

Comparison of the efficacy of ephedrine and lidocaine for reducing pain on propofol injection in Indonesian adult surgical patients

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ABSTRACT

Propofol has been frequently used as an induction and maintenance of general anesthesia. However, it often causes pain at the site of injection. Various premedications have been used to alleviate the propofol-induced pain, but the results does not satisfy. This study was conducted to compare the efficacy of ephedrine and lidocaine for reducing pain on injection of propofol in Indonesian adult surgical patients. This was a double-blind randomized controlled trial study conducted in Dr. Sardjito General Hospital, Yogyakarta and its affiliation hospitals. One hundred and twenty eight patients who underwent elective surgery with general anesthesia and met inclusion and exclusion criteria involved in this study. Patients were allocated into two groups with 64 patients of each group. The first group was patients who given lidocaine 2% 40 mg IV (lidocaine group) and the second group was patients who given ephedrine 30 µg/kg BW IV (ephedrine group). Sixty seconds after lidocaine or ephedrine infusion, patients were then intravenously induced with propofol 2 mg/kg BW. Clinical pain intensity of patients in both groups was then scored and compared statistically using Chi-Square test. The results showed that no significantly different in pain intensity in group receiving lidocaine infusion in comparison with ephedrine infusion was observed ($p=0.201$). Moreover, no significantly different in the incidence of pain in both groups was observed ($p=0.068$). However, clinically ephedrine has the ability to eliminate the pain on propofol injection more better than lidocaine as indicated by lower pain incidence in group receiving ephedrine (7.8%) than in group receiving lidocaine (18.7%). Patients who have no pain were also higher in group receiving ephedrine (92,2%) than in group receiving lidocaine (81.3%). In conclusion, the efficacy of ephedrine 30 µg/kg BW IV and lidocaine 2% 40 mg IV was comparable for reducing pain on injection of propofol in Indonesian adult surgical patients.

ABSTRAK

Propofol sering digunakan untuk menginduksi dan mempertahankan anestesi umum. Namun demikian propofol sering menyebabkan nyeri pada tempat penyuntikan. Berbagai obat premedikasi telah digunakan untuk meredakan nyeri akibat induksi propofol, namun hasilnya masih belum memuaskan. Penelitian ini dilakukan untuk membandingkan efektivitas efedrin dengan lidokain untuk menurunkan nyeri pada penyuntikan propofol pada pasien bedah dewasa Indonesia. Penelitian ini merupakan penelitian klinik menggunakan rancangan uji terkontrol plasebo secara acak tersamar ganda yang dilakukan di RSUP Dr. Sardjito, Yogyakarta dan rumah sakit afiliasi. Seratus dua puluh delapan pasien yang menjalani bedah elektif dengan anestesi umum dan memenuhi kriteria inklusi dan eksklusi terlibat dalam penelitian ini. Pasien dibagi dalam dua kelompok masing-masing kelompok 64 pasien. Kelompok pertama (kelompok lidokain) adalah

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pasien yang diberi 40 mg 2% lidokain secara IV dan kelompok kedua (kelompok efedrin) adalah pasien yang diberi 30 µg/kg BB efedrin secara IV. Enam puluh menit setelah infus IV lidokain atau efedrin, pasien kemudian diinduksi dengan 2 mg/kg BB propofol secara IV. Intensitas nyeri pasien kedua kelompok diukur dan dibandingkan secara statistik dengan uji Chi-square. Hasil penelitian menunjukkan tidak ada perbedaan bermakna terhadap intensitas nyeri setelah pemberian infus IV lidokain dibandingkan dengan efedrin ($p=0,201$). Lebih lanjut terbukti kejadian nyeri pada kedua kelompok juga tidak berbeda nyata ($p=0,068$). Namun demikian, pemberian efedrin secara klinik mempunyai kemampuan menghilangkan nyeri lebih baik dibandingkan lidokain sebagaimana ditunjukkan kejadian nyeri yang lebih rendah pada kelompok yang diberi efedrin (7,8%) dibandingkan kelompok yang diberi lidokain (18,7%). Pasien yang tidak merasakan nyeri juga lebih tinggi pada kelompok yang menerima efedrin (92,2%) dibandingkan kelompok yang menerima lidokain (81,3%). Dapat disimpulkan, efektivitas efedrin dosis 30 µg/kg BB IV dan 2% lidokain dosis 40 mg IV sebanding untuk menurunkan nyeri pada penyuntikan propofol pada pasien bedah dewasa Indonesia.

Key words: pain - injection - propofol - lidocaine - ephedrine.

INTRODUCTION

Propofol is a drug of choice for anesthesia induction. It has been frequently used as an induction and maintenance of general anesthesia due to its advantages such as rapid onset, short duration, smooth induction without excitation, minimal drug accumulation, quality conscious recovered quickly, no headaches, minimal psychomotor sequelae, and having an antipruritus and antiemetic effects.¹⁻³ Propofol is the most popular induction agent for laryngeal mask airway (LMA) insertion because it gives a total intravenous anesthesia (TIVA) and can be used to maintain anesthesia, sedation and to prevent vomiting. Therefore, propofol is often used in some operations such as a short operation, a day surgery cases, surgery cases with high risk of post operative nausea and vomiting (PONV).^{4,5}

Although propofol has become a drug of choice for anesthesia induction, however, the incidence of side effects following propofol induction has been reported. Propofol often causes pain at the site of injection. The quality of pain was described as extremely sharp, aching or burning. This propofol side effect has been noted as one of the most important problems in current practice of clinical

anesthesia by American anesthesiologist.⁶⁻⁸ Moreover, propofol induction was also reported to have cardiovascular side effects, especially hypotension.⁹

Some techniques have been implemented in alleviating pain on propofol injection such as i) injection conducted on a large vein like fossa cubitalis; ii) diluting of propofol preparation; iii) changing the speed of injection and iv) decreasing of propofol preparation temperature during administration.^{7,10} Moreover, the alleviating pain on propofol injection can be performed by a premedication administration. Some premedications have been used to alleviate the pain of propofol injection such as metoclopramide, lignocaine,^{11,12} pethidine,¹² ketamine,¹³ fentanyl,¹⁴ alfentanil,¹⁵ flurbiprofen,¹⁶ and lidocaine.^{7,13,14}

Although many studies have been performed to evaluate premedications for attenuating propofol related injection pain, however, findings from the studies are inconsistent. Therefore, studies to evaluate the efficacy of other premedications for preventing pain on injection of propofol are needed. This study was performed to compare the efficacy of lidocaine 2% 40 mg intravenously (IV) and ephedrine 30 µg/kg BW (body weight) IV for

reducing pain on injection of propofol in Indonesian adult surgical patients.

MATERIALS AND METHODS

Study design

This was a double-blind randomized controlled trial study conducted in Dr. Sardjito General Hospital, Yogyakarta and its affiliation hospital i.e. Banyumas District Hospital, Banyumas District, Central Java, Panembahan Senopati District Hospital, Bantul District, Yogyakarta Special Region, Orthopedi Special Hospital, Solo, Central Java and Saras Husada District Hospital, Purworejo, Central Java. Patients who underwent elective surgery with general anesthesia were randomized and allocated into two groups using a computer program. The first group was patients who given lidocaine 2% 40 mg IV (lidocaine group) and the second group was patients who given ephedrine 30 1/4g/kg BW IV (ephedrine group). The protocol of study has been approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

Subjects

One hundred and twenty eight patients, 64 patients of each group, who met inclusion and exclusion criteria involved in this study. The inclusion criteria were men or women between the age 18-60 years old, with the Body Mass Index (BMI) between 17.5 to 24.5 kg/m² and ASA physical status I or II, underwent elective surgery with general anasthesia, cooperative and willing to be involved in this study as expressed by signing a inform consent. The exclusion criteria were patients with severe hepatic impairment, phychological and neurological disorders, hipertension, using analgesic and sedative drugs 24 hours before

surgery, thrombophleblitis or dorsal vein disorders of the hand, multiple trauma and severe bleeding, and cardiac conduction abnormalities.

Protocol of study

An explanation concerning the background, objectives, benefits of the study was informed before study. Subject who willing to participate in this study was given an informed consent to be signed. Subject then underwent anamnesis and physical examination. The subject who met the inclusion and exclusion criteria was recruited and randomly allocated to one of two groups. The ringer's lactate solution was administered intravenously with a catheter IV no. 18 in a large peripheral vein of left or right arm. In the operating room, hemodynamic status of subjects i.e. blood pressure (BP), heart rate (HR), mean arterial pressure (MAP), oxygene saturation (SpO₂), electrocardiogram (ECG) were measured and recorded as base line data. The subjects in lidocaine group were given given 2% lidocaine 40 mg intravenously, while the subjects in ephedrine group were given ephedrine 30 1/4g/kg BW intravenously. All subjects in both group were not given premedications. Sixty seconds after infusion, subjects were then intravenously induced with propofol 2 mg/kg BW. Clinical pain intensity of subjects in both group was scored as described by Fauzia *et al.*¹³ as follows 0 as no pain; 1 as mild pain (no change in facial expression); 2 as pain (no change patient behavior to move the fingers but not pull the hand and 3 as severe pain (no pull of the hands of patients). One minute after induction as indicated by the negative reflect of eyelash, the hemodynamic status of subjects (BP, HR, MAP, SpO₂ and ECG) were monitored again and recorded. Anesthesia was then maintained as available standard operating procedure.

Statistical analysis

Continuous variable data (age, body weight, body height, MAP, diastolic and systolic BP, HR, SpO₂) of both groups were presented as mean ± standard deviation (SD) and analyzed with independent t-test. Categorical variable data (gender, physical status, pain sensitivity, and adverse drug reaction) of both groups were presented as proportion or percentage and analyzed with Chi-Square test. All statistical analysis were performed using SPSS software version 1.6 with p value < 0.05 as considered significant.

RESULTS

Sixty four patients in lidocaine group and 64 patients in ephedrine group were involved in this study. The characteristics of patients in both groups are presented in TABLE 1. No significant difference (p>0.05) in age, body height, body weight, BMI, sex and ASA physical status of patients between the two groups were observed indicating that the characteristics of patients in both groups were similar.

TABLE 1. Characteristics of subjects of lidocaine and ephedrine groups

Variables	Lidocaine group	Ephedrine group	p
Age (year)	37.39 ± 12.67	34.67 ± 13.18	0.236
Height (cm)	160.22 ± 6.82	160.19 ± 7.87	0.981
Weight (kg)	52.17 ± 6.73	53.27 ± 8.72	0.429
BMI (kg/m ²)	20.31 ± 2.18	20.78 ± 3.32	0.339
Sex (n/%)			
• Male	31 (49%)	32 (51%)	0.860
• Female	33 (51%)	32 (49%)	
ASA physical status (n/%)			
• I	38 (49%)	39 (51%)	0.857
• II	26 (51%)	25 (49%)	

FIGURE 1 shows pain intensity in patients receiving lidocaine 2% 40 mg IV and ephedrine 30 µg/kg BW IV. No significantly different in pain intensity in both groups was observed

(p=0.201). It was indicated that the efficacy of ephedrine in alleviating the incidence and severity of propofol injection was not different from lidocaine.

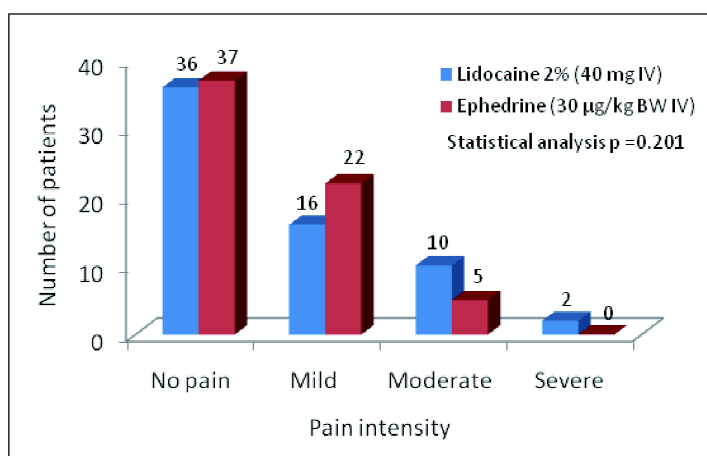


FIGURE 1. Pain response in groups receiving 40 mg lidocaine 2% IV and 30 µg/kg BW ephedrine IV

TABLE 2 shows the incidence of propofol injection pain in groups receiving lidocaine 2% 40 mg IV and ephedrine 30 µg/kg BW IV. No significantly different in the incidence of pain in both groups was observed (p=0.068). However, clinically ephedrine has the ability to eliminate the pain on propofol injection more

better than lidocaine as indicated by lower pain incidence in group receiving ephedrine (7.8%) than in group receiving lidocaine (18.7%). Moreover, patients who have no pain were higher in group receiving ephedrine (92.2%) than in group receiving lidocaine (81.3%).

TABLE 2. Incidence of pain on propofol injection in groups receiving lidocaine 2% 40 mg IV and ephedrine 30 µg/kg BW IV

Pain response	Lidocaine group	Ephedrine group	p
Pain	12 (18.7%)	5 (7.8%)	0.068
No pain	52 (81.3%)	59 (92.2%)	
Total	64 (100%)	64 (100%)	128 (100%)

DISCUSSION

Propofol has been commonly used for induction and maintenance of general anesthesia. However, pain caused by propofol injection can be extremely distressing to the patients.^{7,8} The study reported that the incidence pain on propofol injection is 28% to 90% in adults and 28% to 85% in children.⁷ Various pharmacological and non-pharmacological interventions have been conducted to eliminate the propofol-induced pain.^{7,10,16}

Lidocaine pretreatment has been reported to be the most popular premedication for attenuating propofol related injection pain.¹⁴⁻¹⁷ Lidocaine given mixed with propofol was effective in alleviating pain on propofol injection. The increasing lidocaine dosage significantly reduced pain during propofol injection.¹⁸ Lidocaine was also reported reduce the incidence of pain on propofol injection in comparison with normal saline control.¹⁹

The mechanism of action of lidocaine in reducing pain on propofol injection has been postulated. Lidocaine plays role in pH reduction, propofol concentration reduction in aqueous phase, and as local anesthetic on blood vessel.²⁰ Moreover, as a local anesthetic, lidocaine is well known as a membrane stabilizing drug. Lidocaine reversibly decrease the rate of depolarization and repolarization of excitable membranes leading to an inhibition of the kininogens release.³

This study was conducted to evaluate whether the the efficacy of ephedrine more better than lidocaine for reducing pain on injection of propofol. Lidocaine was used as positive control due to its popularity for reducing pain on propofol injection. The results of this study showed that the efficacy of ephedrine in alleviating the incidence and severity of propofol injection was not different from lidocaine. Furthermore, the incidence of pain after ephedrine pretreatment was not significantly different compare to lidocaine pretreatment. However, clinically ephedrine has the ability to eliminate the pain on propofol injection more better than lidocaine. Therefore, ephedrine could be considered as an alternative premedication for reducing pain on propofol injection.

The use of ephedrine for reducing pain has been investigated by some authors. Cheong *et al.*²¹ reported that pretreatment with a small dose of epehidrine (30 and 70 µg/kg BW) reduced the incidence and intensity pain on propofol induction without significant adverse hemodynamic effects during induction. It was also reported that adding ephedrine 30 mg to 20 mL of 1% propofol is as effective as lidocaine adding in preventing pain on propofol injection and it resulted in more stable in hemodynamic profile.²²

The mechanism of ephedrine in reducing pain on injection of propofol may be associated with its pharmacodynamics properties.

Ephedrine pretreatment one minute before propofol injection will stimulate the norepinephrine release leading to inhibition of the substance P release in cornu dorsal medulla spinalis and free nerve endings such as vascular. Substance P is an important element in pain perception. Substance P is involved in nociception, transmitting information about tissue damage from peripheral receptors to the central nervous system to be converted to the sensation of pain. The inhibition of the substance P release by norepinephrine after ephedrine pretreatment causes an impairment of pain perception.^{3,21}

CONCLUSION

In conclusion, the efficacy of ephedrine 30 µg/kg BW IV and lidocaine 2% 40 mg IV was comparable for reducing pain on injection of propofol in Indonesian adult surgical patients. Furthermore, ephedrine could be considered as an alternative premedication for reducing pain on propofol injection.

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