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A Comparative Study between Ketamine and Lidocaine to Decrease Propofol Injection Pain during Induction of Anesthesia

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Abstract

Introduction: Pain during the injection of anesthetic agents may be distressing to the patients and can reduce the acceptability of an otherwise useful agent such as propofol for short cases and day care surgeries. Lidocaine and ketamine both are used as pre-treatment to decrease propofol-related injection pain. This study aims to compare the effectiveness of ketamine injection to decrease propofol-induced pain in comparison to lidocaine injection.

Method: This is a cross-sectional comparative study. 89 cases were divided into two groups where group K received ketamine 2 ml (0.2 mg/kg) whereas group L received lidocaine 2% 2 ml (0.5 mg/kg) as pre-treatment medication after venous occlusion with rubber tourniquet. 1/4th dose of propofol was injected 1 min after release of tourniquet and pain accessed at 0, 1 and 2 minutes of propofol injection with a verbal response and behavioral signs. Chi-square test and paired T-test were used and a p-value less than 0.05 were considered significant.

Results: Regarding hemodynamic, oxygenation, and adverse effects there was no significant difference between the two groups. Immediately after propofol injection, only one patient from the ketamine group had mild pain (2.22%) while 12 patients from the lignocaine group had mild pain (27.27%) which was statistically significant with a p-value of 0.009. Two minutes after propofol injection, only 12 cases had mild pain i.e. 13.48% (1 from the ketamine group i.e. 2.22% and 11 from lignocaine group i.e. 25%) which was statistically significant (p-value 0.002). Ketamine with its local anesthetic and analgesic effect can be equally effective to lidocaine.

Conclusion: Our study helps prove that low-dose ketamine is more effective in reducing the incidence and severity of pain on injection of propofol in comparison to lidocaine. Better hemodynamic of ketamine with no any emergence incidence improves its efficacy.

Keywords: Propofol; Ketamine; Lidocaine; Pain; Pretreatment

Introduction

Pain during the injection of anesthetic agents may be distressing to the patients and can reduce the acceptability of an otherwise useful agent. It may be a limiting factor in commonly used anesthetic drugs such as propofol. Propofol (2, 6-diisopropyl phenol) is a popular induction agent, especially for short cases and daycare surgeries. It produces a good quality of anesthesia and rapid recovery. It belongs to the group of phenols, and so propofol can irritate the skin, mucous membrane, and venous intima [1].

Many factors appear to affect the incidence of pain, which include the site of injection, size of vein, speed of injection, buffering effect of blood, temperature of propofol, and concomitant use of drugs such as local anesthetics and opiates [2]. The formulation for the preparation of propofol also plays a role regarding pain during injection. Propofol (a 10% emulsion of fat formulated with medium-chain and long-chain triglycerides) might be associated with lesser pain upon injection whereas micro emulsion of propofol produces more severe and frequent pain during injection [3]. Lidocaine pre-treatment is most commonly used to decrease injection-related pain [4,5]. It has a local anesthetic effect. However, it has a failure rate between 13% and 32% [4,6].

Ketamine which is N-methyl-D-aspartate (NMDA) receptor antagonist has also been recognized to reduce pain induced by propofol. Also, it acts peripherally to reduce pain. It has both anesthetic and analgesic effects. It is considered that ketamine when mixed with propofol can decrease the pH of the mixed solution and reduce propofol injection pain [7]. In the sub-anesthetic dose, it also has a local anesthetic effect which may also alleviate propofol-induced pain. There may be undesired effects with the use of ketamine such as sympathetic stimulation, increased secretion, and a rise in intracranial and intraocular pressure.

This study aimed to compare the effectiveness of ketamine injection to decrease propofol-induced pain in comparison to lidocaine injection experienced during the administration of the pretreatment solution and after the release of the tourniquet during propofol injection for the induction of general anesthesia. This study will also help to determine the local anesthetic effect of ketamine and find an alternative drug to lidocaine injection to decrease propofol-induced pain.

Methods

This study was carried out in the Department of Anesthesiology and critical care at Lumbini Medical College and Teaching Hospital (LMCTH), Palpa. Ethical clearance was taken and approved by the Institutional Review Committee (IRC-LMC 09-G/019). Informed and written consent was taken. After approval from the institutional review board, the study was carried out among 89 cases that underwent surgical procedures under general anesthesia (age group 15 to 60 years of age with American Society of Anesthesiologists (ASA) physical status classification system grades of 1 or 2) at LMCTH. This is a comparative randomized study starting from 1st June 2019 to 28th February 2020. Allocation to groups was done based on a random lottery basis and double-blinding was done. Exclusion criteria included unwilling participants, participants with ASA physical status grades 3 and 4, history of allergy to any of the study drugs, hemodynamically unstable, Pregnant women, morbidly obese, psychological disorders, patients with acute or chronic pain syndromes, and patients who had

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received any sedatives and analgesics medications before surgery.

Anesthetic techniques and the study protocol

The pre-anesthetic evaluation was done a day before surgery and informed/written consent was taken. All patients fasted for 8 hrs. On arrival to the operating room, an 18-G cannula was inserted into a vein on the dorsum of the patient's non-dominant hand without local anesthetics. Routine monitoring (Electrocardiogram, Non-invasive blood pressure, and pulse oximeter) were applied. An isotonic saline infusion was started at a rate of 5-6 ml/kg/h before the induction of anesthesia.

Baseline parameters were recorded. Oxygen saturation (SpO_2) was monitored continuously whereas noninvasive BP was recorded at baseline and every 3 min thereafter. De-saturation was defined as SpO_2 below 92%.

Patients were informed that they would be given intravenous anesthetics that might cause pain in the forearm. After this information, the intravenous solution was stopped, and the arm with the intravenous line was raised for 20 seconds for gravity drainage of the venous blood. A rubber tourniquet was placed on the forearm for 60 seconds to occlude the venous blood.

The operating room anesthesia assistant who did not participate in the study had prepared the drugs according to the table of randomization. Anesthesia was given under the supervision of the author and/or Co-author who are also blinded about the patient group. Data collection was done by the anesthesia provider. All patients received pretreatment medication diluted in 10-ml syringes with isotonic saline 0.9%. Group K patients received ketamine 2 ml (0.2 mg/kg) whereas Group L received lidocaine 2% 2ml (0.5 mg/kg).

Occlusion was released and one-fourth of the total calculated dose of propofol was administered over 5 seconds. The level of pain was assessed at 0, 1 and 2 min after administration of propofol by the second observer who was unaware of the group to which the patient had been allocated.

Patients were asked a standard question about the pain on injection of propofol, the verbal response, and the behavioral signs, such as facial grimacing, arm withdrawal, or tears were noted by the anesthesia provider. A score of 0-3 which corresponds to no pain, mild, moderate, and severe pain was recorded at zero, one and two minutes. Adverse effects if any were noted.

Scoring system:

0=No pain.

1=Mild pain (pain reported only in response to a question).

2=Moderate pain (pain reported in response to a question and accompanied by behavioral signs reported spontaneously).

3=Severe pain (strong vocal response or facial grimace, tears, arm withdrawal) [8].

After a complete assessment, general anesthesia was completed by variable doses of propofol till loss of eyelash reflex. The dose of propofol used per kilogram was assessed until loss of eyelash reflex. After that, fentanyl 2 mcg/kg was given intravenously. The tracheal intubation was facilitated with 0.1 mg/kg vecuronium, and anesthesia was maintained with Isoflurane 1.2% and oxygen with controlled mechanical ventilation.

Statistical analysis

Data were analyzed using SPSS version 20.0 computer software. Numerical variables were presented as mean and SD, whereas categorical variables were presented as the frequency and percentage (%). The Chi-Square ($\chi 2$) test was used for comparisons of categorical variables. A paired t-test was used to assess the variance between preoperative and intraoperative values in the respective groups. An unpaired t-test was used to assess the difference between the two groups. A p-value of<0.05 was considered statistically significant.

Results

Eighty nine patients completed the study. 45 patients were in the Ketamine group while 44 patients in the lidocaine group and demographic data are demonstrated as below in Table 1.

Demography	Ketamine group	Lidocaine group	SD
Age (years)*	41 ± 16.72	36 ± 12.35	16.72/12.357
Sex(Male/ Female)**	29/16	25/21	
ASA(I/II)**	34/11	34/10	0.435/0.424
*Mean ± Standard deviation **Number/frequency			

Table 1: Demography table.

Regarding hemodynamic, there was no significant difference between baseline measurements in mean arterial pressure in both groups. No de-saturation was observed among any group, Only 2 cases; 4% of the ketamine group experienced emergence agitation which was statistically insignificant. There was no finding of increased secretions with ketamine injection.

Immediate after propofol injection, 53 cases had No pain (59.5%) while 36 patients experienced pain (40.44%) of which only 13 cases from the ketamine group had some sort of pain while 23 cases from the lidocaine group had pain. Only 1 patient of the ketamine group had mild pain (2.22%) while 12 patients from the lidocaine group had mild pain (27.27%) which was statistically significant with a p-value of 0.009.

After 1 minute of propofol injection, 51 cases had no pain, while 38 cases (42.69%) experienced pain. 17 cases from the ketamine group and 21 from the lidocaine group had mild pain and 3 had moderate pain which was statistically insignificant (Table 2).

	Score 0	Score 1	Score 2	Total
Ketamine group	28	15	2	45
Lidocaine group	23	20	1	44
Total	51	35	3	89

Table 2: Pain score after 1 minute of propofol injection.

After 2 minutes of propofol injection, only 12 cases (13.48%) had mild pain (1 from ketamine group, 2.22% and 11 from lidocaine group, 25%) which was statistically significant. (P value 0.002).

Discussion

This study was conducted to know the efficacy of ketamine in comparison to lidocaine to alleviate Propofol-induced pain.

The exact mechanism of how propofol causes pain is unknown. Scott et al., suggested two mechanisms for pain: the first is direct irritation and the second is an indirect effect through the kinin cascade [4]. Release of kininogen from the vein wall with triggering of local kinin cascade may lead to pain. Several factors affect the propofol injection pain including the site of injection, vein size, speed of the injection of the drug, concentration in an aqueous phase, temperature [4].

The incidence of propofol pain on injection has been reported to be up to 90% if a vein on the dorsum of the hand is used [6]. Multiple pharmacological and physical approaches have been used to decrease

propofol injection pain including pre mixture or pretreatment of propofol with a variable degree of success to alleviate pain completely. Lidocaine, amide local anesthetic agent, has been used more frequently either as premixture or pre-treatment. The dose of lidocaine may be a limiting factor. Pang et al. administrated 60 mg intravenous lidocaine and the pain incidence was 11% whereas we used a low dose of 0.5 mg/kg thus the incidence of pain was 27.27%, 45.45%, and 25% immediately after, 1 min after and 2 min after propofol injection respectively [9]. Turan et al, who administered 0.5 mg/kg intravenous lidocaine, had also a higher incidence of the pain of 33.3% which is similar to our study finding [10]. Picard and Tramèr study also had a higher incidence of pain i.e 40% following 0.5mg/kg of lignocaine similar to our study [5].

Ketamine has also been used as pre-treatment for propofol-induced pain with variable success. Low cost, ease of administration, effectiveness, ease of availability, and relatively better side effect profile makes ketamine an attractive option. It also has a local anesthetic effect thus can be used to attenuate propofol-induced pain. In our study, only 4 cases had severe pain immediately after propofol injection whereas only 2 patients experienced severe pain after 1 minute whereas none had severe pain after 2 minutes.

The incidence of pain after propofol injection was about 26-46% after pretreatment with ketamine at a dose of 0.1-0.2 mg/kg [11]. In a study done by Ayman. Elsayed, 16% had pain even after ketamine pre-treatment [8]. In our study only 2.22% of patients had mild pain immediately after propofol injection, 33.33% after 1 minute and only 2.22% experienced pain 2 minutes later which shows efficacy in comparison to the lidocaine group. Only 8 patients had moderate pain and 4 had severe pain immediately after propofol injection whereas only 2 cases had moderate pain and none with severe pain 1 minute after propofol injection. This also shows the intensity of pain was very low during ketamine pre-treatment.

A study reported that the frequency of propofol injection pain was 14.9% after pretreatment with ketamine at a dose of 0.5 mg/kg but we had used a low dose of ketamine (0.2 mg/kg) [12]. Usage of a larger dose of ketamine 1 mg/kg could eliminate the pain but as shown in our study incidence of pain is very low even at the low dose we had used (0.2 mg/kg) [13]. Wang et al. found that ketamine at 0.3 mg/kg was effective in the elimination of propofol pain which is dose only slightly higher than what we had used [14]. CH Tan et al found ketamine pretreatment reduced the incidence of pain from 84% to 26% which is a similar finding to that of our study where 33.33% had pain after 1 minute of propofol injection [15]. A low dose of ketamine also helps eliminate its potential adverse effects such as increased secretion and emergence reaction which was statistically insignificant in our study.

Polat et al. proved that lidocaine 40 mg, metoclopramide, ketamine (100 mcg per kg), and remifentanil are equally effective but our study showed superior results with Ketamine rather than lidocaine as incidence and intensity of pain was significantly low in the ketamine group [16].

Hemodynamic stability was observed and no significant changes were recorded. Though a transient rise in heart rate and blood pressure was noted, it wasn't clinically or statistically significant. MAP was well maintained which may be due to the sympathetic stimulating effect of ketamine.

Limitations of the study

Tourniquet application may itself cause pain which should be taken into consideration while application. Only one-fourth dose of the required dose of propofol is given. Calculation and delivery of dosage may be difficult thus figure was round up.

Conclusion

Our study proved that low-dose ketamine was more effective in reducing the incidence and severity of pain on injection of propofol in comparison to Lidocaine. Ketamine also preserves hemodynamic even after administration of propofol and do not produce emergence agitation with low dose usage making it a better option than Lidocaine.

Conflict of interest

None.

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