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Research article

Priming with different doses of metoclopramide preceded *by* tourniquet alleviates propofol induced pain: A comparative study with lidocaine

Tamer Fayez Safan[a,*], Ahmed Abdalla Mohamed[a], Ahmed Shaker Ragab[b]

[a] *Department of Anesthesiology & ICU, Faculty of Medicine, Cairo University, Egypt*
[b] *Department of Anesthesiology & ICU, National Cancer Institute, Cairo University, Egypt*

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ABSTRACT

Objectives: To evaluate the outcome of priming by varying-doses of metoclopramide on propofol injection pain in comparison to lidocaine as a standard control.

Methods and materials: 320 patients were randomly allocated into 4 equal groups: Group C received 50 mg lidocaine and Groups M1-3 received metoclopramide 2.5, 5 and 10 mg, respectively. An elastic tourniquet was applied to the mid of left arm, the priming solution was injected over 10 s and 1-min later, tourniquet was removed and one fourth of the total calculated dose of Propofol was injected over 30 s and pain assessment was made, during initial and at end of injection of Propofol total dose, using the 4-point verbal rating scale: no, mild, moderate or severe pain, the remainder total calculated induction dose of Propofol was completed.

Results: Lidocaine and metoclopramide mostly relieved pain of initiation of Propofol injection 174 patients (54.4%) had no pain, 78 patients (24.4%) had mild pain and only 68 patients (21.25%) had moderate pain, while no patient had severe injection pain. At the end of injection of the total trial dose, 40% had no pain totally, 31.3% had mild pain, 19.4% had moderate pain and 9.4% had severe pain. Lidocaine provided significantly better analgesia compared to metoclopramide (2.5 mg), while the difference was non-significantly better compared to metoclopramide, 5 and 10 mg. Metoclopramide provided dose-dependent stepwise pain relieve peaking with 10 mg dose that showed significant superiority compared to 2.5 mg dose, but non-significantly compared to 5 mg dose. The effect of 10 mg priming dose extended till completion of injection of the trial dose with significant difference compared to the other two doses of metoclopramide.

Conclusion: venous priming with metoclopramide 10 mg with mid-arm tourniquet applied for one minute is effective modality for alleviation of Propofol injection pain else Patients received Lidocaine showed significantly better analgesia compared to those received 2.5 mg metoclopramide.

1. Introduction

Propofol is advantageous drug to be used for induction of anesthesia because of being rapidly absorbed in central nerve tissue, redistributed and metabolized peripherally from the central tissue to other tissues, and has short half-life. 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 procedures requiring extended operative time [1–4].

Propofol, used as lipid emulsion Propofol (2,6-diisopropylphenol), has been associated with several drawbacks such as hypercholesterolemia, microorganism proliferation, and pulmonary embolism [5,6] and the incidence of pain secondary to lipid emulsion Propofol injection varies from 59.1% to 100%, when injection is made into a vein on the dorsum of the hand [7]. Microemulsion Propofol is pharmaco-dynamically and biologically equal to ingredients of lipid emulsion Propofol without difference in effects or safety within dose ranges and removed or significantly reduced lipid related adverse effects, but unfortunately injection pain is more severe compared to lipid emulsion Propofol [8–10].

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. However, an enzymatic cascade was assumed as a mechanism for Propofol injection

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* Corresponding author.
E-mail addresses: safan.tamer@hotmail.com (T.F. Safan), ahmed.aboali7268@gmail.com (A.A. Mohamed), asragab1@yahoo.com (A.S. Ragab).

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pain possibly through the plasma kallikrein-kinin system. In this cascade kallikrein converts kininogens to kinins which are chemical mediators of pain. Another mechanism for Propofol injection pain is believed to involve interaction between the active component of the emulsion and the vascular endothelium [11–13].

Several techniques have been tried to minimize Propofol injection-induced pain and showed variable results; two of the most commonly accepted techniques are the administration of lidocaine immediately prior to the injection of Propofol or mixing lidocaine with the Propofol itself; an early study by Brooker et al. [14], found that mixing lidocaine with Propofol was more efficacious than administering it immediately prior to injection. Mangar et al. [15] showed that temporary venous occlusion following premedication with lidocaine did indeed diminish the intensity of pain but did not alter the incidence of pain.

Metoclopramide ($C_{14}H_{22}ClN_3O_{2)}$ is a benzamide with both central and peripheral anti-emetic actions. In addition to this pharmacologic property, metoclopramide has local anesthetic properties like those of lidocaine [16].

The present prospective comparative study tried to evaluate the outcome of priming by varying-doses of metoclopramide on Propofol injection pain in comparison to lidocaine as a standard control [16].

2. Methods and materials

The current prospective controlled blinded comparative study was conducted at Anesthesia Department, NCI, Cairo University Hospitals since January 2017 till September 2017. The study protocol was approved by the Local Ethical Committee. After obtaining fully informed written patients' consent, 320 patients assigned to undergo surgeries under general anesthesia were enrolled in the study. Patients were randomly, using sealed envelops, allocated into four equal groups of patients for each with **exclusion criteria** (Fig. 1).

- ASA III or IV
- History of allergy to the study drugs.
- Thrombophlebitis
- patients with chronic pain for which they were taking sedatives or analgesic medication
- patients with renal, hepatic problems

Group C included patients primed using 50 mg lidocaine (5 ml 1% solution) and Groups M1-3 included patients primed with metoclopramide in dose of 2.5, 5 and 10 mg, respectively, diluted with saline into a 5-ml solution. A 20-G cannula was inserted into the dorsum of the left hand and an intravenous dextrose-saline infusion started. An elastic tourniquet was applied to the mid of the left arm sufficient to block the intravenous infusion and the priming solution was then administered over 10 s. One minute thereafter, the tourniquet was removed and one fourth of the total calculated dose of propofol (2.5 mg/kg body weight) was administered over 30 s and pain assessment was made, during initial and at end of injection of such propofol trial dose, using 4 point verbal rating scale VRSs (no pain = 0, mild = 1, moderate = 2, severe = 3). VRSs are usually scored by listing the adjectives in order of pain severity and assigning each one a score as a function of its rank.

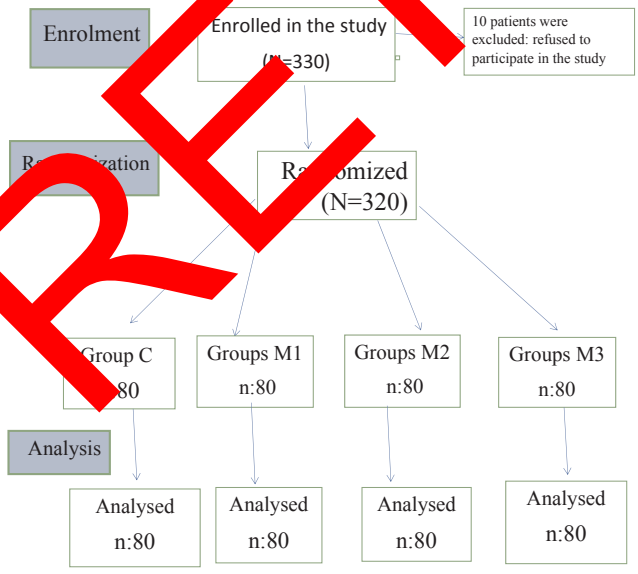

Fig. 1. Consort flow chart.

VRSs are easy to administer and comprehend. Therefore, compliance with use are as good if not better than other scoring systems. They are related positively and significantly to other measures of pain intensity. The VRS also consistently sensitive to treatments that are known to have an impact on pain intensity [17].

Then, the injection of the remainder of the full calculated induction dose of propofol was completed. Patients were monitored non-invasively during induction of anesthesia for heart rate (HR) and mean blood pressure (MAP) and then the anesthetic procedure was completed as usual.

2.1. Statistical analysis

Sample size calculated according to the standard nomogram for power calculation defined a sample size of > 77 patients per group giving the trial 80% power and is sufficient to detect a difference at the 5% significance level. Sample size and power were re-calculated and assured using PowerAnd Sample Size Calculation Software program provided by Department of Biostatistics, Vanderbilt University. Obtained data were presented as mean ± SD, ranges, numbers and percentages. Results were analyzed using One-way ANOVA with post hoc and Chi-square test (X^2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value < 0.05 was considered statistically significant [18].

Results were presented as mean ± SD, ranges, numbers, percentages and ratios. Data were analyzed using Chi-square test (X^2 test) for numbers and percentages and Wilxocon Ranked test for unrelated data for inter-group comparisons. Statistical analyses were conducted using SPSS (Version 10, 2002) program and p value < 0.05 was considered significant [19].

3. Results

A total of 320 patients; 240 males and 80 females with mean age of 36.2 ± 4.3; range: 24–44 years. One hundred forty patients were ASA I and only 20 patients were ASA II. There was non-significant difference between studied groups about age, sex, ASA-grade or body constitutional data (Table 1).

All patients showed significant decrease of heart rate and MAP throughout the study period compared to baseline measures with non-significant difference between studied groups or estimates recorded throughout the operative time till recovery (Table 2).

Priming with either lidocaine or metoclopramide mostly alleviated pain of initiation of propofol injection where 174 patients (54.4%) had no pain 94 patients (29.4%) had mild pain and only 68 patients (21.25%) had moderate pain, while no patient had severe injection pain during initiation of trial dose injection, 128 patients (40%) had no pain totally, while 100 patients (31.3%) had mild pain, 62 patients (19.3%) had moderate pain and 30 patients (9.4%) had severe pain at the end of trial injection. lidocaine priming provided significantly better analgesia compared to patients received 2.5 mg metoclopramide, while the difference was non-significantly better compared to patients received 5 and 10 mg metoclopramide. Metoclopramide provided dose-dependent stepwise pain relieve peaking with 10 mg dose that showed significant superiority compared to patients received 2.5 mg priming dose, but

Table 1
Baseline data.

	Group C	Group M1	Group M2	Group M3	Total
Age (year)	35.6 ± 3.5 (29–43)	37 ± 5.4 (26–44)	36.3 ± 2.8 (29–42)	36 ± 2.8 (24–44)	36.2 ± 4.3 (24–44)
Sex, M:F	27:13	29:11	26:14	28:12	120:40
ASA, I:II	35:5	36:4	35:5	34:6	140:20
Weight (kg)	83.4 ± 6.1 (69–92)	84.4 ± 7.9 (66–93)	86.5 ± 4.7 (69–92)	86.5 ± 6.7 (67–94)	± 6.5 (
Height (cm)	163.8 ± 4 (159–173)	164.2 ± 4.2 (161–175)	163.5 ± 12 (157–168)	164.1 ± 3.8 (162–172)	164 ± (157–17
BMI (kg/m^2)	31.1 ± 2.2 (27.5–35.5)	31.3 ± 2.9 (24.7–35.3)	32.4 ± 2 (28–35.3)	30.9 ± 2.5 (25–35.7)	31.4 ± 2. (24.7–35.7

Data are presented as mean ± SD and ratios; ranges are in parenthesis.

non-significantly compared to those received 5 mg priming dose. However, the effect of 10 mg priming dose was marvelous as it extended till completion of injection of the trial dose with significant difference compared to both other priming doses and non-significantly compared to lidocaine (Table 3).

4. Discussion

The present study tried to evaluate the effect of priming with metoclopramide on propofol injection pain in comparison to lidocaine as control group. Tourniquet was applied for one minute before injection of the priming drug to assure the local preventive effect of the priming drug depending on the results of previous studies that indicated the advantages of preventing the escape of pretreatment drugs into the general circulation for achieving better results.

Metoclopramide provided dose-dependent stepwise pain [illegible] peaking with 10 mg dose that showed significant superiority compared to patients received 2.5 mg priming dose, but non-significantly compared to those received 5 mg priming dose. However, the effect of 10 mg priming dose was wonderful as it extended [illegible] completion of injection of the trial dose with significant difference compared to both other priming doses and non-significantly compared to lidocaine

Fujii & Itakura [20] compared the effectiveness of [illegible] different techniques of flurbiprofen axetil administration provided or not by venous occlusion pretreatment in reducing pain on injection of propofol and found flurbiprofen axetil preceded by venous occlusion is more effective in reducing pain of propofol injection than the other administration strategies tested.

Considering priming as a maneuver for administration, this allowed preparation of the endothelial wall for the coming drug and thus ameliorates its irritative effect. Such maneuver was previously used and proved effectivity with multiple drugs; Fujii & Itakura [21] compared the efficacy of intravenous pretreatment with fentanyl and lidocaine preceded by venous occlusion, for reducing pain on injection of propofol. Kwak et al. [22] evaluated the efficacy of a combined pretreatment of alfentanil with lidocaine on the incidence and severity of propofol injection pain in children.

Metoclopramide 10 mg priming dose was found as effective as lidocaine for prevention of reduction of propofol injection pain with an effect superior to 2.5 and 5 mg metoclopramide. These finding go in hand with Fujii & Nakayama [24] found that combination of lidocaine/metoclopramide was more effective than lidocaine alone for reducing pain on injection of propofol in a peripheral vein. Fujii & Shiga [23] found metoclopramide is effective for reducing propofol injection pain, irrespective patients' age but older people require and respond well to smaller doses. Fujii & Nakayama [24] examined the effects of lidocaine administered with 3 different doses of metoclopramide or saline on pain of propofol injection in adults undergoing elective surgery and found administration of lidocaine with metoclopramide in dose of 5 or 10 mg was associated with lower incidence of pain. Fujii & Itakura [25] compared the efficacy of lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain of propofol injection in adult surgical patients reported an overall incidence of propofol-induced pain of 24%, [illegible]6%, respectively, compared with placebo with non-significantly difference of incidence and severity between the treated groups.

The obtained results concerning the pain alleviating effect of metoclopramide could be attributed to the facts that serotonin, (5-hydroxytryptamine [5-HT]), is a biological amine found in the brain and spinal cord and has a role in neurotransmission [26], animal studies indicated that 5-HT$_3$ antagonists reduce nociceptive responses of dorsal horn neurons when administered intrathecally by altering the 5-HT$_3$ nociceptive receptors and this effect can be attributed to the antagonism to the stimulatory action of serotonin at 5-HT$_3$ receptors that are involved in the nociceptive pathways [27]. Also, Ye et al. [28] found 5-HT$_3$ antagonists to be 15 times than lidocaine as a local anesthetic when injected under the skin in equal amounts. Moreover, 5-HT$_3$ antagonists had been found to have sodium channel blocking action. Furthermore, ondansetron has been shown to bind to opioid μ-receptors in humans and exhibit agonist activity [29]. These properties, as a central, local, and chemical antinociceptive drug, have been postulated to explain the superior results obtained by metoclopramide priming that were

Table 2
Mean (± [illegible] HR changes recorded in the studied groups.

	Group C		Group M1		Group M2		Group M3	
	MAP	HR	MAP	HR	MAP	HR	MAP	HR
Baseline	102 ± 13	73 ± 9	103 ± 16	73 ± 9	97 ± 17	74 ± 13	99 ± 12	74 ± 11
10 min	74 ± 10*	62 ± 10	79 ± 16*	64 ± 17	77 ± 17*	64 ± 11	75 ± 12*	63 ± 10
20 min	73 ± 10*	60 ± 10	79 ± 16*	65 ± 17	78 ± 14*	63 ± 10	77 ± 10*	62 ± 10
30 min	73 ± 12*	63 ± 9	82 ± 14*	69 ± 18	81 ± 16*	63 ± 11	83 ± 16*	63 ± 11
40 min	80 ± 16*	65 ± 8	85 ± 13*	79 ± 18	82 ± 17*	65 ± 10	83 ± 15*	65 ± 9
60 min	92 ± 19*	66 ± 11	93 ± 12*	76 ± 17	94 ± 8*	72 ± 9	93 ± 11*	71 ± 9
Recovery	97 ± 18	68 ± 12	98 ± 14	72 ± 16	101 ± 13	71 ± 14	99 ± 11	73 ± 14

Data are presented as mean ± SD and ratios; ranges are in parenthesis.
* Significant versus baseline levels.

Table 3
Patients' distribution according to pain severity scores determined at initiation and after propofol trial injection.

Time of evaluation	Pain severity	Group C	Group M1	Group M2	Group M3
At initiation	No	46 (57.5%)	30 (37.5%)	38 (47.5%)	60 (55%)
	Mild	22 (27.5%)	24 (30%)	22 (27.5%)	26 (32.5%)
	Moderate	12 (15%)	26 (32.5%)	20 (25%)	10 (12.5%)
	Severe	0	0	0	0
	Statistical analysis		$X^2 = 5.391$, $p_1 < 0.05$	$X^2 = 1.472$, $p_1 > 0.05$ $X^2 = 0.101$, $p_2 > 0.05$	X^2 [illegible] 0.05 [illegible] 6.316, p_2 [illegible] 0.05 [illegible] = 1.472, $p_3 >$ [illegible]
After trial injection	No	38 (47.5%)	20 (25%)	28 (35%)	42 (52.5%)
	Mild	24 (30%)	26 (32.5%)	24 (30%)	[illegible] (32.5%)
	Moderate	14 (17.5%)	18 (22.5%)	20 (25%)	[illegible] 12.5%)
	Severe	4 (5%)	16 (20%)	8 (10%)	2 [illegible]
	Statistical analysis		$X^2 = 7.354$, $p_1 < 0.05$	$X^2 = 1.266$, p_1 [illegible] 05 $X^2 = 2.4$, p_2 [illegible] 05	X^2 = [illegible] 0, $p_1 >$ [illegible] 5 $X^2 = 31$. [illegible] 0.05 $X^2 = 3.934$, [illegible] < 0.05

Data are presented as numbers and ratios are in parenthesis. $p < 0.05$ = significant difference.
p_1: significance versus group C p_2: significance versus group M1 p_3: significance versus group M2.

comparable to xylocaine.

In support of the obtained results multiple studies reported similar effect with other 5-HT_3; Memis et al. [30] found tramadol or ondansetron are equally effective in preventing pain from propofol injection. Dubey & Prasad [31] reported that granisetron pretreatment may be used to reduce the incidence of pain on injection of propofol. Ma et al. [32] investigated the alleviation effect of vein pretreatment with granisetron/lidocaine combination on propofol injection-induced pain and reported pain in 84% of patients received placebo, 46% with lidocaine alone, 52% with granisetron alone and 24% with granisetron/lidocaine combination and concluded that pretreatment with g[illegible]tron/lidocaine is effective in attenuating pains during intraveno[illegible] injection of propofol.

However, considering the cost/benefit effect of drugs to be u[illegible] metoclopramide is the cheapest of 5-HT_3 antagonist[illegible] similar effe[illegible] for venous irritating drugs, in support of this un[illegible]rsality [illegible]jedi et a[illegible] [33] reported that metoclopramide, rather tha[illegible]docaine p[illegible]reatment, may be a reasonable analgesic alternati[illegible]o decrease [illegible]in from a diazepam injection, especially when there [illegible] medi[illegible] which lidocaine should be used very [illegible]utiously

Mohammadreza Safavi et al.[illegible]nd that additi[illegible]metoclopromide 10 mg to lidocaine for intrave[illegible]egional anesthes[illegible]in trauma patients decrease intraoperati[illegible]nd po[illegible]perative analges[illegible]equirement till 24 h, decreased onset of sensory an[illegible]otor block, increased duration of sensory and m[illegible]r block, reduce t[illegible]iquet induced pain, prolonged the rescue [illegible]e for analgesic use, an[illegible]ally enhance the patients' and surge[illegible]s satisfacti[illegible]n without triggering significant adverse effects [34].

In conclusi[illegible] veno[illegible]priming with metoclopramide 10 mg with mid-arm tourniqu[illegible]ied for one[illegible]inute is effective modality for alle[illegible]f propo[illegible]injection [illegible] else Patients received Lidocaine s[illegible]ved sig[illegible]ficantly [illegible]r [illegible]algesia compared to those received [illegible].5 mg meto[illegible]opramide

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D[illegible]rtment of Anesthesia, Surgical ICU and Pain management, Faculty [illegible]Medicine, Cairo University.

Conflict of interest

None.

Author contributions

Tamer Fayez Safan:

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2. Subst[illegible]contribution to [illegible]ception and design, acquisition of d[illegible] and analysis and interpre[illegible]on of data
3. [illegible]afting the article, final approval of the version to be published
4. [illegible]greement to be [illegible]ountable for all aspects of the work thereby [illegible]nsuring that ques[illegible]ns related to the accuracy or integrity of any [illegible]t of the work a[illegible]appropriately investigated and resolved.

Ahme[illegible] Mohamed:

1. [illegible]ntial contribution to conception and design, acquisition of data a[illegible]d analysis and interpretation of data
2. Drafting the article, final approval of the version to be published
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