ORIGINAL ARTICLE

A prospective, randomized, double-blind study to compare the efficacy of lidocaine + metoclopramide and lidocaine + ketamine combinations in preventing pain on propofol injection

Kapil Chaudhary · Pramod Gupta · Anoop Raj Gogia

Abstract

Purpose Propofol injection is known to cause distressing pain, and various methods have been used to decrease this pain. We investigated the efficacy of the lidocaine + metoclopramide and lidocaine + ketamine combinations on modulating propofol injection pain.

Methods Ninety ASA I/II patients aged 20–60 years were randomly assigned to three groups to receive lidocaine 20 mg (group L), lidocaine 20 mg + metoclopramide 10 mg (group LM), or lidocaine 20 mg + ketamine 5 mg (group LK), respectively, with venous occlusion for 1 min using a forearm tourniquet. Propofol 0.5 mg/kg was subsequently administered into a dorsal hand vein, and pain was assessed during its injection using a verbal rating score. The results were analyzed statistically with analysis of variance, the chi-square test, and the Wilcoxon rank sum test, where appropriate. The significance level was set at $p < 0.05$.

Results The incidence of pain was rated to be significantly less in patients in groups LM (40 %) and LK (6.7 %) than in those in group L (83.3 %) ($p = 0.001$ and $p < 0.001$, respectively). The pain score [median (range)] was also significantly less in patients in groups LM [0 (0–3)] and LK [0 (0–2)] than in those in group L [2 (0–3)] ($p = 0.001$ for both groups).

Conclusion The lidocaine–ketamine combination is most effective for decreasing the pain on propofol injection.

Introduction

Propofol is the most common intravenous induction agent used for day care and elective surgeries. However, pain during drug administration is one of the most distressing effects of propofol injection. The incidence of pain varies from approximately 70 to 90 % when it is injected into a vein on the dorsum of the hand [1, 2]. Many techniques have been used to decrease the incidence and intensity of the pain during propofol injection [2]. Of these, lidocaine pretreatment with a forearm tourniquet is the most effective technique when using a hand vein [2, 3]. However, it is also associated with a failure rate of 32–48 % [4, 5]. Consequently, there is a need for using various drug combinations or better agents to decrease the incidence of pain on propofol injection.

This prospective, randomized, double-blind, lidocaine controlled study was designed to examine the analgesic effect of the lidocaine + metoclopramide combination and lidocaine + ketamine combination during propofol injection in a peripheral vein.

Patients and methods

After obtaining approval from the Departmental Ethics Committee and written informed consent from all selected patients, we enrolled 98 adult patients, aged 20–60 years

Present Address:
K. Chaudhary (✉)
Department of Anesthesiology and Intensive Care,
G B Pant Hospital & Associated Maulana Azad
Medical College, New Delhi, India
e-mail: kapsdr@yahoo.com; kapsdr@gmail.com

K. Chaudhary · P. Gupta · A. R. Gogia
Department of Anesthesiology and Intensive Care,
Vardhaman Mahavir Medical College & Associated
Safdarjung Hospital, New Delhi, India

with American Society of Anesthesiologists physical status I–II, who were undergoing elective surgery performed under general anesthesia in this randomized controlled double blind study. The study was conducted in a tertiary care hospital in India. Patients who had difficulty in communication, thrombophlebitis, and a history of adverse reaction/response to propofol, lidocaine, metoclopramide, or ketamine, and patients who had received any analgesics within 24 h prior to surgery were excluded from the study. Patients who were taking sedatives or analgesics, and those with a history of allergic, neurologic, or cardiovascular disease were also excluded from this study.

The patients were not given any premedication apart from ranitidine 150 mg orally 90 min before the induction of anesthesia. On arrival in the preoperative area of the operating room, the baseline pulse rate, mean arterial pressure (MAP), and oxygen saturation (SpO_2) values of each patient were noted as the mean of three readings with the patient at rest. An 18G intravenous (IV) cannula was inserted into the most prominent vein on the dorsum of the non-dominant hand without any local anesthetic application/infiltration at least 60 min before the induction of anesthesia, and an infusion of Ringer's Lactate (1 ml/kg/h) was started to maintain its patency. Patients for whom a cannula could not be inserted into the dorsum of the non-dominant hand were excluded from the study.

Patients were randomly allocated using a computer-generated random numbers list to one of three study groups. Sealed envelopes were used for concealment of study group allocation. Each group received a different drug or drug combination: Group L, lidocaine 20 mg (control group); group LM, lidocaine 20 mg + metoclopramide 10 mg; group LK, lidocaine 20 mg + ketamine 5 mg. The volume of the injection was made up to a total of 5 ml with normal saline. All study drugs were prepared and kept at room temperature and used within 15 min of preparation. The personnel not involved in the induction of anesthesia prepared identically coded study drug syringes so that the investigator assessing the patient's response was unaware of the contents of the solution.

The infusion of Ringer's lactate was closed during the study period. Venous occlusion was done using a forearm tourniquet inflated at 50 mmHg. Patients who complained of tourniquet pain were excluded from the study. The study drug was injected over a 20-s period through a three-way connector, and the venous occlusion was released after 1 min of drug administration. Propofol at room temperature (2 mg/kg) was subsequently injected through the other end of the three-way connector. After administration of the first 25 % of the calculated dose of propofol (0.5 mg/kg), the patients were asked standard questions to ascertain any discomfort during propofol injection.

The propofol-induced pain was evaluated by a researcher blinded to group allotment using a verbal rating score [6, 7]:

1. No pain (negative response to questioning)
2. Mild pain (pain reported only in response to questioning)
3. Moderate pain (pain reported in response to questioning and accompanied by behavioral sign or pain reported spontaneously without questioning)
4. Severe pain (strong vocal response or response accompanied by facial grimacing or arm withdrawal or tears)

Pulse rate, mean arterial pressure, and SpO_2 were recorded 1 min after giving 25 % of the induction dose of propofol. The remainder of the calculated dose of propofol was administered thereafter for the induction of anesthesia. Vecuronium 0.1 mg/kg IV was administered for muscle relaxation and facilitation of tracheal intubation, and anesthesia was maintained with isoflurane 0.6–1 % and nitrous oxide 66 % in oxygen, with controlled ventilation. At the end of the surgery and at 6 and 24 h after surgery, the injection site was checked for pain, edema, and wheal and flare response by a researcher blinded to group assignment. Experienced nurses assessed the patients during the recovery period for extrapyramidal reactions, such as dystonia, dyskinetic reactions, or hallucinations and illusions, if any. Note was made of nausea and vomiting, if any. All such adverse reactions were recorded and immediately reported.

Statistical analysis

A sample size of 25 patients per group was chosen, based on a previously published study [8], to detect a 25 % reduction in injection pain and achieve 80 % power at the 5 % significance level. To remove potential bias, we chose a sample size of 30 patients for each group. An absolute reduction in pain on propofol injection by 25 % in the combination groups as compared to the control (lidocaine only) group and between the combination groups was considered to be clinically significant (primary outcome). A reduction of the percentage increase in the heart rate (HR) of 25 % in the combination groups as compared to the control (lidocaine only) group and between the combination groups was considered to be a clinically significant indicator of a decrease in pain in comparison to the effect of lidocaine (secondary outcome).

Continuous variables are presented as the mean ± standard deviation (mean ± SD) and the median and range, where appropriate, and categorical variables are presented as frequency distribution and percentage [n (%)].

One-way analysis of variance (for continuous variables), the chi-square test (for categorical variables), and the Mann–Whitney test (for non-parametric data) were used to assess for significant differences between groups. Percentage change in the heart rate and MAP was analyzed using Wilcoxon rank sum tests. $p < 0.05$ was considered to be significant. Statistical analysis was done using Stata ver. 9.0 statistical software (Stata Corp, College Station, TX).

Results

A total of 90 patients were included in the study since eight patients had to be excluded due to complaints of pain on initial tourniquet inflation (five patients), difficulty in insertion of the cannula in a dorsal vein on non-dominant hand (two patients), and an inability/confusion in communicating the pain score (one patient). The baseline demographic and hemodynamic data were comparable between the three groups (Table 1).

The overall incidence and severity of pain during propofol injection in the three groups are shown in Table 2. The incidence of pain was significantly less in groups LM (40 %) and LK patients (6.7 %) than in those of group L (83.3 %) ($p = 0.001$ and $p < 0.001$), respectively. Group LK patients also reported a lesser incidence of pain than group LM patients ($p = 0.002$). The pain score [median (range)] was significantly less in groups LM [0 (0–3)] and LK patients [0 (0–2)] than in group L patients [2 (0–3)] ($p = 0.001$ for both groups). No statistically significant difference was found between the patients of group LM and group LK ($p > 0.05$).

The hemodynamic changes following propofol injection is shown in Table 3. The percentage increase in HR [mean ± SD (median)] following propofol injection was significantly less in groups LM [3 ± 6 (4)] and LK patients

[1 ± 6 (0)] than in group L patients [9 ± 9 (7)] ($p = 0.015$ and $p = 0.002$, respectively). Group LK patients also had a significantly less increase in HR than group LM patients ($p = 0.042$). The percentage change in MAP [mean ± SD (median)] after propofol injection was significantly less in group LK [−1 ± 6 (−1.5)] as compared to group L patients [−6 ± 7 (−7.5)] ($p = 0.002$). However, no significant difference was found when comparing group LM [−2 ± 14 (−3.5)] with groups L and LK patients ($p > 0.05$).

No complications, such as pain, edema, and wheal and flare response, were observed at the injection site within the first 24 h after surgery. Extrapyramidal reactions, hallucinations, nausea and vomiting were also not observed.

Discussion

The pain felt by patients receiving propofol injection has been ranked as the seventh low morbidity clinical outcome with regards to clinical importance and frequency [9]. It has an incidence of around 70–90 % [1, 2]. The injection pain is said to be influenced by the temperature of the solution [10], size of the vein, and the speed of injection [11]. All of these factors were controlled in the treatment groups of our study to avoid any bias.

The peripheral actions of lidocaine, metoclopramide, and ketamine have been implicated as the probable mechanisms for the reduction of pain on propofol injection [8, 12, 13]. Lidocaine + metoclopramide as well as lidocaine + ketamine combinations have been independently found to have superior analgesic properties when compared to lidocaine alone. However, there are no reports comparing these two drug combinations for their efficacy to reduce pain upon propofol injection. We therefore studied these combinations using lidocaine injection as the control. The

Table 1 Baseline demographic and hemodynamic data

Variables	Treatment groups[a]			p value
	Group L ($n = 30$)	Group LM ($n = 30$)	Group LK ($n = 30$)	
Age	29 ± 6	29 ± 6	29 ± 6	0.990
Sex (male/female)	14/16	16/14	14/16	0.837
Weight	53 ± 6	53 ± 7	53 ± 7	0.977
Height	158 ± 6	159 ± 7	158 ± 7	0.965
Body mass index	21.09 ± 2.64	21.09 ± 2.62	21.10 ± 2.84	1.00
Propofol dose	26 ± 3	26 ± 3	26 ± 4	0.956
Pre-propofol HR	76 ± 13	79 ± 7	75 ± 10	0.324
Pre-propofol MAP	88 ± 5	87 ± 9	90 ± 5	0.218

Data are presented as the mean ± standard deviation (SD) or numbers

HR heart rate, *MAP* mean arterial pressure

[a] L, Lidocaine only group; LM, lidocaine + metoclopramide combination group; LK, lidocaine + ketamine combination group

Table 2 Propofol injection pain data

Pain score/grade	Group L (n = 30)	Group LM (n = 30)	Group LK (n = 30)
Pain score	2 (0–3)	0 (0–3)*	0 (0–2)*
No pain	5 (16.7)	18 (60)*	28 (93.3 %)*, †
Any pain	25 (83.3)	12 (40)*	2 (6.7 %)*, †
Grading of pain[a]			
0	5 (16.7)	18 (60)*	28 (93.3 %)*, †
1	3 (10)	8 (26.7)	1 (3.3 %)
2	10 (33.3)	2 (6.7)	1 (3.3 %)*
3	12 (40)	2 (6.7)*	0*

Data are presented as the median with the range in parenthesis or as the number with the percentage in parenthesis)

* $p < 0.05$ versus group L; † $p < 0.05$ versus group LM

[a] 0, No pain; 1, mild pain; 2, moderate pain; 3, severe pain

Table 3 Pre- and post-propofol hemodynamic changes

Hemodynamic changes	Group L (n = 30)	Group LM (n = 30)	Group LK (n = 30)
Difference in post-propofol and pre-propofol heart rate	6 ± 6	3 ± 4	2 ± 5*
Difference in post-propofol and pre-propofol MAP	−6 ± 6	−3 ± 12	−1 ± 5
Percentage change in HR	9 ± 9 [7 (−4 to 35)]	3 ± 6 [4 (−8 to 20)]*	1 ± 6 [0 (−12 to 15)]*, †
Percentage change in MAP	−6 ± 7 [−7.5 (−16 to 11)]	−2 ± 14 [−3.5 (−27 to 30)]	−1 ± 6 [−1.5 (−14 to 9)]*

Values are mean ± SD or mean ± SD [median (range)]

* $p < 0.05$ versus group L; † $p < 0.05$ versus group LM

dose of 20 mg lidocaine as pretreatment in group L and its combination with 10 mg metoclopramide in group LM and with 5 mg ketamine in group LK were based on previous studies investigating propofol injection pain [4, 5, 8]. The study drugs were not compared with placebo/saline pretreatment because of the ethical concerns of causing severe pain.

Our results reveal that the patients in the lidocaine-only group had a significantly higher incidence of pain than those in the other two study drug groups. This finding supports earlier reports of increased analgesic efficacy of lidocaine when combined with ketamine [12] or metoclopramide for decreasing the pain on propofol injection. The incidence of pain on propofol injection was statistically lowest with a pretreatment using the lidocaine + ketamine combination (6.7 %) as compared to the lidocaine + metoclopramide combination (40 %) and plain lidocaine (83.3 %). This improved effect on pain could be attributed to the local anesthetic properties and intrinsic analgesic property of ketamine through an action on peripheral N-methyl-d-aspartate receptors [8].

Induction of anesthesia is recalled by some patients as the most painful part of the perioperative period mainly because of the pain associated with the propofol injection. Three of every five patients receiving propofol for induction experience pain on its injection; severe or excruciating pain is reported in one of these [3]. We found that

pretreatment with the lidocaine + ketamine combination was superior to the lidocaine + metoclopramide combination and plain lidocaine as it could prevent pain on propofol injection in almost 94 % patients, with no patient complaining of severe or excruciating pain.

In our study, 25 patients (83.3 %) complained of pain on propofol injection with the lidocaine-only pretreatment. This incidence is high in comparison to that reported in earlier studies [4, 5] investigating pain on propofol injection. Similarly, we observed a higher incidence of pain in the study group population receiving lidocaine + metoclopramide combination (40 %) in comparison to that reported in a previous study. The exact cause for this difference is not known. The dilution of the study drug to 5 ml in our study in comparison to a smaller dilution in previous studies could be a contributing factor. The difference in the ethnicity of the patient populations, race, sex distribution, and increased sensitivity to pain could be other possible attributable factors.

Tachycardia is one of the clinical indicators of pain and was used as a secondary assessment tool for evaluating pain in our study. The lowest percentage increase in the HR following propofol injection was found in patients receiving the lidocaine + ketamine combination, in comparison to those receiving the lidocaine + metoclopramide combination and plain lidocaine. Also, the percentage increase in HR was less with the lidocaine + metoclopramide

combination than with plain lidocaine. These results demonstrate an enhanced analgesic action of lidocaine when combined with ketamine and metoclopramide. Apart from providing maximum reduction in pain, the minimum increase in HR with the lidocaine + ketamine combination may be of importance in patients with cardiac disease where pain and its associated changes in hemodynamics can be deleterious.

The percentage fall in MAP was also less with the lidocaine + ketamine combination in comparison to plain lidocaine, while the lidocaine + metoclopramide combination did not confer any hemodynamic advantage over the lidocaine + ketamine combination and plain lidocaine. The exact reason for this cannot be ascertained, as such a small dose of ketamine is unlikely to cause any adverse effect on the HR and MAP after intubation [8]. The evaluation of MAP at only one time interval, that is, after 25 % of the propofol dose had been administered, is a limitation of our study. Also, since the hemodynamic changes were secondary outcomes, the possibility of Type II error in the interpretation of results cannot be ruled out. These factors do not allow us to form any conclusion on the influence of study drug combinations on the hemodynamic variables. Further evaluation is therefore needed.

In conclusion, pretreatment with lidocaine 20 mg + ketamine 5 mg IV with venous occlusion for 1 min is the most effective procedure for attenuating the pain experienced on propofol injection as compared to pretreatment with the lidocaine + metoclopramide combination or plain lidocaine.

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