Original Article

A 12-week, Randomized, Parallel-group, Phase III Study Comparing the Efficacy of Once-daily Budesonide/formoterol Turbuhaler (160/4.5 µg/d) with Twice-daily Budesonide (400 µg/d) During the Step-down Period in Well-controlled Asthma

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Abstract

OBJECTIVES: Budesonide/formoterol fumarate (BUD/FF) is recommended in the stepwise management of uncontrolled asthma, but data on a once-daily dose of this medication in a step-down period are lacking. We aimed to compare BUD/FF and BUD in terms of the changes in asthma control scores and lung functions.

MATERIAL AND METHODS: This 12-week, randomized, parallel-group, single-center, open-label study was conducted in well-controlled asthmatic patients receiving twice-daily BUD/FF (160/4.5 µg 2 inhalations) randomized into once-daily BUD/FF (160/4.5 µg 1 inhalation) or twice-daily BUD (200 µg 2 inhalations).

RESULTS: At week 12, the medians of Asthma Control Test (ACT) were 23 (interquartile range [IQR]: 22-24) in the BUD/FF group and 23 (IQR: 22-24.5) in the BUD group, while the medians of Asthma Control Questionnaire (ACQ) were 0.43 (IQR: 0.29-0.82) in the BUD/FF group and 0.57 (IQR: 0.43-0.93) in the BUD group. No statistically significant difference was observed in either ACT ($p=0.673$) or ACQ ($p=0.295$) between the treatments. The ACT scores significantly decreased from baseline to week 12 in both treatments. Peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) also had no statistically significant differences between treatments. PEF in the BUD/FF group and FEV_1 in both treatments significantly decreased from baseline to week 12.

CONCLUSION: Compared to twice-daily BUD, once-daily BUD/FF provides equivalent asthma control scores and lung function during the step-down period after switching from twice-daily doses of BUD/FF in well-controlled asthma.

KEYWORDS: Asthma, step down, budesonide, formoterol

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INTRODUCTION

Asthma remains a highly prevalent condition associated with episodic exacerbation that impairs the health status. Based on data from clinical trials, inhaled corticosteroids (ICS) alone or in combination with long-acting β_2 -agonists (LABA) is recommended for stepwise management in uncontrolled asthma patients, because these medications effectively help achieve symptom control, maintain normal activity levels, and minimize future risk of exacerbations and fixed airflow limitations [1-3]. Furthermore, the existing practical guidelines for asthma treatment, including the Global Initiative for Asthma (GINA), suggest that stepping-down treatment is recommended in patients who have achieved good asthma control for 3 months with stable lung function, and stepping-down treatment also helps minimize the cost of treatment and has the potential to reduce side effects [4,5]. Additionally, the recommendation states that reducing low-dose ICS/LABA to a once-daily regimen might be another option for stepping down in asthma management strategy [6]. However, there are no previous studies supporting this recommendation. Moreover, another earlier study has found that discontinuing LABA in a stepping-down therapy was more likely to lead to asthma deterioration [4].

The ICS/LABA combination, budesonide/formoterol fumarate (BUD/FF; 160/4.5 µg/dose) in a Turbuhaler, a dry powder inhaler (DPI) device, has well-established data in terms of efficacy and safety and is recommended during stepping up in asthma management [7,8]. According to the dosing frequency, either once-daily dosing or twice-daily dosing of BUD/FF has well-demonstrated 24-hour bronchodilator action, improving lung function, and stabilizing asthma control. Various studies have also suggested that once-daily dosing could also enhance compliance with the medication [9-11]. A previous study has found that a very low-dose BUD/FF (160/9 µg/d) showed a benefit of asthma control and improved lung function during stepping up

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in asthma therapy, while there are scarce data on stepping-down management. A recent study has confirmed that step-down treatment from medium dose BUD/FF to low dose BUD/FF in controlled asthma helps maintain lung function and quality of life and is equivalent to monotherapy with ICS [10,12]. However, the step-down treatment from twice-daily low-dose BUD/FF to once-daily dosing has been infrequently evaluated.

This investigator-initiated study was designed to compare asthma symptom scores and lung function in stepping-down therapy between once-daily low-dose ICS/LABA (BUD/FF; Turbuhaler; 160/4.5 µg/d) and twice-daily low-dose ICS (BUD; 400 µg/d).

MATERIAL AND METHODS

Patients

The study was designed to include asthmatic patients who attended the asthma clinic at Hat Yai Hospital. The inclusion criteria were designed to enroll patients aged >18 years and were being treated with twice daily BUD/FF 160/4.5 µg in a DPI (Symbicort; Turbuhaler; AstraZeneca; Södertälje, Sweden). Patients were required to have well-controlled asthma, as defined by an Asthma Control Test (ACT) score >21 for at least 12 weeks prior to study enrollment, and the ability to perform spirometry in accordance with the standards of the American Thoracic Society [13]. Patients were excluded if they were current smokers or had a smoking history of >10 pack-years and/or had other chronic pulmonary diseases, such as chronic obstructive pulmonary disease, chronic bronchitis, lung cancer, or pulmonary fibrosis. Additionally, patients who had a history of previous lung infection and/or asthma exacerbation or had taken a systemic corticosteroid within the previous 12 weeks were excluded.

Study Design and Treatments

This was a randomized, open-label, parallel-group, single-center trial (ClinicalTrials.gov identifier NCT02725242) conducted from March 2016 through December 2016. The study was performed in accordance with the principles of the Declaration of Helsinki and was consistent with the International Conference on Harmonization and Good Clinical Practice and the applicable regulatory requirements.

The protocol was approved by the institutional review board of Hat Yai Hospital, and informed written consent was obtained from each participant prior to study entry. The study design is shown in Figure 1. After a screening visit, the patients entered a 2-week run-in period during which eligible patients continued the BUD/FF (160/4.5 µg) one inhalation twice-daily (320/9 µg/d) treatment until the day of randomization. Patients were then randomized into 12-week treatment periods with either BUD/FF 160/4.5 µg (DPI; Symbicort; Turbuhaler; AstraZeneca; Södertälje, Sweden) or BUD 200 µg, in a DPI (Giona Easyhaler; Orion Pharma, Finland) groups. Randomization was performed in accordance with a predetermined block randomization. The BUD/FF was administered once daily at night (total daily dose 160 µg BUD/4.5 µg FF), while the BUD was administered twice daily (total daily dose 400 µg BUD). The use of a rescue pressurized metered dose inhaler (pMDI) of salbutamol or fenoterol/ipratropium was permitted throughout the study as required.

The patients were scheduled for clinic visits at the start and end of the run-in period and at 4, 8, and 12 weeks after randomization at week 0. The patients were evaluated for clinical symptoms at each visit after the step-down treatments began, including asthma control status and pulmonary function. The asthma control status was scored using the ACT and GINA assessments of asthma control at monthly intervals, while the Asthma Control Questionnaire 7-item version (ACQ) was administered at only weeks 0 and 12. Spirometry evaluations, such as forced vital capacity (FVC), pre-dose forced expiratory volume in 1 second (FEV₁), percentage of predicted FEV₁, and FEV₁/FVC ratios were performed at weeks 0 and 12, while peak expiratory flows (PEFs) were assessed at monthly intervals. Baseline characteristics, including age, sex, height, body weight, body-mass index, smoking history, and current medications were collected from the participants' medical records.

Primary and Secondary Outcomes

The objective of the study was to compare the efficacy between once-daily BUD/FF and twice-daily BUD treatments in

Figure 1. Randomized, open-label, double dummy, parallel-group, single-center study design
FF: formoterol fumarate; BUD: budesonide

terms of changes in asthma symptom scores and lung function in a step-down asthma therapy. The co-primary efficacy variables were the ACT and ACQ scores at week 12 and the baseline changes at the end of the study (week 12). The secondary outcomes were the changes in PEF at each clinic visit, changes in FEV₁ at baseline and week 12, and the ratio of participants in each GINA asthma score classification at baseline and week 12.

Asthma Control Test

The ACT includes five symptom/reliever questions plus a patient self-assessed level of asthma control during the preceding 4 weeks: limitation of activities; shortness of breath; awakenings at night; use of reliever medication; and the patient's perception of asthma control. Each question has five response options from 1 to 5, with higher scores representing better control and a total score ranging from 5-25 (higher is better). Scores of 20-25 are classified as well-controlled asthma; 16-20 as not well controlled; and 5-15 as very poorly controlled asthma [14-15].

Asthma Control Questionnaire

The ACQ measures the adequacy of asthma control and changes in asthma control, which occur either spontaneously or as a result of treatment. It has a multidimensional construct assessing symptoms (5 self-assessed items) and rescue bronchodilator use (1 self-administered item) and FEV₁% predicted (1 item) completed by the clinic staff. Scores range from 0-6 (higher is worse). A score of 0.0-0.75 is classified as well-controlled asthma; 0.75-1.5 as a 'gray zone'; and >1.5 as poorly controlled asthma [16-18].

Spirometry

Spirometry was performed using a VIASYS spirometer (CareFusion, California, USA) according to the standards of the American Thoracic Society [13]. The highest of three values of FEV₁, repeatable within 5%, was recorded and the percent predicted was calculated.

Statistical Analysis

Efficacy data were analyzed using the intent-to-treat analysis, which included all patients who were randomized and received the at least one inhalation medication of the study and had at least one post-baseline efficacy evaluation. The minimum number of participants was estimated to be 35 per arm to detect a 30 liter/minute difference between the treatments in PEF with a power of 80% at the 5% significance level using pairwise comparisons, assuming a standard variation of 50 liter/minute. Missing values were accounted for using the last observation carried forward approach. Comparisons between the BUD/FF and BUD groups were conducted using a non-parametric test. Categorical values, expressed as number with proportion, were analyzed using the Fisher's exact test. Continuous or ordinal values were summarized as median with interquartile range (IQR) and were analyzed using the Mann-Whitney U test. The Wilcoxon Signed-Rank test was used to analyze changes between pre- and post-stepping-down treatments in the same subjects. All statistical analyses were performed using the Statistical Package for Social Sci-

Figure 2. CONSORT flow diagrams of the progress of the study
RTI: respiratory tract infection; AE: asthmatic exacerbation; FF: formoterol fumarate; BUD: budesonide

ences version 23 (IBM Corp.; Armonk, NY, USA). A p value of <0.05 was considered significant for the results of all statistical analyses and all the tests were two-sided.

RESULTS

A total of 85 patients were enrolled in this study, of whom 73 were randomized into two groups (Figure 2). The first patient was enrolled in March 2016 and the last completed the trial in February 2017. Thirty-six patients were assigned to the BUD/FF group and 37 to the BUD group. Sixty-four patients (33 in the BUD/FF group and 31 in the BUD group) completed the 12-week study. Twelve patients were excluded and the major reason was previous respiratory tract infection (8 of 12 screened patients [66.7%]). The baseline characteristics data are summarized in Table 1. At enrolment, the median ACT scores were 24 (IQR: 24-25) for the BUD/FF group and 24 (IQR: 23-25) for the BUD group, while the median ACQ scores were 0.43 (IQR: 0.18-0.82) for the BUD/FF group and 0.71 (IQR: 0.29-1.00) for the BUD group. The participants in both groups had well-controlled asthma as confirmed by ACT scores of 20-25 and mean ACQ values <0.75. According to the GINA assessments of asthma control, 36 (100%) patients in the BUD/FF group and 34 (91.9%) in the BUD group were defined as well controlled. The median FEV₁ scores were 1.94 liters (IQR: 1.70-2.54) for the BUD/FF group and 1.76 liters (IQR: 1.43-2.16) for the BUD group, while the median PEF scores were 367 liters/minute ([LPM] IQR: 317-410) for the BUD/FF group and 324 LPM (IQR: 253-368) for the BUD group. The median percentages of predicted FEV₁ were 85% (IQR: 72-101) for the BUD/FF group and 80% (IQR: 64-90) for the BUD group. However, there were no significant differences between the groups for all baseline characteristics.

Primary Outcome: The Changes in Asthma Symptom Scores During Stepping-Down Treatment According to ACT and ACQ scores

We evaluated the ACT and ACQ scores after 12 weeks and compared with those obtained at the beginning of the treatment in 73 patients based on the intent-to-treat analysis. At week 12, the ACT scores had slightly decreased in both groups (Table 2); the median ACT scores were 23 (IQR: 22-

Table 1. Baseline demographics and pulmonary characteristics

	BUD/FF (n=36)	BUD (n=37)
Median age, years (IQR)	49.5 (38.3, 63.1)	50.0 (39.0, 59.0)
Sex, no. (%)		
Male	11 (30.6)	9 (24.3)
Female	25 (69.4)	28 (75.7)
Height (m)	157.5 (152.6, 162.8)	153.0 (147.0, 158.5)
Weight (kg)	62.9 (54.2, 70.7)	62.3 (51.7, 73.7)
Mean body-mass index (kg/m ²)	25.1 (22.0, 29.5)	26.1 (22.3, 28.4)
Smoking status No. (%)		
Former smoker	11 (30.6)	7 (18.9)
Non-smoker	25 (69.4)	30 (81.1)
ACT	24 (24, 25)	24 (23, 25)
ACQ	0.43 (0.18, 0.82)	0.71 (0.29, 1.00)
GINA assessment of asthma control, No. (%)		
Well controlled	36 (100)	34 (91.9)
Partly controlled	0 (0)	3 (8.1)
FEV ₁ /FVC (%)	72.0 (65.3, 76.0)	69.0 (62.5, 74.0)
FVC		
(L)	2.78 (2.42, 3.65)	2.47 (2.21, 2.96)
% predicted	91 (80, 104)	85 (76, 96)
FEV ₁		
(L)	1.94 (1.07, 2.54)	1.76 (1.43, 2.16)
% predicted	85.0 (72, 101)	80 (64, 90)
PEF		
(LPM)	367 (317, 410)	324 (253, 368)
% predicted	100 (84, 117)	90 (69, 106)

Values are shown as median (interquartile range) or number (%)

FF: formoterol fumarate; BUD: budesonide; no: number; m: meter; kg: kilogram; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; L: liter; PEF: peak expiratory flow; LPM: liters per minute; ACT: asthma control test; ACQ: asthma control questionnaire 7-item version; GINA: Global Initiative for Asthma; IQR: interquartile range

24) and 23 (IQR: 22-24.5) for the BUD/FF and BUD groups, respectively, ($p=0.673$). The median ACQ scores were 0.43 (IQR: 0.29-0.82) and 0.57 (IQR: 0.43-0.93) for the BUD/FF and BUD groups, respectively, ($p=0.295$), without significant differences between the groups. The variations of the ACT and ACQ scores from baseline to week 12 are shown in Table 3. There was a significant reduction in the ACT scores from baseline to week 12 in both groups, but no significant difference in the ACQ scores. The median ACT score changes from baseline to week 12 were 1.0 (IQR: -3.0-0) in the BUD/FF group and 0 (IQR: -2.0-0) in the BUD group without significant difference between the groups ($p=0.155$), while the median ACQ score changes from baseline to week 12 were 0 (IQR: -0.25-0.29) in the BUD/FF group and 0 (IQR: -0.36-0.14) in the BUD group ($p=0.38$), again without significant difference between the groups (Figure 3).

Secondary outcome: the changes in lung functions and the ratio of participants in each GINA asthma score classification during step-down treatment

At week 12, the median FEV₁ were 1.85 liters (IQR: 1.66-2.34) for the BUD/FF group and 1.66 liters (IQR: 1.24-2.2) for the BUD group, while the median PEF were 344 LPM (IQR: 279-404) for the BUD/FF group and 316 LPM (IQR: 238-378) for the BUD group (Table 2); however, both FEV₁ and PEF had no difference between the treatments. The median percentages of predicted FEV₁ in the BUD group (72% [IQR: 63-83]) were significantly lower than those in the BUD/FF group (83% [IQR: 71-95]). The variations of the median FEV₁ and PEF between baseline and week 12 were minimal in both groups (Table 3). There was a significant variation of FEV₁ in both the BUD/FF ($p=0.005$) and BUD groups ($p=0.035$), while the significant variation of PEF was found in only the BUD/FF group ($p=0.011$). The ratio of participants between groups at week 12 showed no significant difference in terms of the ratio of GINA scores classification ($p=0.789$, Table 2).

Table 2. Primary and secondary outcome measures at week 12

	BUD/FF (n=36)	BUD (n=37)	p
ACT	23 (22, 24)	23 (22, 24.5)	0.673
ACQ	0.43 (0.29, 0.82)	0.57 (0.43, 0.93)	0.295
GINA assessment of asthma control, no. (%)			
Well controlled	26 (72.2)	28 (75.6)	
Partly controlled	7 (19.4)	7 (18.9)	
Uncontrolled	3 (8.3)	2 (5.5)	0.798
FEV ₁			
(L)	1.85 (1.66, 2.34)	1.66 (1.24, 2.20)	0.065
% predicted	83 (71, 95)	72 (63, 83)	0.034
PEF			
(LPM)	344 (279, 404)	316 (238, 378)	0.077
% predicted	96 (78, 113)	85 (66, 96)	0.058

Values are shown as median (IQR) or number (%)

IQR: interquartile range; FF: formoterol fumarate; BUD: budesonide; ACT: asthma control test; ACQ: asthma control questionnaire 7-item version; GINA: Global Initiative for Asthma; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; L: liter; PEF: peak expiratory flow; LPM: liter per minute

Table 3. Changes in asthma control scores and pulmonary functions between pre- and post-stepping-down treatment

	BUD/FF (n=36)			p	BUD (n=37)		
	Week 0	Week 12			Week 0	Week 12	p
ACT	24 (24, 25)	23 (22, 24)		0.001	24 (23, 25)	23 (22, 24.5)	0.003
ACQ	0.43 (0.18, 0.82)	0.43 (0.29, 0.82)		0.414	0.71 (0.29, 1.00)	0.57 (0.43, 0.93)	0.295
FEV ₁							
(L)	1.94 (1.70, 2.54)	1.85 (1.66, 2.34)		0.005	1.76 (1.43, 2.16)	1.66 (1.24, 2.20)	0.035
% predicted	85 (72, 101)	83 (71, 95)		0.051	80 (64, 90)	72 (63, 83)	0.028
PEF							
(LPM)	367 (317, 410)	344 (279, 404)		0.011	324 (125, 368)	316 (238, 378)	0.566
% predicted	100 (84, 117)	96 (78, 113)		0.010	90 (69, 106)	85 (66, 96)	0.464

Values are shown as median (IQR)

IQR: interquartile range; FF: formoterol fumarate; BUD: budesonide; ACT: asthma control test; ACQ: asthma control questionnaire 7-item version; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; L: liter; PEF: peak expiratory flow; LPM: liter per minute

Figure 3. Changes in ACT and ACQ scores between pre- and post-stepping-down treatment. (A) The median ACT changes between baseline and week 12 were -1.0 (IQR: -3.0-0) in the BUD/FF group and 0 (IQR: -2.0-0) in the BUD group ($p=0.155$). (B) The median ACQ changes between baseline and week 12 were 0 (IQR: -0.25-0.29) in the BUD/FF group and 0 (IQR: -0.36-0.14) in the BUD group ($p=0.38$)

BUD: budesonide; IQR: interquartile range; FF: formoterol fumarate; ACQ: asthma control questionnaire

DISCUSSION

This study was designed to compare once-daily low-dose ICS/LABA (BUD/FF/160/4.5 µg/d) with twice-daily low-dose ICS (BUD, 400 µg/d) during a stepping-down period in clinically stable asthma patients who were receiving twice-daily low-dose ICS/LABA (BUD/FF, 320/9 µg/d). The study found that once-daily low-dose BUD/FF was equivalent to twice-daily low-dose BUD with regard to ACT, ACQ, FEV₁, and PEF at week 12, although the percentage of predicted FEV₁ in the once-daily low-dose BUD/FF group was higher than that in the twice-daily low-dose BUD group. However, we found that ACT scores at week 12 were significantly lower than the baseline scores in both treatment groups, whereas there were no differences in the ACQ scores between baseline and week 12. In the pulmonary function tests, there was a significant reduction in FEV₁ at week 12 in both medications, while PEF had declined in only the BUD/FF group. Moreover, there was no difference in the number of patients in each medication group in each GINA asthma score classification during the step-down treatment.

According to the GINA guideline, although stepping-up therapy is an essential strategy for well-controlled asthma, once control is achieved, stepping down is then also necessary to achieve optimal control and minimizing costs and potential side effects of the medications. Although there are many options for a stepping-down program, reducing ICS/LABA to a once-daily dose has been infrequently studied. In our study, we showed that a once-daily low dose of ICS/LABA (BUD/FF) had similar results in asthma control scores and lung function in stepping-down therapy to a twice-daily low ICS (BUD). Although these findings were consistent with a previous study, which used once-daily BUD/formoterol (160/9 µg/d) pMDI in a stepping-down program, the patients in our study might have had maximum airway inflammatory suppression and bronchodilator response before randomization because of longer durations of twice-daily low-dose BUD/FF (12 weeks) compared to the previous study (4-5 weeks) [19]. A previous meta-analysis suggested that a 3-month interval is feasible and safe for most patients to step down their treatment [20]. Although the recommended dose of BUD/FF is twice daily because of its 12-hour action, previous studies have reported

a 24-hour sustained efficacy with either once-daily low- or medium-dose BUD/FF and that this treatment regime also provided benefits in improved lung function and stabilized asthma control scores in the stepping-up management period [10,13]. We therefore believe that once-daily low-dose BUD/FF could also sustain the action over 24 hours in the step-down period. Although either BUD/FF or BUD resulted in the minimal reduction of ACT scores, those ACT scores after both treatments were classified as well-controlled asthma.

Although the GINA guideline recommends stepping down to low-dose ICS/LABA once daily in a three-step process, there is still little evidence to support this recommendation. Moreover, the guideline suggests that discontinuing LABA is more likely to lead to deterioration [4]. A previous meta-analysis has also supported that LABA step-off in patients with controlled asthma resulted in increased asthma-associated impairment, while another study has reported that most patients were concerned about the risks or costs of daily treatment and a lower dose regime could help alleviate these concerns [5,6]. In the present study, the effect from stepping down to once-daily low-dose BUD/FF could be another option for step-down management besides monotherapy ICS, because either asthma control scores or lung function are eventually the same with either medication. To our knowledge, predicted FEV₁% is an essential predictor for future exacerbation, and once-daily low-dose BUD/FF has been demonstrated to significantly maintain such a parameter compared with twice-daily BUD. However, the clinician should be concerned about the deterioration of FEV₁ and PEF after stepping down to once-daily low-dose BUD/FF in the long-term follow-up. Moreover, we believe that continuing with the same device during the stepping-down process can be a useful strategy to overcome problems related to poor adherence and economize the cost, as study suggested by another study [21].

Our study is the first to examine a stepping-down strategy to once-daily low-dose ICS/LABA from a 3-step process in asthma management. However, the study has several limitations, involving the methodology, sample size, treatment duration, and absence of evaluation of any biomarkers to reflect airway inflammation. Also, because it was an open-label study, performance bias may have occurred. Moreover, it was a single-center trial, and such trials can recruit very few patients leading to a risk of failing to demonstrate a treatment difference and thus an uncertain conclusion. Moreover, the study period was relatively short, and the long-term clinical outcomes in a longer study of asthma exacerbation rate, asthma control, and pulmonary function might be different. Currently, the analysis of biomarkers, such as blood eosinophil and exhaled nitric oxide, plays a major role in the stepwise asthma treatment and guides the clinician in adjusting the patient's medication. Unfortunately, our study did not evaluate these outcomes because of inadequate medical equipment and technical problems.

In conclusion, this study offers more evidence that in a 12-week stepping-down program for clinically stable adults with asthma from twice-daily BUD/FF (320/9 µg/d), either once-daily BUD/FF (160/4.5 µg/d) or twice-daily BUD (400 µg/d)

are equivalent in terms of asthma control scores and lung function tests. However, both of the two step-down strategies may constitute a potential risk to the deterioration of ACT (both groups), FEV₁ (both groups), and PEF (only the BUD/FF group). Future studies should have a larger sample size and longer term evaluation of outcome.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Hat Yai Hospital (Approval No: 064/2014; Approval Date: 03.11.2014).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - N.N., S.U.; Design - N.N.; Supervision - N.N.; Materials - T.P., T.T., P.T.; Data Collection and/or Processing - N.N., T.P., T.T., P.T., S.U.; Analysis and/or Interpretation - N.N., T.P., T.T., P.T., S.U.; Literature Search - N.N.; Writing - N.N., S.U.; Critical Reviews - N.N., T.P., T.T., P.T., S.U.

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