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A comparative study on different doses of metoclopramide priories alleviates propofol injection pain

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Abstract

Patients suffer from pain upon injected of propofol, which is most common administration for anesthesia process. The aim of conducting this work was toevaluate the outcome of priming on propofol injection pain by different doses of metoclopramide compared to lidocaine as a control.

Four equal groups of a total of 640 patients: Groups T1, T2 and T3 have received metoclopramide 2.5, 5 and 10 mg, in sequence, while Group L got 50 mglidocaine. Tourniquet have used to mid left arm, solution was injected ten seconds after and the tourniquet was removed after one minute. The assessment of pain evaluated, at initial and end of injection of Propofol trial dose by four point verbal rating scale: no, mild, moderate or severe pain. ASA classification III or IV have been considered.

Pain have been relieved at the start of Propofol injection with metoclopramide and lidocaine. Since 329 of patients (51.3%) had no pain, 193 (30.1%) had mild pain and118 patients (18.4%)had moderate pain, while no severe injection pain were recorded during initiation of trial dose injection, 251 patients (39.2%) had no pain, while 206(32.1%) with mild pain, 124 (19.3%) of patients had moderate pain and only 59 patients (9.2%) of had severe pain.

We have found that the using metoclopramide 10 mg for venous priming mid-arm tourniquet for a period of one minute has more influence on alleviation of propofol injection pain than those received 2.5 mg metoclopramide. In addition to better analgesia for receiving Lidocaine, which we therefore suggest iv Lidocaine for alleviating propofolrelated pain at operations.

Keywords: Propofol, Metoclopramide, Lidocaine, Tourniquet, Venous priming

Introduction

Propofol is anesthetic drug might be used for induction of anesthesia widely because it has a short half-life, rapid absorption in the central nerve tissue, redistributed and metabolized promptly from the central tissue to other tissues, and. Moreover, multiple studies evaluated Propofol based intravenous anesthesia alone or in conjunction with local blocks and approved its applicability not only for short operative time procedures but also for procedures requiring extended operative time (Ahn et al., 2008; Halstead et al., 2012; Wanat et al., 2014; Chuich et al., 2018).

Despite the widely use of propofol during anesthetic induction, the pain of injection is undesirable, and might cause venous cannula dislodging and hand withdrawal (Ahn et al., 2008). The propofol injection pain incidence, varies from 28% to 90% (Halstead et al., 2012).

Many methods have been used to relieve the pain of propofol injection, such as pretreatment with lidocaine, ondansetron, and methylene blue, but the effectiveness of these methods remains uncertain (Ahn et al., 2008;Chorney et al., 2013; Myles et al., 2003; Gruenheid et al., 2018).

Propofol, used as lipid emulsion (2,6-diisopropylphenol), is associated with some drawbacks such as hypercholesterolemia, microorganism proliferation, and pulmonary embolism and secondary to lipid emulsion Propofol the incidence of pain injection varies from 60% to 100%, when using vein injection on the dorsum of the hand (Gruenheid et al., 2018). Microemulsion Propofol is pharmaco-dynamically and biologically equal to ingredients of lipid emulsion Propofol without difference in effects or safety within dose ranges and removedor significantly reduced lipid related adverse effects, but unfortunately injection pain is more severe compared to lipid emulsion Propofol (Daza et al., 2018; Gruenheid et al., 2018; Wang et al., 2018).

The pain of injected propofol could be alleviate effectively by using alpha-2 adrenoceptor agonist clonidine (Wang et al., 2007). Dexmedetomidine (DEX) is also an alpha-2 adrenoceptor agonist, but is more selective than clonidine and has analgesic and sedative properties (Wanat et al., 2014). Reducing the incidence and intensity of propofol-induced pain have been reported by using DEX (Ayoğlu et al., 2007; Wanat et al., 2014).

The assumed mechanism for Propofol injection pain possibly through the plasma kallikrein-kinin system. In this system, the kallikrein converts kininogens to kinins which are chemical mediators of pain. Interaction between the active component of the emulsion and the vascular endothelium is another mechanism for Propofol injection (Johnson et al., 1990; Tariq and Kamran, 2006). Nevertheless, the mechanism whereby Propofol causes pain is still unclear with no evidence of any relationship between the incidence of pain on injection and the size of catheter used or speed of injection.

In order to minimize Propofol injection induced pain, providing lidocaine prior to Propofol injection or mixing Propofol with lidocaine which proved to be more efficacious than administering it immediately prior to injection (Muzamil et al., 2018).

In this study, we tried to evaluate the results of priming by different doses of metoclopramide on Propofol injection pain comparing to lidocaine as a standard control (Fujii and Nakayama, 2007).

Materials and Methods

The following comparative study was conducted after the approval of the Hospital Ethics Committee of Anesthesia Department, NCI, Baqubah General Hospitals, for a period of nine months. The study protocol was approved upon receiving written acceptance form from patients, 640 cases assigned to undergo surgeries under general anesthesia were considered in the study. Patients were randomly, covered envelops, distributed to 4 equal groups 160patients for each with criteria considerations.

- ASA (American Society of Anesthesiologists) physical classification III or IV
- History of Allergy or hypersensitivity to the study drugs.
- Scheduled for minor elective surgery
- Thrombophlebitis migrans.
- Chronic pain patients using sedatives or analgesic medication.
- Patients with renal, hepatic problems.
- History of drug abuse
- Chronic use of any medication
- Uncontrolled hypertension, or renal or hepatic insufficiency

Group L included patients primed using 50 mg lidocaine (5 ml 1% solution) and Groups T1-3 included patients primed by metoclopramide in dose of 2.5, 5 and 10 mg, respectively, diluted with saline into a5-ml solution.

Before surgery (24 h) the patients did not receive analgesics or sedatives. Before surgery (24 h) the patients did not receive analgesics or sedatives, a 20-G cannula was inserted into the dorsum of the left hand and connected to a T-connector for drug administration and an intravenous dextrose-saline infusion started. Standard ASA monitors were attached, including non-invasive arterial pressure, electrocardiography, and pulse oximetry.

In order to freeze the intravenous infusion, elastic tourniquet used to the mid of the left arm and over 10s the priming solution was then administered. The following step was removing the tourniquet in one to one and half minute and ¼ of the total prpofol dose was injected around 20s-40s.

The pain evaluation was estimated at the start and end of propofol injection. We have used four categories of measuring the pain as verbal rating scale VRSs (no pain = 0, mild = 1, moderate = 2 or severe = 3).

VRSs system is well known aseasy to introduce and better than other scoring systems. In addition, VRS consistently sensitive to treatments that are known to have an impact on pain sensitively (Pushpanathan et al., 2018). Thereafter, remaining dose of propofol was injected completely.

Statistical Analysis

Statistical analyses were performed using Statistical Product for Social Sciences (SPSS) software v. 18.0.Program and p value < 0.05 was considered significant.

Sample size calculated is suffcient to detect a difference at the 5% significance level Sample size and power. Obtained data were presented as mean ± SD, ranges, numbers and ratios. Categorical data such as gender, ASA status, and the number of patients having pain scores >2 were expressed as number, percent, or both, and were compared using the chi-square test or Fischer's exact test as appropriate. Results were analyzed using One-way ANOVA with post hoc and Chi-square test (X2 test) (Kraemer and Blasey, 2016).

Results were presented as mean ± SD, ranges, numbers, percentages and ratios. Data were analyzed using Chi-square test (X2 test) for numbers and percentages and Wilxocon Ranked test for unrelated data for inter-group comparisons (Murphy et al., 2009).

Results

The patients completed the study and the total of 640 patients; 480 males and 160 females with mean age of 38.4 ± 3.7; with a range of: 22–45 years. Two hundred eighty patients were ASA I and only forty patients were ASA II. Regarding the age, sex, ASA-grade or body constitutional data, there were non-significant differences between studied groups (Table 1).

Table 1.Mean ± SD, Groups L, T1, 2, 3. Considering Age, Gender, ASA, Weight, Height and BMI.

	Group L	Group T1	Group T2	Group T3	Total
Age (year)	33.5 ± 2.7	35.2 ± 4.8	35 ± 2.2	35.5 ± 3.1	34.8± 3.2
Gender	54:26	58:22	52:28	56:24	240:80
ASA I,II	70:10	72:8	70:10	68:12	280:40
Weight (kg)	81.2 ± 5.9	82.3 ± 6.7	85.5 ± 4.4	86.1 ± 6.2	83.7 ± 5.8
Height (cm)	164.2 ± 3	165.2 ± 3.1	162.8 ± 11	165 ± 4	164.3 ± 5.2
BMI (kg/m^2)	30.9 ± 2.5	31.1 ± 3	32.5 ± 2.2	31 ± 2.7	31.4 ± 2.6

Regarding the heart rate and MAP, patients showed significant decrease during the study period comparing to the baseline measurement, with non-significant difference between groups (Table 2).

Table 2. Number of patients with pain according to time intervals while administration of analgesic from back of hand. Mean ± SD MAP and HR Dated according to the groups.

	Group L		Group T1		Group T2		Group T3	
	MAP	HR	MAP	HR	MAP	HR	MAP	HR
Baseline	100 ± 10	72 ± 10	102 ± 15	73 ± 9	98 ± 16	72 ± 15	100 ± 11	73 ± 12
10 min	73 ± 11	61 ± 11	80 ± 15	65 ± 16	76 ± 18	65 ± 10	76 ± 11	64 ± 8
20 min	74 ± 11	61 ± 11	80 ± 15	64 ± 17	77 ± 13	62 ± 11	75 ± 12	61 ± 11
30 min	74 ± 12	62 ± 10	83 ± 12	70 ± 17	82 ± 17	64 ± 10	82 ± 17	64 ± 10
40 min	78 ± 18	66 ± 10	86 ± 12	78 ± 19	81 ± 15	64 ± 11	84 ± 14	66 ± 8
60 min	90 ± 20	66 ± 10	94 ± 11	75 ± 18	95 ± 7	71 ± 10	92 ± 12	70 ± 10
Recovery	98 ± 16	69 ± 11	99 ± 13	71 ± 17	100 ± 14	70 ± 15	100 ± 10	74 ± 13

The pain of propofol injection with either lidocaine or metoclopramidealleviated pain since 51.3% of patients had no pain, 30.1% of patients had mild pain and only18.4% patients had moderate pain, while no severe injection pain were recorded during initiation of trial dose injection, 39.2%of patients had no pain, while 32.1% of patients with mild pain, 19.3% of patients had moderate pain and 9.2% of patients had severe pain.

It was obvious that the patients received 2.5 mg of metoclopramide were significantly better than patients of 5 and 7.5 and 10 mg metoclopramide of providing lidocaine.

A dose of 10 mg of metoclopramide provided, showed significant results comparing to patients with 2.5 mg dose, but Non-significantly in compare to patients received 5 mg dose (Table 3).

Table 3. Data are presented as numbers and ratios are in parenthesis. $p < 0.05$=significant difference. p1: significance versus group L p2: significance versus group T1 p3: significance versus group T2.

Time of Evaluation At Initiation	Pain Severity	Group L	Group T1	Group T2	Group T3
	No	99(61.8%)	65 (40.6%)	80 (50%)	85 (53.1%)
	Mild	42 (26.2%)	51 (31.8%)	45 (28.1%)	55 (34.3%)
	Moderate	19 (11.8%)	44 (27.5%)	35 (21.8%)	20 (12.5%)
	Severe	0		0	0
	Statistical Analysis		$X^2 = 5.482, P_1 < 0.05$	$X^2 = 1.892, P_1 > 0.05$	$X^2 = 0.482, P_1 > 0.05$
				$X^2 = 0.204, P_2 > 0.05$	$X^2 = 6.892, P_2 < 0.05$
					$X^2 = 1.592, P_3 > 0.05$
	No	67 (41.8%)	44 (27.5%)	60 (37.5%)	80 (50%)
	Mild	51 (31.8%)	55 (34.3%)	50 (31.2%)	50 (31.2%)
	Moderate	30 (18.7 %)	34 (21.2%)	38 (23.7%)	22 (13.7%)
	Severe	12 (7.5%)	27 (16.8%)	12 (7.5%)	8 (5%)
	Statistical Analysis		$X^2 = 7.892, P_1 < 0.05$	$X^2 = 1.824, P_1 > 0.05$	$X^2 = 0.210, P_1 > 0.05$
				$X^2 = 2.612, P_2 < 0.05$	$X^2 = 29.882, P_2 < 0.05$
					$X^2 = 3.724, P_3 > 0.05$

Discussion

This prospective study was carried out in order to compare the effect of using the metoclopramide on propofol injection painto lidocaine as control group.

In our study we have found that the effect of 10 mg initial dose of metoclopramide was positive as it expanded the time until finalizing the injection of the trial dose, with significant differences in compare to both 2.5 mg and 5 mg in sequence.

In a trial made by Kwak et al., (2009)of combining the pretreatment of alfentanil with lidocaine on the severity of propofol injection pain in children, Metoclopramide 10 mg priming dose was found as effective as lidocaine for prevention or reduction of propofol injection pain with an effect superior to 2.5 and 5 mg metoclopramide. These finding was similar to our finding with considering the period of time and number of patients.

Similarly, Fujii and Itakura, (2009) found that venous occlusion followed by flurbiprofen axetil has significant effect on minimizing pain of propofol injection comparing to the other administration strategies tested. In order to assure the local preventive effect of the priming drug, Tourniquet was applied for one minute before injection which indicated the advantages of preventing the escape of pretreatment drugs into the general circulation for achieving better results.

Fujii and Nakayama (2007)and similarly Fujii and Itakura,(2009) have found that lidocaine/metoclopramide is more effective than lidocaine alone for reducing pain on injection of propofol in a peripheral vein.

Considering priming as a maneuver for administration, this allowed preparation of the endothelial wall for the oncoming drug and thus ameliorates its irritative effect. Such maneuver was previously used and proved effective with multiple drugs;

Fujii and Shiga (2006) have found that the age of patient has no significant effect on reducing propofol injection pain while using metoclopramide. Nevertheless, older people respond better to smaller doses, which we have noticed in our study.

Pain has been induced in adult patients using lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain of propofol injection. Furbiprofen axetil reported to be the highest percent of effect and metoclopramide was moderate while lidocaine was lest comparing to other two agents. This has been recorder in the study of Fujii and Itakura (2009).

The study of Fujii and Nakayama (2007),found administration of lidocaine with metoclopramide in dose of 5 or 10 mg was associated with lower incidence of pain. This study intended to exam the influence of lidocaine administered with 3 different doses of metoclopramide or saline on pain of propofol injection in adults.

Noguchi et al.,(2002), have reported that the propofol, causes irritation of the skin, mucous membranes and intima of the veins in addition to the negative experiences about anesthesia and restricts comfort of patients. The kallikrein-kinin cascade system could be stimulated by propofol, which leads to secretion of bradykinin.

Increase in contact of free nerve endings and liquid phase of propofol might be caused by propofol injection pain which leads to increase of permeability and venous dilatation. In general, every medicine given initial to the use of propofol injection would cause in reduce the pain, because of diluting liquid phase of propofl (Zaho et al., 2012).

It is well known that lidocaine is the most common agent used to reduce the propofol injection pain. The pain caused by propofol injection is divided into two periods; early period which is caused by the effect of propofol while late period is affected by the local secretion of kininogens (Ghai et al., 2010).

Eriksson stated that this agent reduces pain by decreasing pH and concentration. While Scott et al. stated that lidocaine reduces pain by stabilizing kinin cascade (Hughes et al., 2010; Jalota et al., 2011).

A study of Safavi et al., (2014) have been conducted several important points regarding adding metoclopromide 10 mg to lidocaine for intravenous regional anesthesia in trauma patients including: decrease intraoperative and postoperative analgesic requirement till 24 h, decreased onset of sensory and motor block, increased duration of sensory and motor block, reduce tourniquet induced pain, prolonged the rescue time for analgesic use, and finally enhance the patients and surgeons satisfaction (Safavi et al., 2014). On the other hand and in considering the costs and/or benefits effect of drugs to be used metoclopramide is the cheapest antagonists with similar effect for venous irritating drugs, in support of this universality Majedi et al., (2002), reported that metoclopramide, rather than lidocaine pretreatment, may be a reasonable analgesic alternative to decrease pain from a diazepam injection, especially when there is a medical condition in which lidocaine should be used very cautiously.

Conclusion

In conclusion, we have found that the using metoclopramide 10 mg for venous priming mid-arm tourniquet for a period of one minute has more influence on alleviation of propofol injection pain than those received 2.5 mg metoclopramide. In addition to better analgesia for receiving Lidocaine, which we therefore suggest IV Lidocaine for alleviating propofol related pain at operations.

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