International Journal of Surgery Open 27 (2020) 136–139

Contents lists available at ScienceDirect

International Journal of Surgery Open

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

Research Paper

Comparison between ketamine and propofol combined against propofol alone for brachial plexus nerve block in open fixation of forearm fracture: A randomized controlled trial☆

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ARTICLE INFO

Article history:
Received 30 October 2020
Received in revised form
7 November 2020
Accepted 10 November 2020
Available online 16 November 2020

Keywords:
Propofol
Ketamine
Branchial plexus block
Hallucination
Analgesic adjunct
Pain

ABSTRACT

Background: General anesthesia has been successfully replaced by various nervous block for surgeries.
Objective: The purpose of this study was to examine the combined effect of ketamine and propofol for brachial plexus block.
Method: In this double-blind randomized trial, 64 patients who underwent open fixation for forearm fracture were randomly assigned to group A (n = 32); comprising of patients who received both propofol (200 mg) and ketamine (50 mg) or group B (n = 32) who received only propofol (200 mg). The infusion was controlled in the groups to induce light-to-moderate sedation. The visual analogue scale (VAS) was used to evaluate pain in the groups. Additionally, parameters such as nausea and vomiting, patients' satisfaction, blood pressure, heart rate, hallucination and the time of recovery were compared among the groups.
Result: Due to the failure of nerve block, 7 patients were excluded from the study. A total of 64 patients were equally divided into two groups. Pain, nausea, vomiting, hallucination and patients' satisfaction were not statistically different among the two groups. Whereas, changes in the blood pressure and heart rate were lesser in Ketamine-propofol group and however, were not reported to be statistically significant.
Conclusion: Admixture of ketofol, containing a small dose of ketamine, is not an appropriate analgesic adjunct for upper arm nerve block, however, it does not increase the incidence of nausea, vomiting and hallucination.

1. Introduction

Owing to the complications associated with general anesthesia, the use of peripheral nerve blocks has increased [1]. In addition to the significant reduction in the anesthesia-associated adverse events, overall cost and duration of the hospitalization have reduced with a significant increase in patients' comfort [2].

The neural block of the brachial plexus has been used in numerous surgeries associated with upper extremities [3]. However, in many cases, despite the expertise of a specialist and the use of cutting edge neuroscience devices, patients feel pain and discomfort during the procedure because of the inadequate use of anesthesia [45]. Opioids with or without benzodiazepines are the most commonly used nerve block agents. However, these drugs are associated with significant respiratory failure, itching, nausea, vomiting, and discomfort [6].

Ketamine is known to be effective anesthesia [7], however, it is also associated with a significant amount of side effects such as vomiting and prolonged recovery period [8]. Concomitant use of propofol with ketamine (ketofol) has been reported to be pharmacokinetically safe and is known to be associated with decreased dose requirements [9]. Studies have shown that a low dose of ketofol is safe and has a greater sedative and analgesic effect as compared to that of ketamine and fentanyl [2]. The use of benzodiazepines and barbiturates with ketamine reduces the incidence of hallucinations, but these drugs have long-lasting effects and have

☆ This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences. (IR.LUMS.REC.1388.401).

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https://doi.org/10.1016/j.ijso.2020.11.009

undesirable side effects, delaying patients' discharge [10]. However, admixture ketofol has been approved in several studies to reduce ketamine-induced hallucinations, increase analgesia and sedation, as well as control heart rate and blood pressure [11].

However, this admixture is not studied for brachial plexus nerve block [12]. In this study, we aimed to investigate the effects of ketofol in comparison to propofol alone for pain management and the need of general anesthesia in patients undergoing supraclavicular nerve block surgery for forearm plaque [13].

In this study, we compared the incidence of hallucinations, nausea and vomiting, changes in heart rate and blood pressure, patient satisfaction and length of hospitalization among these patients.

2. Methods

In this randomized double-blinded clinical trial, where, all the patients aged 18 years and above who were referred for the repair of forearm fracture were included study after obtaining informed consent. Patients with cardiovascular, pulmonary and liver diseases, history of drug addiction, alcohol or any other substance abuse, major mental illnesses, pregnancy, ones who used analgesia within the last 12 h and those presenting significant pain other than the fractured region were excluded from the study.

After obtaining ethical approval, each patient in ASA class I, II, who was nominated for forearm fracture plaque following the trauma, was randomly assigned into one of the two groups with informed consent. Patients were also matched in terms of gender and weight. We recorded baseline blood pressure and heart rate, followed by the administration of 2–3 mg of intravenous midazolam and 0.01 mg/kg of intramuscular atropine 30 min before the block. The drug was prepared by an anesthesiologist, who did not contribute to patients' evaluation. Brachial plexus block was performed in supine position with upper arm abducted till 90° and elbow flexed to 110°. Axially artery was palpated on the posterior of axilla where local anesthesia was administered using 24-gauge 7-cm Sprotte needle, based on the group. Patients in group A (ketofol) received 200 mg (20 mL) of propofol and 50 mg (2.5 mg/mL) of ketamine (case group). In group B (propofol only) 1 mL distilled water was added to propofol 200 mg (20 mL) (control group). Patients were supplied with oxygen via nasal cannula at the rate of 3 L/min. Furthermore, 10 mg of lidocaine was injected to numb the area.

The assigned groups were initially administered 0.03 mg/kg (maximum 25 mL) of the assigned drugs, as a bolus. Additional drugs were administered 0.5mL/15–20 s until complete immobility of patients' forearm achieved. Patients' names, file numbers and drug types were kept in confidence until the analysis of the results. The block was performed by a single anesthesiologist, who was experienced. The successful block was established by examining motor and sensory nerves, as described before [14].

The complete nerve block was successfully achieved 15 min following the infusion of the anesthesia. Pain and relaxation rate, heart rate and blood pressure were recorded at the time of block and every 5 min during the surgery until the end of the operation. Upon the need, 2.5 mg of sufentanil was injected. After each evaluation, the infusion rate was regulated by 25%, if needed, to achieve the desired level of comfort.

In case of persistence of moderate or severe pain, despite 3 doses of sufentanil, failure of the block was considered and the surgery was continued under general anesthesia. These patients were excluded for further evaluation. Furthermore, anesthesia-associated adverse events such as, nausea and vomiting, hallucinations, nystagmus along vitals following every 15 min were monitored. The research has been reported in line with the SCARE 2018 criteria [15] No serious perioperative or postoperative complication was reported in the patients.

Descriptive statistics such as mean, standard deviation, ratio and percentage were used to describe the data. Independent *t*-test or Mann-Whitney test and Chi-square test were used for comparisons. P-value < 0.05 was considered statistically significant.

This study was approved by the Research Ethics Board of (XXX).

3. Results

Out of 64 patients, 46 (71.9%) were male and 18 (28.1%) were female. Of the 32 patients in each group, 23 (71.9%) were male and 9 (28.1%) were female. According to Fisher's exact test, there was no significant relationship between the gender and the intervention group ($p = 0.6$).

The minimum age of the patients was 18 years and the maximum age was 57 years.

There was no significant difference between the two groups in terms of age, weight, baseline systolic and diastolic blood pressure and baseline heart rate.

In the study of 32 patients who received ketofol as analgesic, 7 patients (21.9%) were presented with hallucinations and 3 patients (9.4%) in the propofol group had hallucinations. Despite a greater percentage of patients in group A, no significant relationship was reported in this regard ($p = 0.151$). Of the 32 patients in group A, 1 (3.1%) had hypertension, while 6 of them in group B were presented with hypertension (18.8%). In general, 7 of 64 patients (10.9%) developed hypertension. Hypertension and the type of intervention was not statistically significant however, p-value obtained ($p = 0.052$) was closed to the level of significance, Table 1.

An elevation in heart rate was reported in 4 patients in group B (12.5%) whereas, none of the patients had increased heart rate in group A. Overall, 4 of 64 patients (6.3%) showed an increase in the heart rate. The difference was not statistically significant ($p = 0.057$), Table 2.

Five patients (15.6%) in group A had nausea and vomiting, whereas, in the propofol group, 3 patients (9.4%) had nausea and vomiting. A total of 8 out of 64 patients (12.5%) were presented with nausea and vomiting. However, the variable was not statistically significant among the two groups ($p = 0.35$).

According to the Mann-Whitney test, there was no significant difference between the two groups in terms of discomfort, relaxation and pain. Furthermore, according to the independent *t*-test, the amount of total drug injected per minute was statistically different among the groups ($p = 0.022$), which was lengthier in the control group. (Table 3) (see Table 4).

Table 1
Consensus table of patients according to the type of intervention and hypertension.

Hypertension Group	Yes	No	Total	p-value
Propofol + ketamine (%)	1 (3.1%)	31 (96.9%)	32 (100%)	0.052%
Propofol (%)	6 (18.8%)	26 (81.3%)	32 (100%)	
Total	7 (10.9%)	57 (89.1%)	64 (100%)	

Table 2
Consensus table of patients according to the type of intervention and increased heart rate.

increase of heart rate Group	Yes	No	Total	p-value
Propofol + ketamine (%)	0 (0)	32 (100%)	32 (100%)	0.057%
Propofol (%)	4 (12.5%)	28 (87.5%)	32 (100%)	
Total	4 (6.3%)	60 (93.8%)	64 (100%)	

Table 3
Descriptive table of patients in terms of total injectable drug and amount of injectable drug in minutes in two intervention groups.

	Group	absolute frequency	Mean	Standard deviation	p-value
The whole drug is injected	Ketamine + Propofol	32	8.9	2.7	0.022
	Propofol (%)	32	10.8	3.6	
Amount of drug injected per minute	Ketamine + Propofol	32	0.193	0.056	0.005
	Propofol (%)	32	0.227	0.033	

Table 4
Descriptive table of patients by age, Weight, Basal systolic and diastolic blood pressure and basal heart rate by type of intervention group.

	Group	Frequency	Mean	Standard deviation	
Age	Propofol + ketamine (%)	32	31	9.863	0.472
	Propofol (%)	32	32.9	11.148	
Weight	Propofol + ketamine (%)	32	72.2	8.807	0.341
	Propofol (%)	32	73.2	8.095	
BPS	Propofol + ketamine (%)	32	120	12.063	0.212
	Propofol (%)	32	123	8.936	
BPD	Propofol + ketamine (%)	32	79.1	9.699	0.750
	Propofol (%)	32	79.9	8.202	
PR	Propofol + ketamine (%)	32	86	10.309	0.244
	Propofol (%)	32	89	9.6	

Additionally, based on the results of the independent *t*-test, there was no significant difference in the recovery time between groups A and B ($p = 0.3$). Finally, according to the Mann-Whitney test, there was no significant difference between the two groups in terms of sufentanil injection and the total time of injection.

4. Discussion

Ketofol is widely used for procedural sedation, globally [16]. A combination of ketamine and propofol is associated with reduced respiratory adverse outcomes and shorter half-life and easy recovery, respectively. Furthermore, the combination is also seen to provide better sedation efficiency [17].

In the present study, the two groups (ketofol and propofol alone) were not significantly different in terms of age, sex, weight, systolic and diastolic baseline blood pressure and heart rate. Cheng et al. [18] in a systematic review and meta-analysis of 6 randomized controlled trials reported that the combination of ketamine and propofol is associated with reduced adverse respiratory events. However, overall adverse events were not significantly different among the groups.

In the study by Jaafarpour et al. [19], ketofol, when used as spinal anesthesia in women undergoing a caesarean section, was seen to be associated with the reduced incidence vomiting and nausea [20]. Nonetheless, in our study, the percentage of nausea and vomiting was higher in ketofol group as compared to the control group. However, the difference was not statistically significant.

Although there was no blockage in the case group, the pain was similar in the two groups.

The drug did not affect patient satisfaction, but ketamine significantly reduced the use of propofol. Furthermore, the addition of ketamine did not prolong recovery and discharge time [2122]. Similar findings are reported in our study.

In a study by Badrinath et al., Propofol was used alone or in combination with 3 different doses of ketamine in women undergoing breast biopsy with local anesthesia [23]. As the dose of ketamine increased, the usage of analgesics was reduced, nonetheless, the incidence of nausea and vomiting, hallucinations, and hospitalization increased.

In a study by Henry et al., among patients undergoing urologic and orthopedic surgery, the effects of ketofol and propofol alone as spinal anesthesia were studied [13]. They reported blood pressure was higher in the propofol group. In our study, blood pressure was higher in the propofol and ketamine group as compared to the control group, however not statistically significant. It should be noted that spinal anesthesia is associated with significant changes in the blood pressure, invariant with the brachial plexus block.

In the study of Adriano and his colleagues, the combination of propofol and ketamine, for colonoscopy, was approximately equal to the dose of our study [24]. None of the patients had nausea and vomiting, and only 3 of the total patients hallucinated, which was resolved in less than half an hour without any therapeutic measures.

A case-control study was conducted by Dalen on the use of propofol and ketamine in the emergency department of outpatient surgeries [25]. The results from the 11 prospective studies showed that ketofol was not significantly different from propofol in terms of hemodynamic changes, nausea and vomiting, hallucinations, and discharge time.

The limitations of our study include small sample size, lack of data regarding salivation and respiratory events associated with the anesthesia. Studies with different doses, more parameters and greater sample size can help to deduce more beneficial conclusions.

5. Conclusion

It can be concluded that the addition of ketamine to propofol as a sedative for patients with forearm fractures under the brachial plexus nerve block does not increase the incidence of hallucinations, vomiting, and retention time; specific to the dose used in this study. There was no statistically significant difference in pain, satisfaction and comfort of patients in case and control groups. In cases of brachial nerve block requiring adjuvant analgesia, higher doses of ketamine may be used without the side effects of propofol.

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding

No funding was secured for this study.

Author contribution'

Dr. Mahmoudreza Moradkhani: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Shahrzad Shabaninia and Dr. Sepideh Vahabi: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

Guarantor

Mahmoudreza Moradkhani.

Registration of research studies

Name of the registry: Lorestan University of Medical Sciences.
Unique Identifying number or registration ID: N/A.
Hyperlink to the registration (must be publicly accessible): N/A.

Human and animal rights

No Animals/Humans were used for studies that are base of this research.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2020.11.009.

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