Current Medicine Research and Practice 9 (2019) 145–149

Contents lists available at ScienceDirect

Current Medicine Research and Practice

journal homepage: www.elsevier.com/locate/cmrp

Original article

Evaluation of analgesic and hemodynamic efficacy of ephedrine versus lignocaine during propofol injection

Sourav Burman [a, *], Raminder Sehgal [b], Subhash Gupta [b], Nishkarsh Gupta [a], Jayashree Sood [b]

[a] AIIMS, New Delhi, India
[b] Sir Ganga Ram Hospital, India

ARTICLE INFO

Article history:
Received 15 October 2018
Received in revised form
5 July 2019
Accepted 8 July 2019
Available online 5 August 2019

Keywords:
Pain
Propofol
Lignocaine
Ephedrine
Infusion
Hemodynamic profile

ABSTRACT

Objectives: To compare the efficacy of lignocaine and ephedrine in preventing pain and adverse haemodynamic profile associated with propofol injection.
Methods: After obtaining Instituitional Ethics Committee approval and written informed consent from patients, 180 adult patients of ASA grade I/ II undergoing day care surgery were recruited for the study. The pain scores was explained to them. They were randomised into 3 groups- Group C (Control group); Group L (Lignocaine); Group E (Ephedrine). Baseline haemodynamic parameters (pulse, systolic, diastolic and mean blood pressure) were recorded. Standard premedication were administered intravenously. Propofol infusion was administered at a predetermined standard rate via infusion pump in all the three groups. The study drug was prepared and administered by a separate infusion pump at a calculated rate. The subject was asked to rate the pain sensation till loss of eyelash reflex and the total volume of propofol consumed was calculated. Haemodynamic variables were recorded at one minute interval till 10 minutes from the start of induction. All statistical analysis was done using standard tests. A difference of 30% reduction in pain was considered significant. In order to obtain a 90% power of study and to exclude dropouts sixty patients in each group were considered adequate.
Results: The number of patients having mild to moderate pain was comparable between ephedrine and lignocaine groups. No patient experienced severe pain. Ephedrine maintained better haemodynamic profile than lignocaine.
Conclusion: Ephedrine when combined with propofol decreases the adverse effects of pain and hypotension.

1. Introduction

Propofol is an intravenous induction agent commonly used nowadays because of its favorable kinetics. However, its use is associated with pain on injection in 40–86% of patients.[1] Cheong et al.[1] confirmed that the incidence of moderate to severe pain after propofol injection was around 63%. The mechanism of pain is a complex combination of irritant effect of phenol side chain, noxious kininogens released from endothelium, and higher pH of propofol.[2] Several methods have been described in literature to reduce the pain of propofol injection with varying success rates. These include cooling or warming the propofol emulsion, diluting the propofol solution with distilled water, injecting the solution in a large vein, location of the vein, and administering certain additives such as opioids, magnesium, metoprolol, ondansetron, metoclopramide, thiopentone, and lignocaine.[3] Lignocaine admixture with propofol is the most common modality used to decrease the injection pain, but it may not be successful in up to 32% of cases.[4] The mechanism of lignocaine action is alteration of the pH of the resultant mixture because of the hydrochloric acid present in lignocaine. The pH of the admixture is 6.46 which renders more propofol in the lipid phase, thereby attenuating pain of propofol injection.[2] Ephedrine when mixed with propofol works similarly to reduce the pH of propofol to 6.91 and may be instrumental in reducing the pain associated with propofol.

* Corresponding author. Neuroanesthesia Office 7th Floor, Room no- 709A, C N Centre, AIIMS, New Delhi, 110029, India.
E-mail addresses: wowsourav@gmail.com (S. Burman), ramindersehgal@hotmail.com (R. Sehgal), s_grh99@yahoo.com (S. Gupta), drnishkarsh@rediffmail.com (N. Gupta), jayashreesood@hotmail.com (J. Sood).

https://doi.org/10.1016/j.cmrp.2019.07.004

Induction with propofol is associated with hypotension especially in elderly patients. This may be due to combination of venous and arterial vasodilation, impaired baroreflex mechanisms, and depression of myocardial contractility.[5] Ephedrine is a sympathomimetic amine and is effectively used to counteract the bradycardia and hypotension associated with spinal anesthesia.[6] Pretreatment with ephedrine also decreases the hypotension commonly seen after propofol induction.[7] In this study, we performed a randomized controlled trial to compare lignocaine with ephedrine in controlling the pain and hypotension associated with propofol injection.

1.1. Aims and objectives

The aim of the study was to assess and compare the efficacy of intravenous propofol-ephedrine combination with propofol-lignocaine combination with regard to

1. effect on pain associated with injection of propofol
2. effect on propofol-induced hypotension and bradycardia.

2. Materials and methods

After obtaining the institution and ethics committee approval, written informed consent was obtained from the patients at the time of preanesthetic checkup. The patients and relatives were thoroughly explained the study procedure and pain scales in their own language.

Hence, a prospective randomized double-blind study was undertaken in 180 adult (18–60 years of age) American Society of Anesthesiologists (ASA) I/II patients of either sex undergoing ambulatory procedures requiring general anesthesia using propofol.

The patients with a history of pregnancy, unstable angina, ischemic heart disease, hypertension, and allergy to study drugs and those on alpha and beta blockers or any analgesics were excluded from the study.

The patients were premedicated with tab alprazolam (0.25 mg) at bedtime the night before surgery and tab ranitidine (150 mg) the following morning. In the preoperative visit, the patients were familiarized with the verbal rating scale (VRS) advocated by Mc Crirrick and Hunter.[8] The VRS is used in measurement of acute pain assessment also and has been used by several studies assessing acute pain of propofol injection.[9] It has been advocated in the Initiative on Methods, Measurement and Pain Assessment of Clinical Trials (IMMPACT) guidelines for pain assessment published by the International Association for the Study of Pain.[10]

2.1. Randomization and allocation

The patients were randomly allocated into 3 groups, each comprising 60 patients, by means of computer-generated software. The randomization chart of serial numbers will be preserved in an opaque sealed envelope which was opened by an anesthesiologist not involved in the study. He prepared the drugs and handed it over to the principal investigator.

The subjects received propofol with lignocaine (group L, N = 60), propofol with normal saline (group C, N = 60), and propofol with ephedrine (group E, N = 60).

2.2. Anesthesia technique

In the operation theater, standard monitors (Syncmaster 152S; Samsung Inc. USA) were attached and a baseline reading of standard parameters was recorded. The monitor is a digitally calibrated device and uses an oscillometric method for measurement of blood pressure (BP). The mean BP obtained by this method is reliable and accurate for all practical purposes.[11]

A 20-G cannula was placed on the dorsum of the forearm, and premedication of 1 mg of midazolam and fentanyl (1.5 mcg/kg) was administered.

2.3. Preparation of test solution

Propofol was loaded in a 20-ml syringe. Group-specific study solutions were loaded in a separate 20-ml syringe as follows:- group L- 4 ml of 2% lignocaine was mixed with 16 ml of normal saline (4 mg/ml or 0.4% lignocaine); group C- 20 ml of normal saline; and group E- 1 ml of 3% ephedrine was mixed with 19 ml of normal saline (1.5 mg/ml or 0.15% ephedrine).

Both propofol and the study drug were administered simultaneously with the help of two separate infusion pumps via a three-way stopcock. The patients were asked to grade pain sensation according to the VRS until the time they were conscious. Propofol infusion started at 200 ml/h until the loss of consciousness, the volume of propofol infused was noted, and the rate was reduced to 100 ml/h for the rest of the study period. The study drug was administered simultaneously at 100 ml/h. Patients were administered oxygen and nitrous oxide in the ratio 40:60, after loss of eyelash reflex, with a face mask, and ventilation was assisted. No extraneous noxious stimuli were allowed during the study period.

The hemodynamic parameters (mean BP and pulse rate) were recorded at baseline and then every minute interval till 10 min. After that, anesthesia technique was standardized as per requirement of the case.

3. Different assessment tools

The VRS advocated by Mc Crirrick and Hunter is as follows:[8]
0 = no pain;
1 = mild pain or soreness;
2 = moderate pain;
3 = severe pain associated with grimacing or withdrawal of the forearm or both.

4. Statistical analysis

Statistical testing was performed using the social science system SPSS, version 17.0, (IBM Corporation, 2011, USA). Continuous and categorical data were analyzed using Student *t*-test and Chi-square test as appropriate. For all statistical tests, a *P* value less than 0.05 was taken to indicate a significant difference. Comparison between the groups was performed by repeated-measures analysis of variance (ANOVA) or ANOVA on ranks for analyzing the hemodynamic variables.

A difference of 30% reduction in pain among the groups was considered significant, and with an alpha value of 0.05, a sample size of 50 patients was required for a power of 90%. To make up for data loss due to drop outs, we recruited 60 patients in each group [Fig. 1].

5. Results

The study population was comparable in their age, gender, weight, and ASA physical status (Table 1). The baseline pulse rate and hemodynamic parameters were also comparable. The fall in the pulse rate in the control group and ephedrine group was 16% and 8%, respectively, which was significant ($p = 0.018$). The fall in mean BP in the control group and ephedrine group was 24% and 8%, respectively, ($p = 0.001$) (Fig. 2). The results were statistically significant.

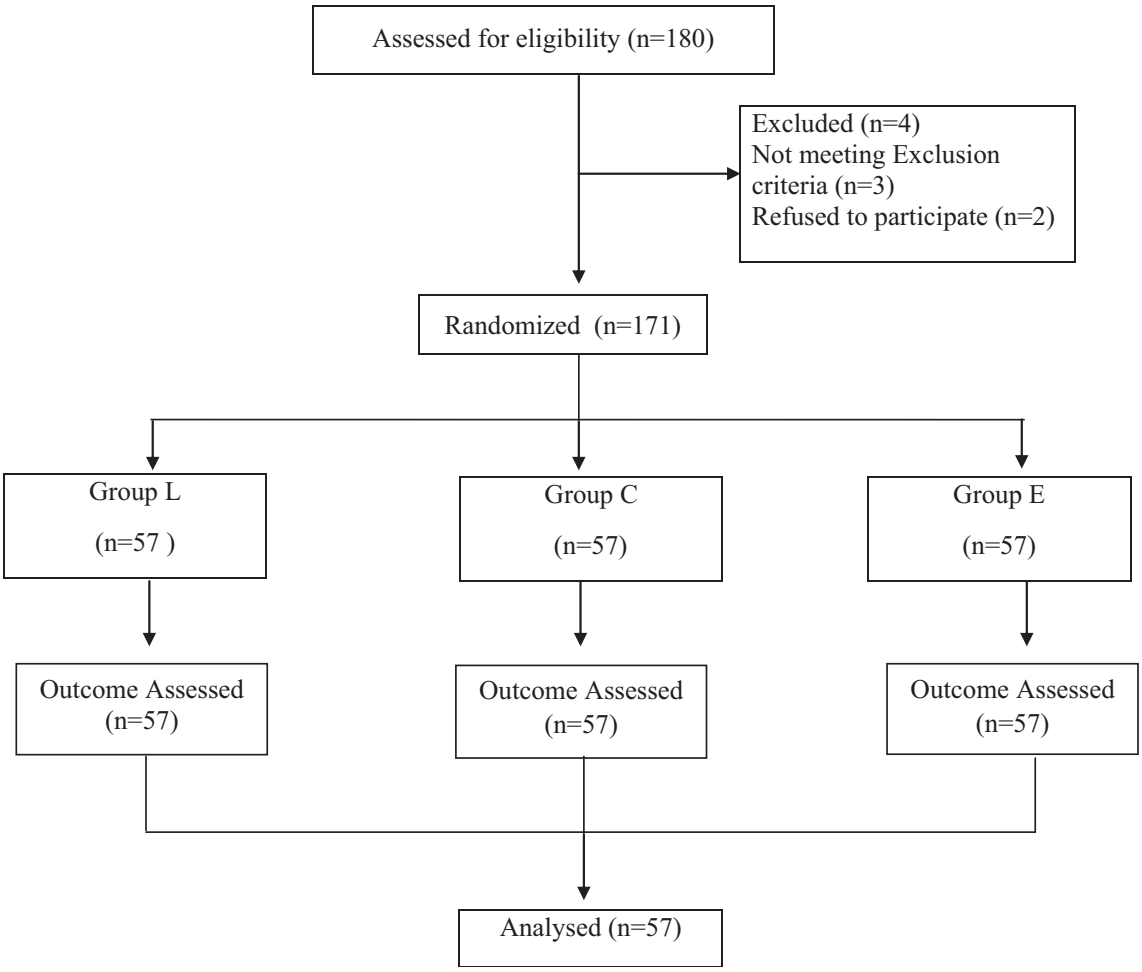

Fig. 1. CONSORT diagram.

Pain was assessed at the start of propofol and study drug mixture until loss of consciousness (usually 60–90 s), and grading was carried out using the VRS.[8] The pain reduction after propofol injection was similar among lignocaine and ephedrine groups ($p = 0.261$).

6. Discussion

Propofol is the preferred induction agent for day care surgeries because of its smooth recovery, minimal postoperative nausea, vomiting, and residual psychomimetic effects. However, it may lead to pain on injection and its incidence is variably reported between 40% and 86%.[1] The pain of propofol has an immediate and a delayed component. The phenol side chain of propofol has been held responsible for causing immediate pain due to its local irritant effect on the vein.[12] An indirect action on the endothelium releases kininogens which trigger painful stimuli at the nerve endings between the intima and the media of the vessel wall to cause delayed pain.[13] The pH of propofol is alkaline ($pH = 7.8$) which irritates the endothelium and is responsible for causing pain.[14] Several drugs have been used to alleviate the pain of propofol injection: lignocaine, fentanyl, remifentanil, flurbiprofen, magnesium, dexmedetomidine, and ketamine. Lignocaine admixture is by far the most standard practice to reduce propofol pain.[2] In our study, the incidence of mild- to moderate-intensity pain on injection of propofol was 45%. The percentage of patients having pain in the lignocaine group was 16.7%, and in the ephedrine group, it was 25%.

Lignocaine mixed with propofol or a pretreatment is the commonest agent used to relieve pain of propofol, but it has a failure rate of 13–32%.[2,13] It attenuates the delayed onset of pain with propofol by reversibly blocking the peripheral nerve pathways.[4] Pretreatment with lignocaine is less effective than admixture unless tourniquet is used. Adding lignocaine to propofol makes pH of the emulsion acidic (6.46), thereby rendering more propofol in the lipid phase which reduces the pain of propofol injection.[14] Lignocaine also affects the bradykinin release which counteracts the pain. It is commonly mixed with propofol, but this mixture is unstable and has a potential to

Table 1
Showing demographical data and baseline vital parameters among 3 groups.

Parameters	Group C	Group L	Group E	P Value
Age	40.3±13.7	43.5±11.8	43.9±12.7	0.244
Gender (M/F)*	28/72	38/62	48/52	0.079
Weight*	66.6±9.3	69.6±9.0	70.4±9.9	0.128
ASA (I/II)*	57/43	55/45	68/32	0.267
Pulse rate* (baseline)	87.6±16.6	85.0±12.4	89.1±12.7	0.276
Mean BP* (baseline)	97.3±9.8	101.7±13.2	101.1±10.3	0.070

BP, blood pressure; ASA, American Society of Anesthesiologists.
Data expressed as mean ± SD.
* Numbers.

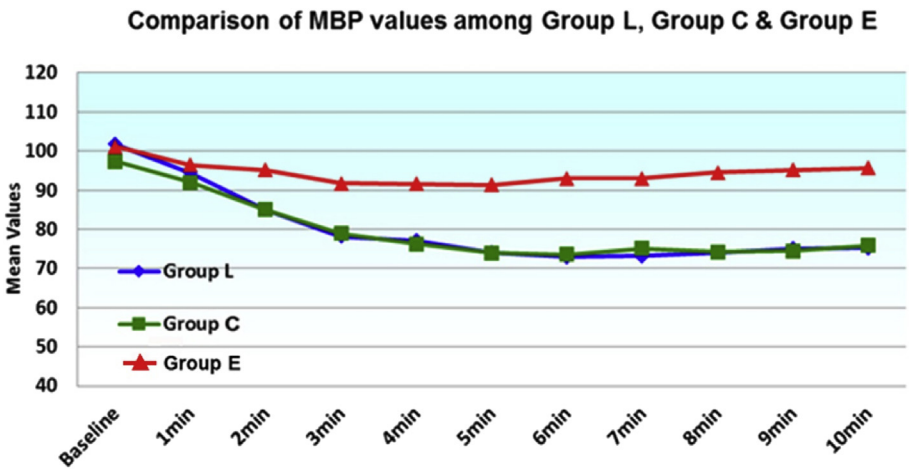

Fig. 2. Line diagram showing mean blood pressure (MBP) changes among three groups. Group L, lignocaine; Group C, control; Group E, ephedrine.

precipitate the lipid particulates of emulsion and increase the risk of pulmonary embolism.[15] We have infused propofol and the study drugs using separate syringe pumps to avoid this complication.

Ephedrine, a vasopressor drug, acts on alpha and beta receptors as well as indirectly by beta adrenergic receptors and also by releasing norepinephrine from sympathetic nerves and endothelium.[16] It causes a significant amount of initial venodilation and hyperpermeability which results in delaying the contact between propofol and free nerve endings. Ephedrine attenuates the bradykinin release from sympathetic nerve endings from the endothelium, thus attenuating the delayed pain.[12,17]

As discussed earlier, propofol-ephedrine mixture has an acidic pH (6.91). Hence, the propofol and ephedrine combination acts in a similar manner as propofol-lignocaine to reduce pain of propofol.[18] In our study, a higher dose of ephedrine (40 mg) was used than in other studies which may be the reason for attenuation of both immediate and delayed pain of propofol.

Studies have shown that pretreatment with intravenous ephedrine has been effective in attenuating pain of propofol injection.[1,2] Austin and Parke[18] also showed that admixture of ephedrine (15–30 mg) with propofol was as effective as propofol-lignocaine admixture to prevent the injection pain. Sharifnia et al.[19] did not compare ephedrine with lignocaine but assessed two doses of ephedrine (30 mcg/kg versus 70 mcg/kg) and found better pain relief with higher ephedrine dose.

Kinthala et al.[20] used lower doses of ephedrine (2.5 mg), and the incidence of pain was high (70.4%) in the ephedrine group as compared with the lignocaine group (51%). This difference in results may be attributed to low dose of ephedrine which failed to produce the desired pain relief associated with propofol injection. Similarly, Ozkocak et al.[21] studied the effect of ephedrine pretreatment (70 mcg/kg) with tourniquet applied 5 s before propofol injection and found it ineffective to reduce the propofol pain although hypotension was attenuated. Another study clearly demonstrated that 10–20 s is required for onset of analgesic action of ephedrine to set in prior propofol injection for adequate pain relief,[18] which the previous study workers did not allow and the dose of ephedrine was low. Both these cumulative concerns may have added to increased pain perception. In our study, we used higher dose (40 mg) of ephedrine, and our results were comparable among both the groups.

Hypotension is a common phenomenon with propofol induction. After an inducing dose of propofol, hypotension is seen in 90–100%.[17] In our study, after administration of propofol, we experienced a fall in mean arterial pressure (MAP) of around 20% and also the PR reduced by 15–20% from baseline values. Although the effect of pretreatment with ephedrine in doses of 5–30 mg on hypotension associated with propofol injection has been studied,[16] to the best of our knowledge, no study has been conducted to evaluate the efficacy of concomitant intravenous ephedrine infusion in controlling the side effects of propofol injection.

Cheong et al.[1] observed that pretreatment with a small dose of ephedrine (30–70 mcg/kg) reduced the incidence of propofol-induced hypotension. Michelsen et al.[16] showed that preinduction with ephedrine (0.1–0.2 mg/kg) abolished the fall in BP associated with propofol. There was more than 20% fall in BP in elderly patients. However, we did not experience the fall in BP of that magnitude as our dose of ephedrine was higher (0.4 mg/kg) and administered by continuous infusion, which resulted in sustained BP throughout the study period. Even Austin and Parke[18] used 15–30 mg of ephedrine which is almost similar to our study and found that it is effective in providing a stable hemodynamic profile without causing excessive tachycardia and hypertension.

A recent study conducted by Masjedi et al.[22] used a combination of propofol and remifentanil for induction and simultaneously used ephedrine to counteract the adverse hemodynamic parameters. They confirmed that ephedrine in a dose range (0.07–0.15 mg/kg) attenuates hypotension associated with combined effect of propofol and remifentanil. Hypotension was better managed with 0.15 mg/kg of ephedrine, which states the fact that higher doses of ephedrine is better to control hypotension.

El Tahan[23] studied the preoperative effects of phenylephrine and ephedrine on propofol- and opioid-based anesthesia during valve repair surgeries. He concluded that prophylactic use of small dose of ephedrine (0.07–0.1 mg/kg) is safe and effective in counteracting propofol-induced hypotension in patients with cardiac comorbidities.

Our study demonstrates that ephedrine in moderate to high doses (0.4 mg/kg) is comparable with lignocaine in counteracting the pain associated with the injection of propofol. In addition, ephedrine is also useful in maintaining a sustained and stable hemodynamic profile during induction with propofol.

7. Conclusion

Propofol is a standard drug in day care surgery practice, and pain associated with its administration needs to be addressed by mixing it with novel drugs with minimum side effects. One such is

ephedrine which in moderate to high doses is comparable with lignocaine for pain attenuation of propofol injection, and it provides a stable hemodynamic profile.

The result of our study has some limitations. First, pain is a subjective sensation, and its threshold varies with every individual. The use of the VRS as an assessment tool also relies on the subjective description of pain. Second, we administered fentanyl as a standard premedication to all patients, which is a routine practice in our institute, and hence, it should not influence the pain scores.

Source(s) of support

Nil.

Presentation at a meeting

None.

Conflict of Interest

Nil.

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