

Comparison of Dexamethasone and Ondansetron with Lidocaine on Propofol Injection Pain

Poonyanuch Charoenkoop, Naruemol Prachanpanich, Prateep Lertmongkonaksorn, Wichai Ittichaikulthol
Department of Anesthesiology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand

Background: Propofol has widely used as an anesthetic induction and maintenance agent. Sixty percent of patients experienced pain on propofol injection. There were evidences that both dexamethasone and ondansetron can reduce propofol injection pain. But the effectiveness of each drug is inconclusive when compare to lidocaine. We hypothesized that combination of dexamethasone and ondansetron is non-inferiority to lidocaine for reducing propofol injection pain.

Methods: 178 adult patients, ASA physical status I-III, undergoing elective surgery were randomly assigned to two groups. Group L received 2 mL of 2% preservative free lidocaine, group DO received dexamethasone 10 mg and follow by ondansetron 4 mg intravenously, 1 minute prior to 0.3 mg.kg⁻¹ of propofol injection. Pain score, facial grimacing, vocalization and hand withdrawal were recorded 10 seconds after propofol injection.

Results: Overall incidences of propofol injection pain after pretreatment (34.83% versus 42.69% in group L and group DO, respectively, $p = 0.26$) and moderate to severe pain (11.24% versus 12.36% in group L and group DO, respectively, $p = 0.81$) were not different between the two groups. In order to prove the non-inferiority of dexamethasone and ondansetron combination against lidocaine, the upper limit of the 90% confidence interval must be lower than the predefined margin of non-inferiority (3%). The upper limit of the incidence of moderate to severe pain was 2.99% which was lower than the predefined 3%.

Conclusion: Combination of dexamethasone 10 mg and ondansetron 4 mg was comparable to lidocaine 40 mg for pretreatment on propofol injection pain.

Keywords: Dexamethasone, lidocaine, ondansetron, propofol injection pain

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Introduction

Propofol has widely used as an anesthetic induction and maintenance agent.¹ However, its main disadvantage is a propofol injection pain (PIP). Approximately 60% of patients experienced pain on propofol injection and 20% of patients reported as a severe pain.²

The mechanism of PIP is still doubtful. There has been described by the release of nitric oxide (NO) from vessel of both in animal and human.³⁻⁶ NO determines as a direct irritation of free nerve ending within vein walls.

Systematic reviews and meta-analysis show those using antecubital vein and pretreatment by lidocaine

with venous occlusion technique were the most effective interventions to reduced pain from propofol injection.^{2,7} In case of inadvisable with lidocaine, the alternative prevention should be consider.

Beside pain, postoperative nausea vomiting (PONV) is the second most common complaint in patients undergoing anesthesia.⁸ The most frequently used drugs for PONV prophylaxis are dexamethasone and ondansetron.⁹ In addition, there were evidences that both dexamethasone¹⁰ and ondansetron¹¹ can reduce propofol injection pain. But compared with lidocaine, the effectiveness of each drugs are inconclusive.⁷

Correspondance to: Naruemol Prachanpanich, M.D., E-mail: nolruema@hotmail.com

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The purpose of our study is to find alternative drugs for reducing PIP. We hypothesized that combination of dexamethasone and ondansetron is non-inferiority to lidocaine for reducing propofol injection pain. Concerning PONV prophylaxis, dexamethasone and ondansetron dose were determined at 10 mg and 4 mg respectively.¹²

Methods

Following the approval by Ethic Committee Institution of Ramathibodi hospital, Mahidol University (ID 01-60-22), informed consent has been signed by subjects aged from 20 to 60 years old, American Society of Anesthesiologist (ASA) physical status I-III. They were scheduled for various elective surgeries under general anesthesia. Subjects were excluded if they had history of propofol, soybean, egg, specific 5-hydroxytryptamine (5HT₃) receptor antagonist hypersensitivity, lipid metabolism disorder, chronic pain or infected patients.

To calculate the sample size for the proposed non-inferiority design, the historical incidence of moderate to severe PIP was considered. From the previous study, those values were 14.3% when pre-injected with lidocaine, and 5.7% with dexamethasone.¹³ Considering a one-tailed alpha of 5% and a statistical power of 80% for the study to obtain a maximum absolute difference of 3% in the rate of moderate to severe PIP between the two groups, 81 patients should be included in each study group. Assuming a dropout rate of approximately 10%, 89 patients were anticipated in each arm, for a total of 178 patients.

One hundred and seventy eight patients were randomized, double-blinded and assigned to receive pretreatment of lidocaine 40 mg (Group L) or dexamethasone 10 mg and follow by ondansetron 4 mg (Group DO). Standard monitoring was applied to all subjects. No other drugs were injected before administration of the study drugs. After monitoring, pretreatment drug(s) was injected by the anesthesiologist and 5 mL of normal saline was flushed for each injection.

After one minute, the prepared room temperature propofol formulated in medium- and long-chain tri-glycerides (MCT/LCT) (Lipuro®, B. Braun, Germany) was injected as for a testing dose (0.3 mg.kg⁻¹) by 10 mL.second⁻¹ speed. Pain score was rating by numeric rating scale (0 - 10) within 10 seconds after injection. Nurse anesthetist evaluated and recorded facial grimacing, hand withdrawal and vocalization but not added in pain score measurement. Both subject and observer (nurse anesthetist) were blinded with respect to pretreatment used. Following the archived pain assessment, the remained induction dose of propofol (1.5-2 mg.kg⁻¹) was administered.

Statistical analysis

All continuous data were not normally distributed and are reported as median (interquartile range). Mann-Whitney U tests were used to determine if results differed significantly between two groups of patients. Categorical data were reported as n (%) and were analyzed using Chi-square or Fisher's exact test. Non-inferiority will be concluded when the upper limit of the two-sided 90% confidence interval for moderate to severe pain is less than 3%. All statistical analyses were conducted using SPSS for Windows (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). The p value < 0.05 was used as significance level for all tests.

Results

One hundred and seventy-eight patients were enrolled. No patient was excluded from the study. All patients were alert and awake until pain assessments were done. There were no differences in demographic data between 2 groups (Table 1). No statistically significant differences were found in injection pain and other outcomes between the L and DO group (Table 2). Incidence and intensity of pain in the DO group was non-inferior to L group (12.36% vs. 11.24%; absolute difference: 1.12%; 90%CI: -6.82 to 9.08%).

After propofol injection, 6 patients (6.74%) in DO group and 7 patients (7.87%) in L group were shown rash and spontaneous disappear. This rash is suspected to be an allergic reaction. Three patients (3.37%) in DO group experienced perineal itching after

injection of pretreatment. No intervention was done to treat this symptom and it was subsided within seconds. Beside allergic reaction and perineal itching, no other side effects were observed in any patient along the case.

Table 1 Patient characteristics data, dose and site of propofol induction

	Dexamethasone/ Ondansetron (n=89)	Lidocaine (n=89)	P-value
Age (years)	48 (34-60)	52 (42-62)	0.082
Male/Female (n)	29/60	26/63	0.627
BW (kg)	60 (54-70)	58 (50-68)	0.144
ASA Status			0.155
I	25 (28.09%)	18 (20.22%)	
II	49 (55.06%)	46 (51.69%)	
III	15 (16.85%)	25 (28.09%)	
Hand/Antecubital (n)	72/17	69/20	0.579
Dorsal/Volar (n)	78/11	79/10	0.816
Propofol dose (mg)	90 (81-105)	87 (75-102)	0.223
Propofol dose + testing dose (mg)	93(825.112-5.)	90 (81105-)	0398.

Data are presented as median (IQR), n or n (%) as appropriate.

Table 2 The results of pain between dexamethasone/ondansetron and lidocaine groups

	Dexamethasone/ Ondansetron (n=89)	Lidocaine (n=89)	Difference (90%CI)	P-value
Median pain score (IQR); maximum	0 (0-1); 8	0 (0-1); 9		0.359
Pain group				0.672
No pain (0)	51 (57.3%)	58 (65.17%)		
Mild pain (1-3)	27 (30.34%)	21 (23.6%)		
Moderate pain (4-6)	8 (8.99%)	6 (6.74%)		
Severe pain (7-10)	3 (3.37%)	4 (4.49%)		
Severe pain (vs. Non-severe)	3 (3.37%)	4 (4.49%)	-1.12% [(-5.91)-3.67%]	>0.999
Moderate to severe pain (4-10)	11 (12.36%)	10 (11.24%)	1.12% [(-6.82)-9.08%]	0.816
Pain (vs. no pain)	38 (42.7%)	31 (34.83%)	7.87% [(-4.11)-19.84%]	0.282
Hand withdrawal	-	-	-	-
Face grimacing	3 (3.37%)	1 (1.12%)	2.25% [(-1.4)-5.89%]	0.621
Vocalization	2 (2.25%)	3 (3.37%)	-1.12% [(-5.2)-2.95%]	>0.999

Data are presented as median (IQR), n or n (%) as appropriate, CI= confidence interval.

Discussion

Propofol is widely used in anesthetic clinical practice.¹ PIP is the common side effect. Sixty percent of untreated subjects were found PIP.² This pain

describes as an extremely sharp, aching or burning.¹⁴ From 33 of clinical anesthesia outcomes to avoid in anesthesia panel, PIP was ranked at seventh by expert anesthesiologists.¹⁴ Moreover, this pain can cause a

hyperdynamic cardiovascular changing and leads to an adverse events, especially in patients who had coronary artery disease.¹⁵

The studies of PIP prevention had been investigated for decades and purposed in various methods. According to the meta-analysis that enrolled 177 RCT studies (25,260 subjects), the most effective non-pharmacological single intervention is using antecubital vein for propofol injection.² However, this method is not compatible with most of practices. Patient's veins are usually cannulated before arriving operating theatres. Although, large bore vein or antecubital vein is desired, the additional cannulation will be done after induction of anesthesia by the propofol.

The successful pharmacological intervention is the pretreatment of lidocaine injection. Picard *et al.*⁷ reported meta-analysis of 56 studies (6,264 subjects) that lidocaine 0.5 mg.kg⁻¹ with tourniquet on forearm 30-120 seconds before propofol injection can prevent PIP by 60% of the subjects. In patients with congestive heart failure, acute myocardial infarction, low body weight, and liver disease that decrease hepatic clearance of lidocaine might not be candidate for pretreatment PIP with lidocaine.¹⁶ In our institute, preservative free lidocaine for parenteral route was available few years ago. If lidocaine is prohibited or inaccessible, other methods are needed to establish.

Dexamethasone is a steroid with potent anti-inflammatory, analgesic and antiemetic effects.¹⁷ Single dose of dexamethasone reduces postoperative pain, provides opioid-sparing effects but does not associated with intraoperative hyperglycemia and postoperative wound infection.^{5,9} It also has been proved for reducing PIP in wide-ranging dose (up to 0.25 mg.kg⁻¹).¹⁰ The mechanism of dexamethasone reducing PIP remains unclear, it may involve by the inhibition of prostaglandin and bradykinin synthesis. The effectiveness is not superior from lidocaine.^{10,13} Kwak *et al.* compared pretreatment with 6 mg of dexamethasone versus 20 mg of lidocaine with venous occlusion for 1 minute. Dexamethasone has fewer

incidence of moderate to severe pain but has more incidence of mild pain.¹³ No pain and mild pain are presumed to be acceptable for PIP. So the analgesic efficacy of dexamethasone 6 mg was comparable to lidocaine 20 mg in preventing PIP.¹³ In our study, dexamethasone 10 mg and ondansetron 4 mg are injected without venous occlusion. In DO groups, the results of moderate to severe pain are comparable but the results of no pain to mild pain are inferior to study of Kwak *et al.*¹³

The unpleasant effect after dexamethasone injection was perineal itching. The mechanism is not known, but hypothesize that associated with phosphate ester of corticosteroid.²⁰ We found perineal itching 3 cases (3.37%) and the symptom disappears in seconds.

Ondansetron is a specific 5-hydroxytryptamine (5HT₃) receptor antagonist. It has antiemetic property that prevent PONV.²¹ Ye *et al.* had found that ondansetron produces numbness under skin injection. It has local anesthetic effect more potent than lidocaine fifteen times in rat's brains. The mechanism is blocking sodium channel.²² Many 5HT₃ receptor antagonist drugs²³⁻²⁶ had reported their abilities to alleviate PIP successfully. For pretreatment with ondansetron, the dose was designated at 4 mg as same as this study.^{11, 26} Nevertheless, the studies show an inferior effect than lidocaine on propofol pain reduction.¹¹

In general anesthesia, either dexamethasone or ondansetron is usually given for PONV prevention.^{8,9} These drugs can also prevent PIP but the each of their efficacy is not satisfactory as lidocaine pretreatment.^{2,7,10,11,13,26} So we altered the sequence of PONV prophylaxis administration and given before propofol injection. The results of this combination can reduce pain intensity not inferior to lidocaine pretreatment. Both groups eradicated PIP approximately 60%, similar to the incidence in systematic review of Picard *et al.*⁷

To prove the hypothesis of the combination of dexamethasone and ondansetron for preventing PIP, the study does not design the dexamethasone and

ondansetron group for comparison. The effective dose for PIP treatment from previous study compare to this study is different due to the various dose of dexamethasone.^{10,13} The overall pain results in DO groups are still not comparable with lidocaine. Further investigation should be taken in the future research.

Study limitations

Dexamethasone is precipitated with ondansetron when mix together in the same syringe. Therefore, the combination cannot be mixed in one syringe and unable to perform venous occlusion. As well as Investigator cannot be blinded while administer the pretreatment.

The injection pain was assessed before loss of consciousness from propofol. All subjects were able to stay awake and rated pain score. The results might not be reliable as in fully conscious subject.

Additionally, subjects were cannulated intravenous catheter by varying personnel. Most of the needles were small (lesser than 20 Gauge). So we record only the location of cannulation but did not record the bore size which might affect the PIP.

Conclusion

The combination of dexamethasone 10 mg and ondansetron 4 mg was not inferior to lidocaine 40 mg for pretreatment of propofol injection pain.

Clinical implication: Dexamethasone and ondansetron are the alternative drugs for prevent propofol injection pain, especially in case of lidocaine is not applicable.

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