should be avoided until the viral load is as low as possible. A heat moisture exchanger (HME) device is used instead of the trach collar during the weaning for preventing the virus spread or re-infection of the patients.

Pediatric tracheostomy

In the children, the tracheal intubation is often better tolerated. The ideal timing for performing the tracheostomy is not established but some authors suggest if there is no chance of weaning by two weeks, then tracheostomy can be considered.[2] During prolonged intubation, optimum care must be given for adequate size of the endotracheal tube with low pressure cuff and avoid movement of the tube.

Percutaneous dilatational tracheostomy

Percutaneous tracheostomy affects extensive airway manipulation like bronchoscopy and or serial dilations at the time of the tracheal entry. Patient having high ventilatory settings may need repeated disconnection and connection from the ventilatory support. There is increased chance of aerosolization in comparison to the open tracheostomy.[28] In open tracheostomy, the tracheostomy tube is entered quickly by making an opening of the trachea so aerosolization has less chance to spread. The open tracheostomy is more favorable than percutaneous tracheostomy during COVID-19 pandemic.[28] However, as per recommendation of French Anesthesiology and ENT Societies, percutaneous tracheostomy is preferable to minimize the aerosolization and chance of viral contamination of the surrounding health care personnel.[29] The surgical tracheostomy is performed in case of anatomical contraindication, failure of the percutaneous tracheostomy or exhaustion of the percutaneous kits. Two techniques are possible, the Percutaneous technique and the open technique. In accordance with the recommendations of French Anesthesiology and ENT Societies (SFAR and SFORL), in the COVID-19 context[28], the percutaneous technique is to be preferred to reduce aerosolization and the risk of viral contamination for the nursing staff and to avoid having to move the patient to an operating room.

Use of personal protection equipment during tracheostomy

The surgeon, assisting surgeon and nursing staff should wear proper personal protection equipment (PPE) (Fig 1). Head protection should be done by a hood cap

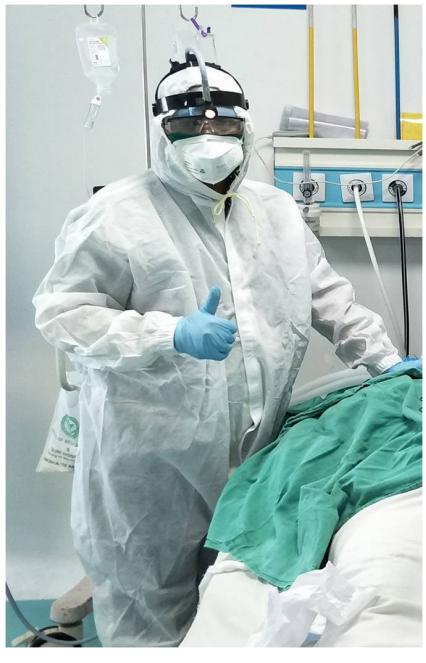

Fig 1. Surgeon with PPE before performing tracheostomy.

rather than with a simple cap for better protection of the exposed skin in head and neck area. The protective eye glass should be used for preventing exposure of the infection to the eye. Face mask must be FFP (N95) or FFP3. The head light used for light source during tracheostomy should be covered by a head cap. An impermeable protective apron or an overcoat must be worn under the surgical gown because it is sterile. After removal tracheostomy, the appropriate time to doff the PPE is at least 20 minutes. This doffing should be done at a designated area with standard practice of current guidelines.

Prognosis

Some patients with tracheostomy during COVID-19 pandemic may develop some complications such as ulcers in the pharynx and bleeding from the stoma or tracheostomy tube which need further care by Otorhinolaryngologists. Tracheostomy should be avoided or delayed even beyond two weeks because of the high chance of the infections during the procedure and subsequent tracheostomy care.[29] When the acute phase of infection is subsided or the likelihood of the recovery of infection is high, tracheostomy can be done for less likelihood of infection transmission. Early tracheostomy should be avoided in case of COVID-19 patients because of the higher viral load. Early tracheostomy is not related to the improved mortality or less ICU stay.[29]

Preventing measures

The primary method of transmission of the infections during tracheostomy is droplets from the tracheal airway via the tracheostomy tube which carry the virus particles. PPE is known to be very effective measures for reducing the transmission of the infections from the trachesotomy. Although the safety recommendations for health care personnel have continued to change depending on the resources. The center for disease control and prevention (CDC) and WHO recommended the gown, gloves, goggles, head shield and N95 mask for preventing the transmission of the droplets from the tracheostomy.[30] Health care personnel should learn proper technique for donning and doffing of the PPE effectively to protect them. If the post-tracheostomy care is done in a health care facility or in home, there is no diagnostic facility and the care givers do not know whether patient is infected with SARS-CoV2 or not. So the precautions are justified and must be with FFP2 (N95) mask, protective glasses, head shield and gown. All the disposable materials that have been in touch with tracheostomy tube or tracheal filters and suction probes must be removed from this infectious waste. The overall surgical procedure for tracheostomy should thoroughly and appropriately planned, explained to all concerned staffs and executed in order for ensuring the safety of the staff and patients.[31]

CONCLUSION

COVID-19 is a real challenge for global medical community. Acute respiratory distress syndrome and respiratory failure need mechanical ventilation. As the COVID-19 infection escalates, the staying of the patient in ICU extended with ventilator. So, tracheostomy is required in prolonged ventilation. It is thus crucial for ICU teams and surgical personnel and they should be well prepared for performing the tracheostomy when required. As surgeon perform tracheostomy closely with anesthetist/intensivist and nursing staff, so the surgery should be done in safely manner for preventing transmission of infections. This worldwide pandemic reinforced the requirement of the adaptable and reflective surgical practice. The need of surgical tracheostomy will increase in coming time so for this reason, we have to manage this in a robust, repeatable and safe manner.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270-3.
2. Tay JK, Khoo ML, Loh WS. Surgical considerations for tracheostomy during the COVID-19 pandemic: lessons learned from the severe acute respiratory syndrome outbreak. JAMA Otolaryngology–Head & Neck Surgery 2020 Mar 31.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 Published February 24, 2020. doi:10.1001/jama.2020.2648
4. Coronavirus disease 2019 (COVID-19)Situation Report –66. World Health Organization. March26,2020https://www.who.int/docs/defaultsource/coronaviruse/situation-reports/20200326-sitrep-66-covid- 19.pdf?sfvrsn=81b94e61_2 March 27,2020.
5. Chee VW, Khoo ML, Lee SF, Lai YC, Chin NM. Infection control measures for operative procedures in severe acute respiratory syndrome-related patients. Anesthesiology 2004; 100:1394-98.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020; 323:1061-9.
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497-506.
8. Zhejiang University School of Medicine: Handbook of COVID-19 Prevention and Treatment, 18/03/2020.2.
9. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, et al. Washington State 2019- nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. N Engl J

Med 2020;382:929-36.
10. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382:1199-207.
11. Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection [Internet]. The Royal College of Surgeons of England, Published Online, 2020, Mar 22 [cited 2020 Mar 24]. Available from: https://www.entuk.org/sites/default/files/files/Loss%20of% 20sense%20of%20smell%20as%20marker%20of%20COVID.pdf.
12. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420-22.
13. Swain SK, Sahu MC, Choudhury J, Bhattachaeyya B. Tracheostomy among pediatric patients:Our experiences at a tertiary care teaching hospital in Eastern India. PediatricaPolska-Polish J Paediatrics 2018;93:312-17.
14. Tay JK, Chung Khoo ML, Loh WS. Surgical Considerations fortracheostomy during the COVID-19 Pandemic. Lessons learned from the severe acute respiratory syndrome outbreak. JAMA OtolaryngolHead Neck Surg. Published online 31/03/2020. https://dx.doi.org/10.1001/jamaoto.2020.0764.
15. Damian B, Panayiotis K, Kevin S, Alistair S, Chetan K, Leandros V. Surgical tracheostomies in Covid-19 patients: Important considerations and the "5Ts" of safety. British Journal of Oral and Maxillofacial Surgery. 2020 Apr 16.
16. Ormandy D, Kapoor V, Kyzas PA, Vassiliou LV. Tracheostomy suspension:a modified approach for securing the airway. BJOMS 2020. In press.
17. Surgeons ACo. COVID-19: Guidance for Triage of Non-Emergent Surgical Procedures. 2020.
18. Wei WI, Tuen HH, Ng RW, Lam LK. Safe tracheostomy for patients with severe acute respiratory syndrome. Laryngoscope 2003;113:1777-9.
19. Chee VW, Khoo ML, Lee SF, Lai YC, Chin NM. Infection control measures for operative procedures in severe acute respiratory syndrome–related patients. Anesthesiology 2004; 100:1394-8. doi:10.1097/00000542- 200406000-00010
20. Tien HC, Chughtai T, Jogeklar A, Cooper AB, Brenneman F. Elective and emergency surgery in (SARS). Can J Surg 2005;48: 71-74.
21. Hosokawa K, Nishimura M, Egi M, Vincent JL. Timing of tracheotomy in ICU patients: a systematic review of randomized controlled trials. Crit Care 2015;19:424.
22. Wang F, Wu Y, Bo L, Lou J, Zhu J, Chen F, et al. The timing of tracheotomy in critically ill patients undergoing mechanical ventilation: a systematic review and meta-analysis of randomized controlled trials. Chest 2011;140:1456-65.
23. Cui Chong, Yao Qi, Zhang Di, Zhao Yu, Zhang Kun, Nisenbaum Eric. Approaching Otolaryngology Patients during the COVID-19 Pandemic.Otolaryngol Head Neck Surg 2020 May 12; 194599820926144. doi: 10.1177/0194599820926144.
24. Yu S, Yujuan H, Hongjun X. Recommendations for diagnosis and treatment of emergency diseases in ENT surgery during the prevention and control of new coronavirus. Zhonghualiuxingbingxuezazhi = Zhonghualiuxingbingxuezazhi. 2020.
25. Liu Y, Sun W, Li J, Chen L, Wang Y, Zhang L, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. MedRxiv 2020 Jan 1.
26. Guidance for Surgical Tracheostomy and Tracheostomy Tube Change during the COVID-19 Pandemic https://www.entuk.org/tracheostomy-guidance-during-covid-19-pandemic March 27, 2020.
27. UW Medicine COVID-19 Resource Site - Minimizing Aerosolizing Procedures. University of Washington. https://covid-19.uwmedicine.org/Covid19 Policy Statements/Minimizing Aerosolizing Procedures.pdf. Published 2020. Accessed March 17, 2020.
28. Recommandations des sociétéssavantes franc¸aised'ORLet-ChirurgieCervico-faciale (CNPORL S, SFORL, Collège Franc¸aisd'ORL& CCF) 2020.
29. Young D, Harrison DA, Cuthbertson BH, Rowan K, TracMan C. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. JAMA2013;309:2121-29.
30. Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. Centers for Disease Control. https://www.cdc.gov/coronavirus/2019-ncov/infection-control/controlrecommendations. html. Published 2020. Accessed March 17, 2020.
31. Swain SK, Behera IC, Sahu MC. Bedside open tracheostomy at intensive care unit-our experiences of 1000 cases at a tertiary care teaching hospital of eastern India. Egyptian J Ear, Nose, Throat and Allied Sciences 2017;18(1):49-53.

The Effect of Myoma Uteri on Infertility

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ABSTRACT

Myoma Uteri is the most commonly found tumors in women of reproductive age. Their effects on reproductive function and fertility are unknown. Treatment is dependent on myoma's location and size. While there is medical consensus on the treatment of submucosal myoma, there exists controversy in treatment and management of intramural myoma in infertile patients. Surgical treatments include hysteroscopic, laparoscopic and open myomectomies (laparotomy). Results from endoscopic and open myomectomies are comparable. Endoscopic treatment is generally favored due to lower morbidity, same day treatment, shorter hospitalizations and lower costs. Alternative methods, including medical and radiological intervention, are discussed.

Keywords: Myoma uteri; infertility (Siriraj Med J 2020; 72: 443-450)

INTRODUCTION

Myoma Uteri is the most commonly found tumors in 50-60% of reproductive age women. One quarter of patients seeking reproductive assistance present with myoma. They might be the sole cause of infertility in 1-3% of patients.[1]

Mechanisms of Infertility[1-3]

Myomas vary considerably in size, location and number, and mechanisms by which they may cause infertility. Several theories explain myoma's role in infertility.

Mechanisms involving alteration of local anatomy

Myomas are associated with anatomical distortion of the endometrial cavity and the obstruction of tubal ostia or cervix. They may cause changes in the uterine contour, and impair the movement of eggs, sperm and embryos. Histological observations include elongation and distortion of glands, cystic glandular hyperplasia, polyposis and endometrial venule ectasia.

Mechanisms involving functional change

Increased uterine contractility, chronic endometrial inflammation, endometrial blood supply impairment are all potential complications. Myomas can interfere with sub endometrial arterial blood flow, which depresses implantation rates and in vitro fertilization (IVF) outcomes. Myomas can also lead to impaired physiologic decrease of uterine peristalsis during embryonic implantation. This disrupts typical reproductive processes, resulted in decreased pregnancy rates, especially in submucous or intramural myoma cases. The higher myometrial contractility was postulated to come from too much cytokines in myoma capsule. Neuropeptides, growth factor, enkephalin and oxytocin modulators in myoma capsule may also be involved. Glandular atrophy and ulceration affecting the proximal and distal endometrium are the most frequently observed histological changes.

Endocrine mechanisms

The theory of abnormal local hormonal milieu supports the possibility of an endocrinal mechanism for infertility.

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Paracrine molecular effects on adjacent endometrium

Myoma may induce paracrine molecular effects on adjacent endometrium. The secretion of vasoactive amines and local inflammatory might cause impaired fertility function.

Cytokine factors

Many early pregnancy intrauterine cytokines are instrumental in implantation and initial embryonic development. Glycodelin, a progesterone-regulated glycoprotein, promotes angiogenesis and suppress natural killer (NK) cells. Ben-Nagi and his group reported that interluekin 10 and glycodelin levels were significantly decreased in mid luteal uttering washings submucous myoma's patients.[4]

Endo-myometrial Junctional (EMJ) zone alteration

EMJ, represented a 1/3 of the myometrium abutting the endometrium, produces macrophages and uterine natural killer cells (uNK). Macrophages and uNK cells are instrumental in endometrial decidualization during the window of implantation in mid luteal. Japanese researchers documented a clear reduction of macrophages and uNK cells concentration in EMJ of women with uterine myoma. That corresponded to negative effects on implantation.[5] The presence of intramural and/or submucosal myoma possibly disrupts EMJ. It also affects steroid receptors and cause implantation problem or failure.

Endometrial receptivity[6-7]

Examining myoma's effect on endometrial receptivity illuminates a potential mechanism of how myomas can affect fertility without a mechanical component. Embryonic implantation requires endometrial receptivity, which is moderated by levels of cytokines, hormones, growth factors and other signaling molecules. HOXA10 and HOXA11 genes, as well as leukemia inhibiting factors, are theorized to be necessary components for the implantation process. Reduced gene expression was shown in women with myomas. Lower amount or the absent of uterine endometrium HOXA10 can prohibit implantation, later leading to infertility. Rackow and coworkers reported endometrial HOXA10 and HOXA11 mRNA levels reductions in follicular phase of infertile patients who presented submucosal myoma's (FIGO L0 to L2). The drop of endometrial HOXA10 and HOXA11 mRNA expression were noted for the entire uterine cavity. The presence of intramural myomas seemed to lower endometrial HOXA10 and HOXA11 mRNA levels, but not at a significant levels.[8] By contrast, Matsusaki et al. demonstrated a significant decrease in HOXA10 concentrations during luteal phase in infertile patients with intramural myomas when compared to control groups.[7] Myomectomy of intramural fibroid has been demonstrated to increase HOXA10 and HOXA11 expression in the endometrium.

Effect on sexual function

Myomas are associated with higher incidences of pelvic pain and dyspareunia. Decreased libido or sexual dysfunction might be reported due to bulk effect on the vagina. Orgasm might also be affected. Mass effect on the urinary system may increase urination frequency or incontinence leading to stress and embarrassment. While not directly connected to fertility (Assisted Reproductive Technology is unaffected), these factors may contribute to decreased frequency of sexual intercourse and thus a corresponding reduction in opportunity for natural conception.

Classification of myoma uteri

Myomas are classified by their relative uterine wall placement. Subserosal myomas manifest on the outer surface and grow outwards. Intramural myomas grow inside the uterine wall. Submucosal myomas develop around the endometrium and typically grow inwards towards the cavity. Subserosal and submucosal pedunculated myomas both grow on stalks.

FIGO provides additional guidance for users of the myoma subclassification system. They include tertiary classification of myoma categories, with subcategorization for intramural, subserosal and intramural lesions. Fig 1 shows FIGO myoma subclassification system 2018.[9]

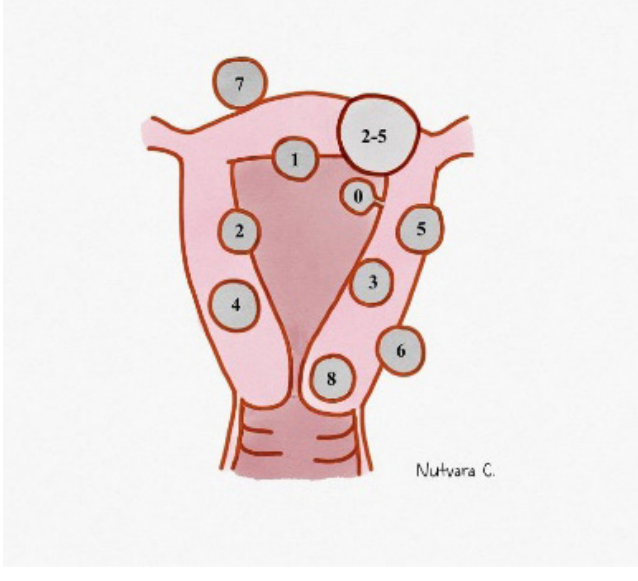

Fig 1. FIGO myoma subclassification system 2018

Submucous type

Type 0: intracavitary lesions are attached to the endometrium by a narrow stalk (< 10% or the mean of three diameter of the myoma).

Type 1: requires a portion of the lesion to be intramural and one diameter <50% of the mean diameter.

Type 2: requires a portion of the lesion to be intramural and at least 50% of the mean diameter.

Type 3: lesions are completely intramural and around the endometrium.

Intramural myoma: transmural lesions are categorized by their relationship to both the endometrium and the serosal surfaces. The endometrial relationship is noted first, followed by the serosal relationship.

Type 4: intramural myomas that are entirely within the myometrium, with no extension to the endometrium surface or the serosa.

Subserous myoma

Type 5: ≥50% intramural

Type 6: <50% intramural

Type 7: attached to the serosa by a stalk that is also < 10% or the mean of three diameters of the myomas.

Other types

Type 8: myomas that do not relate to the myometrium at all, including cervical lesions (demonstrated), those that exist in the round or broad ligament without direct attachment to the uterus, and other 'parasitic' lesions.

Impact of myomas on reproductive function

The effect on fertility depends on the myoma's location

Subserous myoma

The consensus based on clinical experience implies very little causation linking subserosal myomas and infertility. It is not evidence based to perform a myomectomy to remove subserosal myomas to treat infertility.[2]

Submucous myoma

Submucosal myomas that distort the uterine cavity lower implantation rates and increase early pregnancy losses when compared to myoma free patients. Pritts et al. reported a meta-analysis showing submucosal myomas patients with significantly decreased live birth rates/ ongoing pregnancies (RR=0.318, 95% CI: 0.119–0.85, P < 0.001), pregnancy rates (RR=0.363, 95% CI: 0.179-0.737, P = 0.005) and implantation rates (RR=0.283, 95% CI: 0.123-0.649, P= 0.003). This class of myomas is also correlated with increased risk of spontaneous abortion (RR=1.678, 95% CI: 1.373–2.051, P = 0.022).[10] Casini and his group studied a RCT in myomas patients with unexplainable infertility. Patients with clear subserous myomas were excluded. Consented subjects were randomized either to undergo myomectomy or not receiving the procedure. Patients then reported if they could conceive by themselves, and the conception rate was recorded for the following 12 months or longer. Patients who received hysteroscopic or open myomectomy showed increased pregnancy rates. Baseline myoma staging showed no statistical difference. Statistically significant pregnancy rate increases were only observed in patients with submucosal myoma (pregnancy rates between myomectomy/ no myomectomy; submucosal group = 43.3/27.2 %, p < 0.05; intramural with submucosal component = 40/15 %, p < 0.05; all submucosal = 40.4/21.4 %, p < 0.05).[11] To summarize: submucosal myomas demonstrably lower fertility rates, and studies have shown their removal improve both conception and live birth rates.

Intramural myoma

Many hypotheses explain infertility from intramural myomas without uterine cavity involvement. Alterations of uterine peristalsis and vascular flow could disrupt sperm and ovum transportation and embryo implantation. Meta-analysis of Sunkara et al. work showed a significant decrease in clinical pregnancy rate (RR=0.85, 95% CI: 0.77–0.94, P < 0.002) and live birth (RR=0.79, 95% CI: 0.70–0.88, P < 0.0001) in women with non-cavity-distorting intramural myomas compared with those without myomas, following an IVF treatment.[12] Literature review produced a single non-randomized controlled trial investigating pre-IVF myomectomy effects. Patients had one to 5 myomas, with at least one of 5 cm, with no submucosal component. The study revealed many benefits of pre-IVF myomectomy demonstrated by a 25/12 % birth rate in treated/ control group.[13] A Cochrane's review of the RCTs concluded that there was insufficient evidence to recommend myomectomy to improve fertility in cases of asymptomatic intramural myoma.[14] The evidence for using myomectomy to treat infertility in intramural myoma is weak.

Diagnosis[15]

Uterine myomas, can be identified and characterized by the use of transabdominal or transvaginal ultrasounds, sonohysterogram, hysterosalpingogram, MRI and hysteroscopy. Each modality has its own advantage used to characterize the involvement of the uterine cavity.

Ultrasounds are adequate, rapid, safe, and cost-effective in evaluating the size, number, and location

of myomas. Transvaginal ultrasound might be used to identify myomas of up to 5 mm in diameter. Transvaginal ultrasound yielded accurate result in submucous myomas evaluation. Older studies showed a sensitivity of 100% and specificity of 94%.[15] Ultrasound, due to acoustic shadowing, may be suboptimal for multiple myomas as well as endometrial impingement. Additionally, inter-observer variation has been found to be greater with this method compared to MRIs.

Hysterosalpingogram is often performed to assess tubal patency in women with infertility and to exclude intrauterine pathology. However, the sensitivity and positive predictive value of this test for the identification of intrauterine lesions can be as low as 50 and 28.6% respectively. Therefore hysterosalpingography cannot reliably be used to exclude endometrial distortion secondary to submucosal myomas.

Sonohysterography gives similar results to hysteroscopy for submucous myomas diagnosis. Both techniques are superior to transvaginal ultrasound. The 3D sonohysterography is comparable to 2D sonohysterography and hysteroscopy.

MRI has been well studied in the evaluation of uterine myomas, especially for myoma mapping and submucosal penetration. It was shown to be the most reliable evaluation method (100% sensitivity and 91% specificity) compared to transvaginal ultrasound, hysterosonography and hysteroscopy. The gold standard is the pathological examination. The disadvantages of MRI evaluation are the low accessibility and prohibitive cost.

Hysteroscopy provides both diagnostic and therapeutic value. Direct evidence of intrauterine pathology or submucous myoma that distorted the uterine cavity was demonstrated by hysteroscopy. The sensitivity and specificity were 82 and 87 %, respectively.[16]

Treatment[17-18]

Medical management

There is limited data with regards to the medical management of myomas in patients attempting conception. Surgery has associated risks. Not all patients are qualified as candidate for surgery.

Gonadotropin-Releasing Hormone Agonists (GnRH agonist)

These medications work by decreasing estrogen-dependent myoma growth through down regulation of GnRH receptors in the pituitary gland. Follicle-stimulating hormone, luteinizing hormone release and estrogen availability are decreased. By inducing a state of hypoestrogenism and temporary menopause with amenorrhea, GnRH agonists have been used to shrink myomas and restore hemoglobin levels in symptomatic women. Preoperative use of GnRH agonist appears to be relevant and beneficial in patients with submucous myomas. Benefits include resolution of preoperative anemia, decrease in myoma size, reduction of endometrial thickness and vascularization with subsequently improved visibility and reduced fluid absorption.[19] However, GnRH agonists have significant side effects, including medically induced menopause leading to possible hot flashes, vaginal dryness, and osteoporotic effects in bone. When used as a pretreatment to myomectomy, GnRH agonists show no apparent effect on pregnancy rates after surgery, nor is there a difference in the recurrence rate of the myomas.

Selective Progesterone Receptor Modulators (SPRMs)

Oral SPRMs, i.e., ulipristal acetate (UPA) can be used in uterine myoma management. Studies suggested the role of progesterone in the growth of myomas but not in normal myometrial cells. SPRMs could inhibit myoma growth and induce apoptosis selectively.[20] UPA reduces the amount of vascular endothelial growth factor (VEGF) and Bcl-2 expression while increases caspase-3 expression. All events led to impaired vascularization, cell growth, and myoma proliferation.[20] UPA was found to significantly reduce myoma size. Its use could possibly reduce the morbidity rate of the surgery. Or potential patients would no longer require surgery. Adverse effects include headaches, hot flashes, and breast discomfort. Adhesions, uterine rupture, and cesarean rates may be decreased for those patients who could avoid myomectomy or repeat myomectomies by the use of medication. UPA is an alternative preoperative medical treatment prior to myomectomy.

Type 1 myomas - If a myoma is type 1 but >3cm, or if the patient presents with anemia, pre-hysteroscopic medical therapy (SPRMs or GnRH agonist) is indicated. UPA may be given in one or two courses of three months. In a majority of cases, type 1 myomas respond to preoperative therapy and decrease in size, facilitating hysteroscopy conditions. It should be pointed out that in some cases, myomas regress sufficiently that surgery may be avoided.[19,21]

Type 2 myomas - UPA can be proposed. Myomas often respond to this preoperative therapy and regress in size. This reduction also allows a hysteroscopic approach after the first menstrual bleed. In some cases, myomas regress enough that they no longer distort the uterine cavity. Surgery may not be further required.[19]

Type 2 or type 2-5 myomas (single or multiple) distorting the uterine cavity – When multiple myomas (≥2) or myomas of multiple types (type 2–5) are observed, UPA can be administered over two to three month courses. Myoma regression is expected to be very significant (>50% decrease), with no longer distorted uterine cavity. The patient can then attempt natural conception or undergo assisted reproductive techniques.[22-23] If myoma regression is significant (≥25% but <50%), but the uterine cavity remains distorted or if the myoma remains large due to great volume at baseline, a surgery will be indicated. In young patients with symptomatic myomas desiring future fertility, UPA can be administered long term, i.e., in four courses of three months.[22]

SPRMs are beneficial, because long-term intermittent therapy (repeated in case of recurrence during the interval) might help to avoid or postpone surgery until the patient seeks to conceive.[19]

Aromatase Inhibitors (AIs)

The use of AIs in reducing myoma volume has been demonstrated. This medication class works by inhibiting aromatase, a cytochrome p450 enzyme, which blocks the conversion of androgens to estrogens. AIs appear to be as or more effective than GnRH agonists at reducing myoma volume but have significantly fewer adverse effects during short term use.

In one randomized control trial, an AI was shown to decrease the total myoma volume comparatively to GnRH agonists (45.6 versus 33.2%, respectively).[24] Aromatase appears to be prevalent within myoma tissue but not in myometrium, allowing these medications to specifically target myoma. One retrospective study revealed that myomas had triple aromatase amount than in normal myometrium.[25] AIs might work to decrease the complexity of myoma surgery, leading to improved fertility outcomes.[20]

Surgical treatments[3]

When patients' conception difficulties or recurrent miscarriages are attributed to myomas, surgical removal is a recommended option. Removal of submucous myomas was shown to increase clinical pregnancy rates compared to controls where myomas were left in situ. However, myomectomy in cases of intramural myomas is more controversial.

Hysteroscopy

Hysteroscopic myomectomy is a popular surgical method. It is a choice for up to 4-5 cm submucous myomas. It can be performed on type 0, 1 or 2 myomas. But type 2 myomas often require multiple procedures for a complete resection. Uterine perforation, fluid overload, bleeding, and intracavitary adhesion formation are common hysteroscopic myomectomy complications. Several techniques are available for hysteroscopic myomectomy, including electrocautery resection, morcellation, laser ablation and vaporization.

Laparoscopic versus laparotomy

It is known that all myomas FIGO L3 and large L2 are best removed by laparoscopy or laparotomy. Reproductive outcomes appears comparably improved in both methods.

Laparotomy (Open myomectomy)

Laparotomy is a method of choice, especially with multiple complicating intra-abdominal adhesions. All large myomas (i.e., >20 cm in diameter) or any malignant ones require a conventional open approach. The standard risks of open abdominal surgery are increased blood loss and longer recovery times compared to less invasive choices.

Laparoscopy

Laparoscopic myomectomy yields improved visualization, decreased blood loss, faster recovery and reduced postoperative pain compared to laparotomy. Pregnancy outcomes and the risk of myoma recurrence are comparable.[26] Uterine rupture during pregnancy following laparoscopic myomectomy is a great concern, However, the real risk has never been documented. The concern originates from the technical difficulty of performing a multilayer closure. The actual rate of uterine rupture following laparoscopic myomectomy is extremely low.

Robotic-assisted laparoscopy

The Food and Drug Administration (FDA) gave a green light to the da Vinci system for laparoscopic surgery in 2000, and for the use in gynecologic procedures in 2005. Since then, the use of robotic-assisted laparoscopic procedures, including hysterectomy and myomectomy has become increasingly common. The robotic system improves visibility in 3D viewing and intuitive movement of the operating arms. The short-term outcomes are comparable to traditional laparoscopy in terms of blood loss and recovery time. A recent retrospective cohort study displayed pregnancy outcomes following robotic myomectomy to be comparable to traditional laparoscopy. The system incurs higher costs and longer operative time.[27]

Other treatment methods[3]

Uterine artery embolization (UAE) and magnetic resonance focused ultrasound surgery (MRgFUS) are minimally invasive alternative treatments for symptomatic myoma. Pregnancy is possible after these treatments. However, increased obstetrical complications including miscarriage, abnormal placentation and postpartum hemorrhage are reported. The evidence supporting these modalities for patients seeking fertility is limited.

Uterine Artery Embolization (UAE)

UAE was first described in 1995 as an alternative radiological treatment option for women with large myomas no longer seeking to preserve fertility (Fig 2). A transient ischemia is shown by MRI imaging in the body of the uterus and the endometrium lasting for up to 72 hours. This ischemic change is intended to be irreversible only within myoma tissue[15] and temporary within healthy uterine muscle and endometrium. The uterine and ovarian artery has also been shown to anastomose on angiography in at least one side in approximately 46 % of patients.[3]

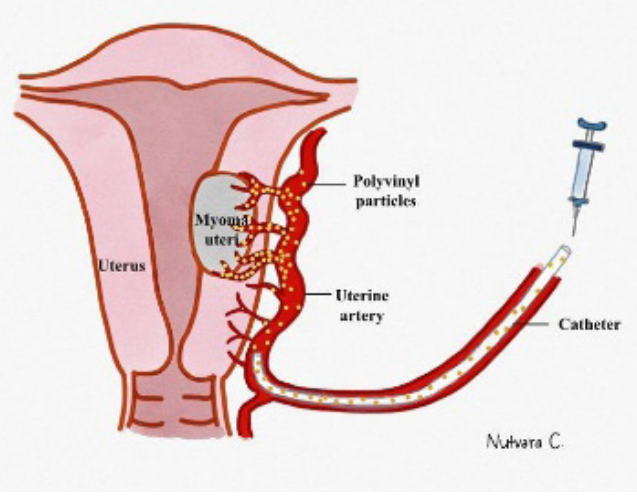

Fig 2. Uterine Artery Embolization

Inadvertent embolization of ovarian tissue may result in ovarian insufficiency and failure, especially in older patients or those with low baseline ovarian reserve. The incidence of amenorrhea is <1% in patients under 40. RCT was conducted for evaluating UAE versus abdominal myomectomy in an infertile population with pregnancy rates of 50 and 78 % respectively.[28] They recruited young patients below age 35 which may explain the high overall conception rates. Time to conception was longer for patients with UAE compared to myomectomy, 18 versus 13 months, respectively. Considering the poor reproductive and obstetric outcomes (increased rate of miscarriage, preterm delivery, abnormal placentation and postpartum hemorrhage), UAE is not a preferred choice for women with infertility or those desire future fertility. It is to be reserved for poor surgical candidates.

Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

MRI-directed beams of ultrasound capable of heating an area of myoma tissue to up to 70 °C is used in this method (Fig 3). MRgFUS will cause destruction by coagulative necrosis.[15] Rabinovici et al. reported pregnancies following MRgFUS. Fifty four pregnancies were reported in 51 women. The mean age at MRgFUS was 37.2 years and mean time to conception was 8 months.[29] The miscarriage rate was 28%. The preliminary findings are successful with a high rate of delivered and ongoing pregnancies. There is limited evidence for the use of these methods in patients who later want to get pregnant. It is too early to recommend MRgFUS in the infertile patient desiring conception until further study.

Current practice

When patients seek pregnancy (agnostic to IVF), gynecologists should establish an integrated approach based on the current knowledge by considering patients's age as well as myomas' size, number, and location. The following parameters should be considered before deciding on a surgical treatment: (1) How would the lesion impact patient fertility? (2) What is the efficacy of surgical intervention? (3) What are additional clinical indications associated with the presence of myoma? The current practice for myoma treatment is presented in Table 1.

The recurrent of myoma uteri after treatment[16]

Surgical treatments: Candiani and his group found overall 10-year cumulative new appearance rate at 27 percent. Diagnostic tool in their study was clinical examination with ultrasound confirmation. The new appearance of myomas from both laparoscopic and abdominal approaches were not statistically significant. Malone reported the subsequent surgery rate among single and multiple myomectomy at 11 and 26 percent during an average of 7.6 years follow-up period, respectively.

Other treatment methods: There were limited recurrence rate data among women who initially underwent non-surgical treatment, namely medical and radiological intervention treatments.[16] GnRH agonist, SPRMs and AIs were medical treatments which caused temporary myomas' size reduction. However myoma would return

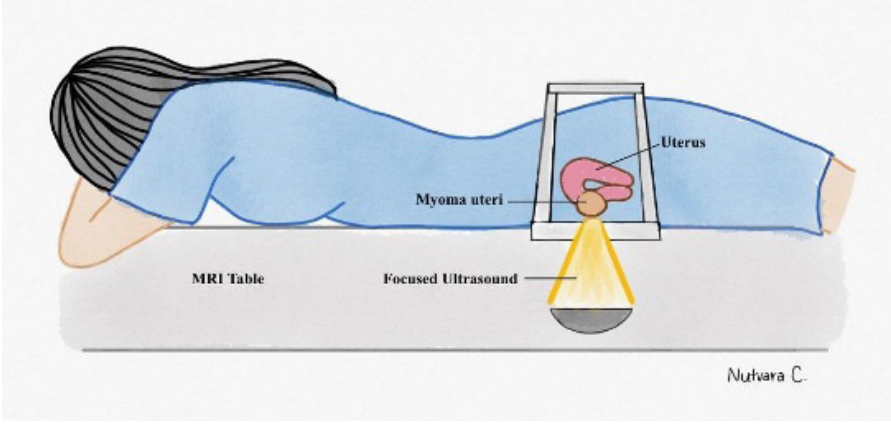

Fig 3. Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

TABLE 1. Current recommended practice for the treatment of myomas.

Type	Indication for surgical treatment			Recommendations
	Impact	Effectiveness	Additional	
Submucosal	A	B	AUB	Hysteroscopy
Intramural				
> 4 cm	A	C	PPC, S	Laparoscopy
< 4 cm	D	D	D	Expectant[a]
Subserosal	E	E	PC	Expectant[b]

Impact: Impact on reproductive potential, Effectiveness: effectiveness of surgical intervention, Additional: additional indications, Submucosal: type 0-2, Subserosal: type 5-7, A: significant impairment, B: significant improvement, C: improvement that needed further evidence, D: unclear, E: no significant, AUB: abnormal uterine bleeding, PPC: potential pregnancy complications, S: symptomatic myoma, PC: potential complications, Hysteroscopy: excision via hysteroscopy, Laparoscopy: excision via laparoscopy (preferable), Expectant: expectant management, [a] : Surgery indicated only in cases of multiple IVF failures or poor obstetrical outcome, [b] : Surgery indicated only in the presence of associated symptoms or poor obstetrical outcome.

to its original size when medication was stopped. The use of these agents would be recommended only for preoperative myomectomy but not for any definitive treatment. Radiological intervention treatment was appropriated for women who were not fit for surgery. Radiological hazard made the method not suitable for the women who needed future fertility function. The use of any non-surgical treatment should be under the physician's consideration on a case by case basis.

CONCLUSION

The evidence regarding the effect of myomas on infertility and reproductive outcomes is weak and largely inconclusive. In infertile patients, appropriate evaluation and classification of myomas is important. Submucosal myoma (FIGO L0-L2) should be treated hysteroscopically (or laparoscopic for large L2) to improve conception rates. The management of any intramural myomas should be an individualized case. Subserosal myomas impact on fertility are rather insignificant. Conservative treatment measures (medical, UAE and MRgFUS) should not be routinely offered to women who wish to maintain or improve their fertility due to lack of safety and efficacy data.

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REFERENCES

1. Zepiridis LI, Grimbizis GF, Tarlatzis BC. Infertility and uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2016;34:66-73.
2. Lisiecki M, Paszkowski M, Woźniak S Fertility impairment associated with uterine fibroids - a review of literature. Prz Menopauzalny 2017;16:137-40.
3. Purohit P, Vigneswaran K. Fibroids and Infertility. Curr Obstet Gynecol Rep 2016;5:81-8.
4. Ben-Nagi J, Miell J, Mavrelos D, Naftalin J, Lee C, Jurkovic D. Endometrial implantation factors in women with submucous uterine fibroids. Reprod Biomed Online 2010;21:610-5.
5. Kitaya K, Yasuo T. Leukocyte density and composition in human cycling endometrium with uterine fibroids. Hum Immunol. 2010;71:161–63.
6. Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. Hum Reprod Update 2011;17:242-53.
7. Matsuzaki S, Canis M, Darcha C, Pouly JL, Mage G. HOXA-10 expression in the mid-secretory endometrium of infertile patients with either endometriosis, uterine fibromas or unexplained infertility. Hum Reprod 2009;24:3180-7.
8. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril. 2010;93:2027-34.
9. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018;143 393-408.
10. Pritts EA, Parker WH, Olive DL. Fibroids and infertility: an updated systematic review of the evidence. Fertil Steril 2009; 91:1215-23.
11. Casini ML, Rossi F, Agostini R, Unfer V. Effects of position of fibroids on fertility. Gynecol Endocrinol 2006;22:106-9.
12. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod 2010;25:418-29.
13. Buletti C, De Ziegler D, Polli V, Flamigni C. The role of leiomyomas in infertility. J Am Assoc Gynecol Laparosc 1999;6:441-5.
14. Metwally M, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev 2012; 11:CD003857.
15. Carranza-Mamane B, Havelock J, Hemmings R. The management of uterine fibroids in women with otherwise unexplained infertility. J Obstet Gynaecol Can. 2015;37:277-285.
16. William H, Jonathan S, Deborah L. Uterine Fibroids. Berek and Novak's Gynecology.16th ed. Philadelphia: Lippincott Williams and Wilkins; 2019. p.223-50.
17. Siristatidis C, Vaidakis D, Rigos I, Chrelias G, Papantoniou N. Leiomyomas and infertility. Minerva Ginecol 2016;68:283-96.
18. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet 2020;149:3-9.
19. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update 2016;22:665-86.
20. Whynott RM, Vaught KCC, Segars JH. The Effect of Uterine Fibroids on Infertility: A Systematic Review. Semin Reprod Med 2017;35:523-32.
21. Donnez J, Donnez O, Dolmans MM. With the advent of selective progesterone receptor modulators, what is the place of myoma surgery in current practice? Fertil Steril 2014;102:640-8.
22. Donnez J, Hudecek R, Donnez O, Matule D, Arhendt HJ, Zatik J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertil Steril 2015;103:519-27.
23. Lo Monte G, Piva I, Graziano A, Engl B, Marci R. Ulipristal acetate prior to in vitro fertilization in a female patient affected by uterine fibroids: a case report. Eur Rev Med Pharmacol Sci 2016;20:202-7.
24. Parsanezhad ME, Azmoon M, Alborzi S, Rajaeefard A, Zarei A, Kazerooni T, et al. A randomized, controlled clinical trial comparing the effects of aromatase inhibitor (letrozole) and gonadotropin-releasing hormone agonist (triptorelin) on uterine leiomyoma volume and hormonal status. Fertil Steril 2010;93: 192-8.
25. Kashani BN, Centini G, Morelli SS, Weiss G, Petraglia F. Role of medical management for uterine leiomyomas. Best Pract Res Clin Obstet Gynaecol 2016;34:85-103.
26. Frishman GN, Jurema MW. Myomas and myomectomy. J Minim Invasive Gynecol 2005;12:443-56.
27. Van Heertum K, Barmat L. Uterine fibroids associated with infertility. Womens Health (Lond) 2014;10:645-53.
28. Torre A, Fauconnier A, Kahn V, Limot O, Bussierres L, Pelage JP. Fertility after uterine artery embolization for symptomatic multiple fibroids with no other infertility factors. Eur Radiol 2017;27: 2850-59.
29. Rabinovici J, David M, Fukunishi H, Morita Y, Gostout BS, Stewart EA; MRgFUS Study Group. Pregnancy outcome after magnetic resonance-guided focused ultrasound surgery (MRgFUS) for conservative treatment of uterine fibroids. Fertil Steril 2010;93: 199-209.