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A Randomized Control Trial of Hyoscine N-Butylbromide versus Lidocaine Pretreatment for Alleviating Pain on Propofol Injection

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Introduction

Propofol is commonly used in anesthesia practice according to its rapid and smooth induction, short duration, and low incidence of postoperative nausea and vomiting. However, discomfort from pain on propofol injection still be a problem.[1-4] The incidence of this pain in adults ranged from 28 to 90% and its pain severity was moderate (average numeric rating scale (NRS) was 5.6±2.3).[5-7] The mechanism of propofol injection pain was hypothesized that propofol likely irritates the innermost layer of vessels that causes directly stimulating free nerve ending and indirectly releasing of mediators and results in pain on injection.[6-8]

Several methods were used for alleviating propofol injection pain such as pretreatment of intravenous lidocaine with or without tourniquet, lidocaine mixed with propofol, and pretreatment with opioids, non-steroidal anti-inflammatory drugs, ketamine, or metoclopramide.[6-9] Pretreatment of lidocaine is a common technique to prevent propofol pain because of its local anesthetic effect on the vein and ease to application.[7-9] Pretreatment of 30 to 60 mg of intravenous lidocaine with tourniquet was presumed to reduce this pain.[9-11] However, appropriate dosages and methods of lidocaine administration were inconclusive and the efficacy of lidocaine administration on propofol injection pain was still varied.

From earlier study, 20 mg of Hyoscine N-butylbromide (HBB) significantly alleviated propofol pain on injection when compared to placebo.[12] HBB, a quaternary ammonium derivative which an anticholinergic drug, bound to peripheral anti-muscarinic receptors which are located notably in smooth muscle cells of gastrointestinal tract and blood vessels.[13,14] It is used for relief abdominal, ureteric colic, labor pain, and prevent spasms of the gastrointestinal tract prior to invasive radiologic and diagnostic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and colonoscopy.[13-16] Common adverse effects of HBB were tachycardia, dry mouth, and blurred vision.[14]

This study was intended to compare the efficacy between pretreatment of HBB and lidocaine in adjunction with tourniquet to alleviate propofol pain on injection.

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Methods

This prospective, double blinded, randomized controlled trial was approved by the Ethics Committee in Human Research, Faculty of Medicine, Khon Kaen University (HE 621416) and the study was also registered at the Thai Clinical Trials Registry (TCTR), identification number was TCTR20211028005. All patients were written informed consent before recruitment into the study. The study was conducted between January to August 2020 in an endoscopic unit of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. We enrolled patients aged 18-60 years old, scheduled for elective procedure under propofol-based total intravenous anesthesia (TIVA), and American Society of Anesthesiologists physical status (ASA PS) class I-II. Exclusion criteria were patients with allergy to study drugs, BMI < 18 or > 25; prescribed other analgesics, antimuscarinic or anti-inflammatory drugs; chronic pain conditions; difficulty in communication or pain assessment; neurological disease; diabetes mellitus; other contraindication for hyoscine such as untreated glaucoma, gut obstruction, benign prostate hyperplasia with urinary retention, and cardiovascular disease; and other contraindication for lidocaine such as severe bradycardia, Wolf-Parkinson-White syndrome, and other tachyarrhythmias. At preoperative visit, after patients decided to participate in the study and obtained inform consent. All patients were instructed about how to assess pain score by using visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain not imaginable) by study personals team.

All patients were randomly allocated into two group to receive either HBB (group H) or 2% lidocaine (group L) by block of 4 randomization using a computer-generated random number (http://www.randomizer.org/). In a sealed opaque envelope, the sequential random number code was enclosed to ensure concealment of allocation. In group H, 20 mg of HBB was diluted with normal saline up to 3 mL, and in group L, 60 mg of 2% lidocaine was the same intervals. Both study solutions, transparent and colorless, were prepared by nurse anesthetist who was not involved to the study. For group allocation, all patients, health care providers participating in postoperative management, data collectors, and outcome adjudicators were blinded.

Before procedure, all patients were re-instructed about VAS pain score assessment. The venous cannulation with 22-gauge intravenous catheter was assessed at dorsum of hand. Standard anesthetic monitoring was monitored and recorded as baseline and then every 5 minutes intraoperatively. All patients received 3 L/min of 100% oxygen via nasal cannula. Before receiving HBB or lidocaine as per protocol, the tourniquet was inflated by manual sphygmomanometer to 60 mmHg at the arm of patient which intravenous catheter was placed. After 1 minute of the study drug was administrated, the tourniquet was totally deflated and then 30 mg of 1% propofol (Fresofol® 1% MCT/LCT, Fresenius Kabi India Pvt. Ltd.) was administrated using target-controlled infusion (TCI) with the injection rate of 600 mL/hour. VAS pain score was assessed after 10 seconds of administration of propofol and then induction of anesthesia was completely conducted.

Data collection and assessment

Baseline characteristics of the patients including age, sex, body weight, height, BMI,

ASA PS, and underlying disease were recorded. The primary outcome measure was VAS pain scores after propofol injection. The secondary outcome variables were tachycardia and hypotension occurring any time within 5 minutes after injection of intervention drugs. Tachycardia was defined as the increase of heart rate more than 20% from baseline. Hypotension was defined as the systolic blood pressure below 90 mmHg.

Sample size and statistical analysis

According to previous study of Jeong and colleagues, propofol injection pain in patients receiving lidocaine pretreatment (mean±SD, 4.31±2.32) was significantly reduced (mean difference, 1.81; 95% CI, 0.63-3.00; *P*=0.003) when compared with patients receiving placebo.[17] The sample size of 56 was based on a power 0.8 and α of 0.05 with compensate for dropouts of 5%. Continuous data were presented as mean and standard deviation (SD) or median and inter-quartile ranges (IQR), as appropriate. Categorical data were presented as number and percentile. The VAS pain scores of propofol pain on injection between two groups were compared using Mann-Whitney U test. The incidence of tachycardia and hypotension between two groups were compared using Fisher's exact test. A p-value less than 0.05 was considered statistical significance. Statistical analysis was performed using STATA software for windows (Version 10.0; STATA Inc, College Station, TX).

Results

Fifty-six patients were enrolled in the study with 28 patients in each group (Figure 1). The mean age was 49.64±9.73 and 47.96±10.18 years in group H and L, respectively. Mostly patients were male in group H but mostly were female in group L. All patients' baseline characteristic including age, gender, BMI, and ASA physical status were not statistically significant difference in both groups (Table 1).

The VAS pain score of propofol pain on injection in group H was significantly higher than in group L (*P*< 0.001) (Table 2). The incidence of tachycardia within 5 minutes after intervention agent injection was significant higher in group H than group L (35.7% vs. 3.6%, respectively, *P*=0.005). The incidence of hypotension within 5 minutes after intervention agent injection was not statistically significantly different between the two groups (Table 3).

Discussion

This study compared pretreatment between 20 mg of HBB and 60 mg of lidocaine in adjunction to tourniquet for venous occlusion. Our data demonstrated that VAS pain score in patients receiving HBB were significantly higher than those receiving lidocaine (4.5 vs. 0; *P*<0.018). When compared to previous study of Sargin and colleagues, which found that the incidence of propofol injection pain was reduced from 73.3% to 43.4% in patients receiving placebo vs. pretreatment with 20 mg of HBB (*P*<0.018).[12] This might be that HBB probably help to decreased propofol injection pain, but it could not be more effective than lidocaine with tourniquet.

Pain on propofol injection might be caused by direct irritant effect of propofol itself to vessels endothelium and indirect irritant via the release of mediators such as kininogen from kinin cascade.[6-8] Lidocaine has a local anesthetic effect, so it was proposed to be a common drug use for reducing propofol injection pain.[11] The mechanism

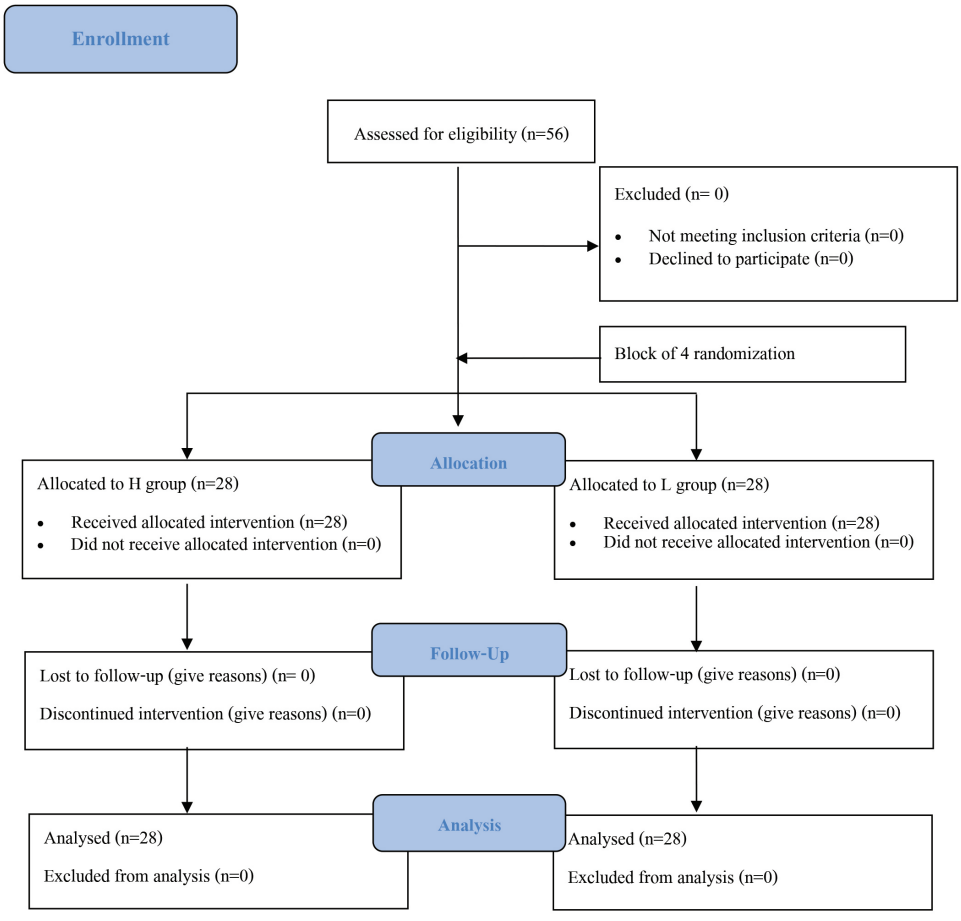

Figure 1 Flow diagram of the study

of HBB to decrease propofol pain is exactly unknown. HBB has peripheral anticholinergic effect, so it might inhibit the transmission of neural impulses in the intraneural parasympathetic ganglia and inhibiting cholinergic transmission in the synapses.[12,13] Nowadays there is limited evidence to presume the efficacy of HBB in order to reduce pain on propofol injection, so further studies are warranted

In a previous study, 86.6% of patients received HBB reported none to mild pain; while; 59.9% of patients in placebo group reported moderate to severe pain.[12] In our study, patients received HBB experienced moderate pain after propofol injection. The difference of pain scale might be explained by; firstly, the difference size of vein: dorsum of hand in our study vs. radial vein at wrist in those study. Current data showed that larger vein might be able to reduce propofol injection pain.[4,7] In this study we chose the dorsum of hand for intravenous site because this area has high incidence of propofol injection pain (30-39%).[4] Secondly, technique of propofol injection, a previous study demonstrated the rate of propofol injection was over 2-3 seconds, while our study was slower. Scott et al. found that decreasing the speed of propofol injection caused the greater discomfort.[18]

Tachycardia is a concern adverse effect of HBB.[13] So, the incidence of tachycardia and hypotension were observed in this study. Our study found that the incidence of tachycardia in patients received HBB was higher than patients received lidocaine. However, this tachycardia was self-limiting and did not progress to severe

Table 1 Demographic data of patients

Characteristics	Group H (n=28)	Group L (n=28)	*P*-value
Age (years); mean±SD	49.6±9.7	47.9±10.2	0.53
Male; n (%)	15 (53.6)	11 (39.3)	0.28
Weight (kg); mean±SD	61.6±10.3	58.7±6.8	0.21
Height (cm); mean±SD	164.0±8.5	160.2±6.6	0.07
BMI (kg/m^2); mean±SD	22.8±2.9	22.8±1.8	0.99
ASA physical status; n (%)			0.11
I	12 (42.9)	18 (64.3)	
II	16 (56.1)	10 (35.7)	
Comorbidities; n (%)			
Hypertension	3 (10.7)	3 (10.7)	1.00
Anemia	3 (10.7)	0	0.24
Hyperthyroidism	1 (3.6)	2 (7.1)	1.00
Asthma	1 (3.6)	0	1.00
Cirrhosis	1 (3.6)	0	1.00
Renal impairment	1 (3.6)	0	1.00
Dyslipidemia	0	1 (3.6)	1.00

BMI = body mass index, ASA = American Society of Anesthesiologists
* Significant as *P*-value < 0.05

Table 2 Visual analogue scale (VAS) of propofol pain on injection between two groups

	Group H (n=28)	Group L (n=28)	*P*-value
VAS	4.50 (1.95, 8.00)	0.00 (0.00, 1.10)	< 0.001*

All data was presented as median (IQR)
* Significant as *P*-value < 0.05

Table 3 Incidence of tachycardia and hypotension within 5 minutes after intervention drugs administration

	Group H (n=28)	Group L (n=28)	*P*-value
Tachycardia	10 (35.7)	1 (3.6)	0.005*
Hypotension	5 (17.9)	4 (14.3)	>0.999

All data were presented as n (%)
* Significant as *P*-value < 0.05

tachyarrhythmia as same as the study of Tytgat who mentioned that tachycardia from HBB administration was mild and self-limiting.[14]

This study has several limitations. Firstly, the temperature of propofol was not controlled as this might affect to pain score. Secondly, we did not follow-up the clinical effect of tachycardia in patients who received HBB during postoperative period, besides we did not collect other adverse effects of HBB.

In conclusion, pretreatment with 20 mg of HBB with tourniquet was not effective as pretreatment with 60 mg of lidocaine with tourniquet in order to alleviate pain on propofol injection. However, further studies might be required to evaluate the efficacy of HBB on propofol pain injection

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