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Low Dose Ketamine in Prevention of Propofol Injection Pain

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ABSTRACT

Background: Propofol is the most widely used intravenous anesthetic agent for induction and maintenance of anesthesia as well as for sedation inside and outside operation theatre. Propofol is almost an ideal intravenous (IV) anesthetic agent, but pain on its injection still remain a problem. Pain may not be a serious complication, but most patients remember it as one of the unpleasant encounters with anesthetists. In one survey pain on propofol injection stands seventh most important problem in the current practice of clinical anesthesia. Ketamine is (NMDA) receptor antagonist agent and a dissociative anesthetic with neurostimulatory side effect, multiple research trials suggest ketamine as a strong analgesic agent in sub anesthetic IV doses.

Objective: The aim of the current study was to prove the effectiveness of low dose ketamine in preventing propofol injection pain.

Methodology: Two groups each included 60 patients (middle age females who performed ovum pick up surgery: Ketamine group 60 patient received ketamine 0.2 mg/kg with propofol. Saline group 60 patient received normal saline 10 ml with propofol. **Results:** In the current study pain and hemodynamic changes (BP, pulse) were observed. Regarding pain: The incidence of propofol injection pain in the current study was reduced from 93.2% in saline group to 55% in ketamine group, the incidence of severe pain was completely abolished with ketamine. Regarding hemodynamics: There was no statistical significance between both groups regarding heart rate, regarding BP the degree of drop in BP in ketamine group was to less extent than in saline group that proves the role of ketamine in hemodynamic stability.

Conclusion: Finally ketamine in low dose was effective in reduction of propofol injection pain.

Keywords: Propofol - Intravenous – Blood pressure - N-methyl-D asparate.

INTRODUCTION

Propofol is considered the most common intravenous (IV) anesthetic agent used for induction and maintenance of general anesthesia with rapid onset and short duration of action. However, the incidence of pain following propofol injection varies between 28 and 90% in adults if vein on dorsum of hand is used [(1)].The quality of pain was described as extremely sharp.

Aching, or burning. It has been arranged as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists.

Strategies to reduce the incidence of pain on propofol injection include adding lidocaine to propofol, cooling or warming propofol, diluting propofol solution, injection to large vein and pretreatment with IV injection of lidocaine, ondansetron, metoclopramide, an opioid, magnesium or thiopental with or without tourniquet; all have been tried with variable results [(2)].

AIM OF THE WORK

The aim of this study is to try to prove the effectiveness of low dose of ketamine in reduction of propofol injection pain.

METHODOLOGY

The aim of the present study is to ensure the effect of low-dose ketamine in reduction of propofol injection pain.

PATIENTS AND METHODS

This comparative observational study was conducted at Ain Shams University, Obstetrics and Gynecology Hospital on patients undergoing ovum pick up surgery after obtaining approval of research ethical committee. A written informed consent was obtained from each patient. This study was a prospective, randomized, and double-blinded comparison.

According to a sample: 60 cases per each group were needed: Group K: 60 patients received ketamine 0.2 mg/kg with propofol. Group S: 60 patients received normal saline 10 ml with propofol. Inclusion criteria: ASA I and II adult patients with age between 18-40 years old scheduled for ovum pick up surgery under general anesthesia were included in the study. Intensity of injection pain was assessed using a four point verbal response scale. Exclusion criteria: Patients who refused to participate, ASA physical status III, IV, patients younger than 18 years or > 40 years old, BMI > 30, history of epilepsy. Patients having a history of parenteral or oral analgesics within the last 24 hours before initiation of operation or those having allergy to study agents will be excluded.

Methodology

On arrival to operating theatre, the standard monitors were applied to the patients including electrocardiogram, pulse oximetry and

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noninvasive blood pressure monitors. A 20 gauge venous cannula was inserted into a vein on the dorsum of the patient's non-dominant hand and a bivalve to facilitate injections was attached. It was connected to an infusion of saline 0.9% at 5 ml/kg/hr.

After the three-way tap was closed to saline the pretreatment drug was injected. The patients were either given ketamine 0.2 mg/kg in a total volume of 10 ml or 10 ml of 0.9 % normal saline by an operator who was unaware of the content of the injected solution and was thus blinded to it.

The patients were unaware of the study drug used. After 30 seconds of pretreatment with the study drug or saline, 3 ml bolus of 1% propofol was given over 3 seconds and the three-way tap was opened to the saline infusion. The 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. A score of 0-3 which corresponds to no pain, mild, moderate and severe pain was recorded at zero, one and two minutes.

The patients were instructed about the pain scale before the operation. The question 'do you feel anything uncomfortable in your hand or arm' was addressed to each patient when propofol was injected. Pain score was graded as follows: 0 – No pain. 1– Mild pain (discomfort in the hand or arm which is acceptable to the patient). 2 – Moderate pain (discomfort in hand or arm which is unacceptable). 3 – Severe pain (grimace or limb withdrawal). Induction of anesthesia was completed with the remaining calculated dose of propofol (2 mg/kg) and fentanyl bolus doses (1 μg/kg). After loss of consciousness confirmed by the absence of verbal response the laryngeal mask was facilitated and anesthesia was maintained by isoflurane (MAC 1) and 100% O_2 with a total fresh gas flow of 3 L/min con. The end-tidal carbon dioxide partial pressure was maintained within the range of 30 to 35 mmHg.

At the end of surgery, isoflurane was stopped and the laryngeal mask was removed and patients were transferred to the recovery room. Metoclopramide 0.15 mg/kg IV was prescribed for the patients as a premedication. NiBP, HR, were noted at 0 (base line), 1, 2 and 3 minutes after propofol injection.

Data will be collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20 and the following will be done: Qualitative data will be presented as number and percentages while quantitative data will be presented as mean, standard deviations and ranges. Pearson correlation coefficients will be used to assess the relation between two studied parameters in the same group.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $P > 0.05$: Non significant. $P < 0.05$: Significant. $P < 0.01$: Highly significant.

RESULTS

Table (1): Comparison between saline group and ketamine group regarding Age and BMI

		Saline group	Ketamine group	Test value Independent t-test	P-value	Sig.
		No. = 60	No. = 60			
Age	Mean±SD Range	27.23 ± 4.06 20 – 38	27.03 ± 3.55 20 – 35	0.287	0.774	NS
BMI	Mean±SD Range	26.27 ± 2.21 22 – 30	25.97 ± 2.36 22 – 30	0.718	0.474	NS

Independent t-test

Table (2): Comparison between saline group and ketamine group regarding pain score.

Pain score	Saline group		Ketamine group		Test value	P-value	Sig.
	No.	%	No.	%			
No pain	4	6.60%	27	45%	44.841	< 0.001	HS
Mild pain	8	13.30%	18	30%			
Moderate pain	28	46.60%	15	25%			
Severe pain	20	33.30%	0	0%			

Table (3): Comparison between saline group and ketamine group regarding heart rate.

		Saline group	Ketamine group	Test value	P-value	Sig.
		No. = 60	No. = 60			
Pulse rate 0	Mean±SD Range	79.32 ± 11.17 60 – 105	76.73 ± 9.86 55 – 100	1.343	0.182	NS
Pulse rate 1	Mean±SD Range	81.50 ± 11.15 56 – 103	82.23 ± 8.99 63 – 105	-0.397	0.692	NS
Pulse rate 2	Mean±SD Range	79.93 ± 10.58 52 – 99	80.27 ± 8.67 61 – 95	-0.189	0.851	NS
Pulse rate 3	Mean±SD Range	79.47 ± 11.78 53 – 104	80.90 ± 12.30 61 – 100	-0.652	0.516	NS
Measure ANOVA test	**Test value** **P-value**	**0.713** **0.507 (NS)**	**4.393** **0.020 (S)**			

Table (4): Comparison between saline group and ketamine group regarding systolic blood pressure.

		Saline group	Ketamine group	Test value	P-value	Sig.
		No. = 60	No. = 60			
SBP 0(base line)	Mean±SD Range	115.35 ± 11.14 95 – 140	116.60 ± 10.58 99 – 139	-0.630	0.530	NS
SBP 1min	Mean±SD Range	107.38 ± 6.71 92 – 125	120.90 ± 7.46 105 – 139	-10.428	<0.001	HS
SBP 2min	Mean±SD Range	100.22 ± 6.38 87 – 119	114.53 ± 7.72 99 – 128	-11.077	<0.001	HS
SBP 3min	Mean±SD Range	105.22 ± 5.52 92 – 115	111.50 ± 6.69 93 – 122	-5.615	<0.001	HS
Measure ANOVA test	**Test value** **P-value**	**51.737** **<0.001**	**30.358** **<0.001**			

Table (5): Comparison between saline group and ketamine group regarding diastolic blood pressure

		Saline group	Ketamine group	Test value	P-value	Sig.
		No. = 60	No. = 60			
DBP 0(base line)	Mean±SD Range	69.40 ± 8.91 48 – 90	69.30 ± 10.96 39 – 90	0.055	0.956	NS
DBP 1min	Mean±SD Range	67.87 ± 8.14 55.00 – 89.00	68.88 ± 7.60 47.00 – 89.00	-0.707	0.481	NS
DBP 2min	Mean±SD Range	54.87 ± 6.72 39.00 – 69.00	66.00 ± 6.32 50.00 – 79.00	-9.345	<0.001	HS
DBP 3min	Mean±SD Range	55.93 ± 7.87 39 – 71	62.10 ± 6.90 41 – 79	-4.562	<0.001	HS
Measure ANOVA test	**Test value** **P-value**	**70.297** **<0.001**	**17.102** **<0.001**			

DISCUSSION

Propofol is a widely used intravenous anesthetic that is known to cause distressing local pain at the site of injection. Several methods to attenuate this pain with varying efficacy have been described. Ketamine pretreatment is one of the methods proposed to reduce propofol injection pain due to its local anesthetic properties. Propofol is a versatile intravenous anesthetic. The mechanism by which propofol causes pain at local site of injection, is unclear but it may be due to: 1) direct irritation. 2) indirect effect through kinin cascade. Bradykinin produce local vasodilatation, it increase the permeability, which may increase the contact with free nerve endings [(3)]. There are multiple factors that affect propofol injection pain like site, size of the vein, the speed of injection, its concentration in aqueous phase and the temperature of the propofol syringe material. The incidence of propofol pain on injection has been reported to be up to 90 % if a vein on dorsum of hand is used [(4)].

Most of the drugs studied for use as pretreatment to attenuate propofol injection pain did not offer any hemodynamic advantage so we decided

to study ketamine, which has hemodynamic effects quite opposite to those of propofol.

Regarding pain:

The incidence of propofol injection pain in the current study was reduced from 93.2 % in saline group to 55% in ketamine pretreatment group. The incidence of severe pain was completely abolished with ketamine. Our observations were consistent with those seen by Tan et al. where they found ketamine pretreatment reduced the incidence of pain from 84% to 26% [5].

In a study done by **Özkoçak** et al., the intensity of pain was lowered but the incidence was as high as 76% in the ketamine group [6].

Administration of ketamine 100 µg/kg immediately before propofol injection provided the optimal dose and timing to reduce propofol-induced pain on injection was demonstrated by Koo et al. By giving ketamine as a pretreatment it could act as a preventive analgesia to prevent sensitization of the local nerve endings from noxious inputs [7].

Thus, this drug is useful for pain relief due to its local action. A comparison between peripheral ketamine pre-treatment and ketamine added to propofol was done, the results supported pH changes as a more important cause for the decrease in propofol injection pain with the addition of ketamine to propofol than a peripheral effect of ketamine [8].

In a double-blind randomized study 500 Patients (ASA I, II) scheduled for elective strabismus surgery under general anesthesia were randomly allocated into five groups. After obtaining the informed consent, patients received normal saline (Group NS), lidocaine 1 mg x $kg^{(-1)}$ (Group L), and different doses of ketamine 50-75-100 µg x $kg^{(-1)}$ (Group K50-K75-K100 respectively), immediately before the injection of 2.5 mg x $kg^{(-1)}$ propofol. The incidence and intensity of pain in all study groups were significantly lower than placebo group (Group NS) ($P < 0.005$). Patients in the K100 Group had significantly lower incidence of pain and lower pain scores compared with the K50 and L Groups ($P < 0.0001$). There were no significant differences in hemodynamic parameters between groups. Administration of ketamine 100 µg x $kg^{(-1)}$ immediately before propofol injection is a safe and effective method in preventing propofol injection pain [9].

In another study, patients were randomly assigned to 4 groups. Group S (control) received normal saline as a placebo; Group K1, Group K3, and Group K5 received 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg of ketamine, respectively. Fifteen seconds after the ketamine injection, patients were injected with propofol at a rate of 12 mL/min until loss-of-eyelash reflex. Pain was evaluated blindly at the time of induction using a 4-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Adverse effects were recorded. Characteristics of induction of anesthesia, such as dose of propofol and time from propofol injection to loss of consciousness (induction duration), were noted. 39 (84.8%) Group S (control) patients had pain. Pretreatment with ketamine reduced the frequency of pain significantly to 56.5%, 17.0%, and 14.9% in Groups K1, K3, and K5, respectively. Furthermore, the frequency of moderate and severe pain in Group K1 (21.8%), Group K3 (6.4%), and Group K5 (4.3%) was significantly ($P < 0.001$, respectively) reduced compared with Group S (76.1%). Moreover, the dose of propofol for induction in Group K5 was smaller than in Group S, Group K1, and Group K3 ($P < 0.05$). One patient in Group K5 had emergence agitation. Pretreatment with a small dose of ketamine (0.3 mg/kg) reduced the frequency and intensity of propofol injection pain without severe adverse effects [10].

Propofol injection during induction of anesthesia induces pain. Ketamine has been shown to reduce the injection pain. However, ketamine has unfavorable adverse effects, including increased secretion production and hemodynamic responses, which might induce pulmonary or hemodynamic adverse events, especially in patients undergoing lung surgery who require a double-lumen tube (DLT). The aim of that study was to determine whether ketamine can safely reduce propofol injection pain during induction of anesthesia for lung surgery. Forty-five patients scheduled for elective lung surgery requiring DLT were randomly allocated into three groups. Patients received saline (control), ketamine 0.5 mg $kg^{(-1)}$ (0.5 ketamine), or ketamine 1.0 mg $kg^{(-1)}$ (1.0 ketamine), followed by 5 ml propofol 30 s later. An anesthesiologist blinded to the study group assessed pain score during induction, hemodynamics during DLT placement, and secretion production during anesthetic management. Pretreatment of 0.5 mg $kg^{(-1)}$ ketamine reduced the incidence and intensity of propofol injection pain, whereas 1.0 mg $kg^{(-1)}$ ketamine completely eliminated the pain. There were no significant differences regarding oxygenation during one-lung ventilation (OLV) and hemodynamics during induction among the three groups, although ketamine increased secretion production [11].

Several methods have been described to reduce propofol-induced pain, however, complete inhibition has not been achieved. One randomized, placebo controlled, double blind study was conducted to compare the analgesic efficacy of IV pretreatment of ketamine, meperidine, thiopental, lidocaine to minimize the injection pain of propofol. 125 patients ASA I and II were randomly allocated into 5 groups and received. Group K, ketamine 0.4 mg/kg; Group T, thiopental 0.5 mg/kg; Group M, meperidine 0.5 [corrected] mg/kg; Group L, lidocaine 1 mg/kg; Group S, saline 3 ml. All pretreatment drugs were made into 4 ml solutions and were accompanied by manual

venous occlusion for 1 min, followed by tourniquet release and slowly IV administration of propofol. Pain was assessed with a four point scale. All treatment groups had a significantly lower incidence of pain than placebo group ($p < 0.05$). However, it was observed that pretreatment with ketamine was the most effective in attenuating pain associated with propofol injection ($p < 0.05$). For painless injection of propofol, routine pretreatment with ketamine 0.4 mg/kg along with venous occlusion was recommended [(12)].

A study conducted by Wang et al. found that ketamine at ~0.3 mg/kg was effective in the elimination of propofol pain [(13)].

It was reported that the incidence of pain after propofol injection was about 26–46% after pretreatment with ketamine without the use of tourniquet when using ketamine at a dose 0.1–0.2 mg/kg [(14)].

In accordance to current study, ***Zhao et al.*** [(10)] reported that the frequency of propofol injection pain was 14.9% after pretreatment with ketamine at a dose of 0.5 mg/kg despite the fact that propofol was injected after only 15 s of ketamine injection, unlike current study (30 s).

Regarding hemodynamics:

The current study showed no statistical significance regarding heart rate between ketamine and saline groups but there was statistically significant rise in heart rate in ketamine group.

Regarding blood pressure there was statistical significance between the two groups regarding systolic blood pressure at 1,2,3 minutes after propofol injection.

Also there was statistical significant difference between the two groups regarding diastolic blood pressure at 2, 3 minutes after propofol injection.

The degree of drop in blood pressure in ketamine group was to less extent than in saline group which confirms the role of ketamine in hemodynamic stability. Furuya and colleagues found that administration of ketamine 0.5 mg/kg, one minute prior to propofol induction prevented an excessive decrease or increase in arterial pressure after intubation. The mechanism causing the decrease in arterial pressure and heart rate induced by propofol, include inhibition of myocardial contractility, decrease in peripheral vascular resistance and sympathetic inhibition leading to a decrease in vascular resistance and cardiac output [(15)].

Ketamine has the effect of sympathetic stimulation leading to increase in arterial pressure and heart rate [(16)].

CONCLUSION

The current study proved that low-dose ketamine was useful in reducing the incidence of pain on injection of propofol. The drug preserves hemodynamics for a short interval after administration of propofol and does not produce emergence phenomenon in low dose.

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