http://www.cjmb.org doi 10.34172/cjmb.2022.xxx

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. x, No. x, xx 2022, x–x
eISSN 2148-9696

Comparing the Effectiveness of Metoclopramide, Low Dose of Propofol, Ondansetron, and Magnesium Sulfate on Propofol Injection Pain: A Double-Blind Clinical Trial

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Abstract

Objectives: Despite a variety of strategies, propofol injection pain (PIP) is still one of the most distressing adverse effects of the drug. This study aimed to compare the effectiveness of metoclopramide, low dose of propofol, magnesium sulfate, and ondansetron in the prevention of PIP.

Materials and Methods: This double-blind clinical trial was conducted at Al-Zahra hospital an academic and referral center affiliated with Guilan University of Medical Sciences, Rasht, Iran. A total of 120 eligible women candidates for elective gynecologic surgeries were divided into four equal groups of magnesium sulfate (30 mg/kg), ondansetron (4 mg), metoclopramide (10 mg), and propofol (15 mg). The primary outcome of this study was to decrease the pain severity of propofol injection.

Results: The participants' demographic characteristics, including age, American Society of Anesthesiologists classification, and body mass index, had no significant differences between the four groups. A significant decrease in heart rate and mean arterial pressure were observed in four groups; however, the difference was insignificant. The mean pain intensity in the magnesium sulfate group was 1.57 ± 0.9, ondansetron 1.37 ± 0.89, metoclopramide 0.95 ± 0.93, and in propofol group was 1.25 ± 1.1 (P=0.036).

Conclusions: Metoclopramide could appropriately alleviate PIP. Considering some additional advantages, including antiemetic properties, preventing esophageal reflux, and less risk of postoperative ileus, this drug could be a safe and acceptable choice.

Keywords: Propofol, Injection, Pain, Metoclopramide, Ondansetron, Magnesium sulfate

Introduction

Propofol is widely used in modern anesthesia and is very popular due to its rapid onset and recovery easy titration (1, 2). However, intense pain on injection as a bad experience is its major adverse effect, ranking seventh among 33 unsolved clinical problems (3). In untreated cases, it has been demonstrated that the incidence of propofol injection pain (PIP) varies from 28% to 90% (4, 5). It is supposed that interaction between the active component of the emulsion and vascular endothelium causes immediate PIP (6). Another assumed mechanism for delayed pain is an enzymatic cascade in which kallikrein converts kininogens to kinins as pain mediators. Supporting this theory, studies show that cooling propofol alleviates PIP. It is also believed that venous intima irritation due to phenol causes PIP. However, the real underlying mechanisms of PIP remain unexplored (7).

So far, pharmacological and non-pharmacological methods such as pretreatment with a low dose of propofol, opioids, 5H3 receptors, α-2 agonists, Valsalva maneuver, nitroglycerine, paracetamol, cold saline, and diluted drug have not been able to suppress PIP completely (1, 5, 8-13). The problem is much more highlighted in some situations, such as rapid sequence induction for cesarean section (CS). Because of the safety of the fetus, no premedication is administrated. Here, four available and easy-to-use drugs with additional advantages were compared to find a safe and effective agent for reducing PIP.

Materials and Methods

Study Design and Participants

In this double-blind, randomized clinical trial, 120 women aged 18-45 years with American Society of Anesthesiologists classification (ASA class) I-II referred to the Alzahra hospital, Rasht, Iran, from April 2017 to September 2017 for elective gynecologic surgeries under general anesthesia (GA) were enrolled (Figure 1).

The exclusion criteria were any contraindications for study drugs, neurological diseases, psychiatric disorders, addiction, and use of analgesic or sedative drugs during 24 hours before surgery, chronic pain syndrome, those who required rapid sequence induction, difficulty in venous access, and having difficulty in communication skills.

Received 7 January 2021, **Accepted** 28 November 2021, **Available online** 19 May 2022

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Interventions

All 120 women received routine hospital preparation protocol for elective gynecologic surgeries. At the operating room, a checklist containing baseline demographic characteristics and medical history was filled out through a face to face interview by a responsible resident of anesthesiology. Our participants were randomly divided into four groups by computer-generated numbers: magnesium sulfate (30 mg/kg), ondansetron (4 mg), metoclopramide (10 mg), and propofol (15 mg). A nurse who was not involved in the research process prepared study drugs in identical numbered syringes diluted to 10 mL using 0.9% normal saline.

All participants received no drug as premedication. An air-filled tourniquet (pressure inflated to 70 mm Hg) occluded the venous drainage of the upper arm. Then according to the treatment group, the mentioned drug was injected and after 30 seconds the occlusion was released. Firstly, one-fourth of dose (0.25 mg/kg) of propofol was injected over 10 seconds. If the women lost her conciseness, she was excluded from the survey. The severity of the pain was assessed by McCrirrick and Hunter scale. None (0): No complaint of pain after asking; Mild (1) Pain reported after asking, without any behavioral signs; Moderate (2): Pain reported after asking, accompanied by behavioral signs or pain reported without asking; Severe (3): Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears. After the assessment of pain severity, anesthesia induction was completed with the remaining dose of propofol. Mean arterial pressure (MAP) and heart rate were documented at baseline T0 and 1, 3, 5, 10 minutes after induction (T1-T5). Finally, the results were compared among four studied groups.

Key Messages

- Although propofol is known to be an effective and favorite anesthetic agent, it has an important side effect, and that is the pain on injection.
- The current study suggests that metoclopramide can be an effective drug with several other benefits for this purpose.

Outcomes and Data Collection

The primary study outcome was pain severity due to propofol injection measured by McCrirrick and Hunter scale. The secondary outcomes were MAP and heart rate at baseline and 1, 3, 5, 10 minutes after injection.

Sample Size

According to a pilot study in which the percentage of (feeling no pain) in the metoclopramide group was approximately 40% and in the magnesium sulfate group was 10%, with an accuracy of $d = 0.3$ and $\alpha = 0.05$ and $\beta = 0.10$, the sample size for each group was calculated 30.

Randomization and Sequence Generation

An anesthesia technician who was not involved in study process performed the sequence of randomization blocks with a ratio of 1: 1 through a list of eligible women. These women were assigned into four groups of magnesium sulfate (30 mg/kg), ondansetron (4 mg), metoclopramide (10 mg), and propofol (15 mg) by computer-generated random quadruple blocks

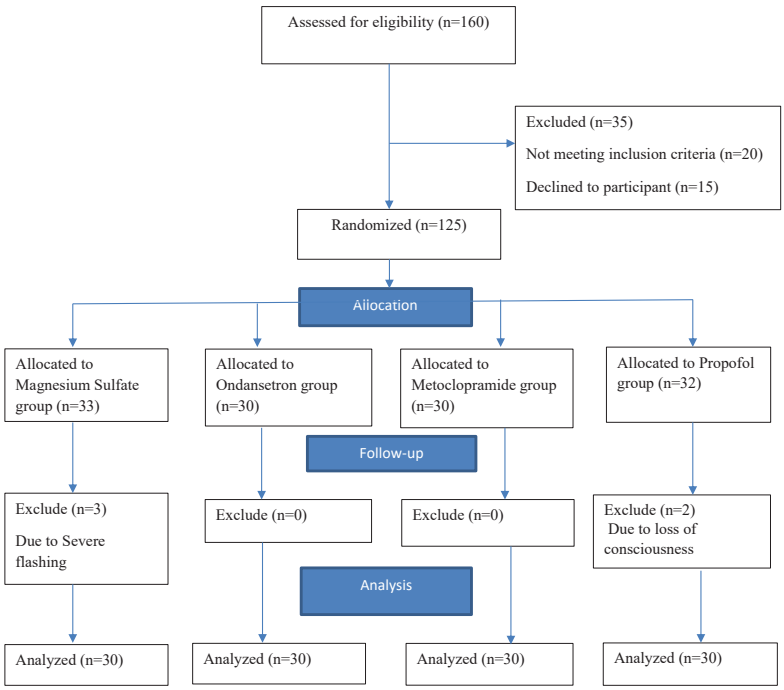

Figure 1. CONSORT Flow Diagram of the Study.

Allocation Concealment Mechanism and Blinding

This study was a double blinded clinical trial. In this way, the participants and the person in charge of recording the information were unaware of the treatment group and only the anesthesiologist (the person prescribing the drugs) was aware so that he could make the necessary treatment decisions in case of drug side effects.

Statistical Analysis

The data were analyzed by SPSS 16 (SPSS Inc. Released 2007, Chicago, IL, USA). Quantitative data were presented as the mean and standard deviation. Moreover, chi-square test, one-way ANOVA, Kruskal Wallis, and repeated measures were performed to compare the groups and a *P* value less than 0.05 was considered statistically significant.

Results

A total of 120 women were enrolled in the study. The participants' demographic characteristics, including age ($P=0.65$), ASA classifications ($P=0.217$), and body mass index (BMI) ($P=0.661$), had no significant differences between the study groups (Table 1). There was no significant difference between the study groups regarding pain severity (Table 2). The mean pain intensity scores in the magnesium sulfate group were 1.57 ± 0.9, ondansetron 1.37 ± 0.89, metoclopramide 0.95 ± 0.93, and 1.25 ± 1.1 in the propofol group ($P=0.036$). A significant decrease in heart rate and MAP was observed in four groups from T0 to T5. However, no significant difference was observed (Table 3).

Table 1. Demographic Characteristics of the Study Participants

Variables	Groups				*P* Value
	Metoclopramide	$MgSO_4$	Ondansetron	Propofol	
Age (y), mean ± SD	36.4 ± 7.99	36.55 ± 6.96	35.15 ± 5.19	35.0 ± 7.3	0.65[a]
BMI (kg/m²), mean ± SD	26.64 ± 3.42	26.93 ± 2.49	26.08 ± 2.98	26.54 ± 3.06	0.661[a]
ASA class, No. (%)					
I	33 (82.5)	24 (60.0)	29 (72.5)	32 (80.0)	0.217[b]
II	7 (17.5)	16 (40.0)	11 (27.5)	8 (20.0)	

BMI: Body mass index; ASA: American Society of Anesthesiologists' classification; MgSO4: Magnesium sulfate.
[a] One-way ANOVA; [b] Chi-square test.

Table 2. Comparison of the Pain Severity in Four Study Groups

Pain Severity	Groups				*P* Value
	Metoclopramide	Magnesium Sulfate	Ondansetron	Propofol	
No pain	16 (40.0)	4 (10.0)	6 (15)	14 (35.0)	0.033[a]
Mild pain	12 (30.0)	16 (40.0)	18 (45)	8 (20.0)	
Moderate pain	10 (25.0)	13 (32.5)	11 (30)	12 (30.0)	
Severe pain	2 (5)	7 (17.5)	5 (12.5)	6 (15.0)	
Mean pain severity	0.93 ±0.95	0.9±1.57	0.89±1.37	1.1±1.25	0.011[b]

*Data presented as n(%). $P < 05$: Statistically significant.
[a] Chi-square, [b] Kruskal Wallis test.

Table 3. Comparison of the Mean Heart Rate (n/min) and the Mean Arterial Blood Pressure (mm Hg) in Four Study Groups

	Metoclopramide	Magnesium Sulfate	Ondansetron	Propofol	*P* value[a]
Blood pressure					
Baseline	92.25±2.88	92.24± 3.1	91.2±2.55	92.26± 3.12	0.415
At 1 min	87.34± 2.93	87.95±3.2	86.17±2.61	87.4±3.09	0.132
At 3 min	83.46±3.7	81.67±3.77	82.36±3.67	83.18±2.96	0.196
At 5 min	81.16±3.7	81.01±3.87	81.41±2.6	82.84±3.18	0.143
At 10 min	82.86±3.7	84.11±3.8	83.2±2.59	83.74±3.2	0.495
P value[b]	0.0001	0.0001	0.0001	0.0001	
Heart rate					
Baseline	84.16±7.42	80.7±6.74	85.13±6.67	82.43±7.76	0.088
At 1 min	77.23±7.91	76.76±5.78	78.2±6.88	78.03±6.3	0.813
At 3 min	76.26±7.15	77.83±5.77	77.7±6.64	76.5±7.36	0.735
At 5 min	77.46±6.27	77.8±5.79	77.56±6.74	76.33±7.54	0.831
At 10 min	78.23±7.02	79±6.39	78.66±6.07	78.66±7.84	0.979
P value[b]	0.003	0.132	0.0001	0.0001	

*Data presented as mean ± SD. $P < 05$: Statistically significant.
[a] One-way ANOVA, [b] Repeated Measures test.

Discussion

The present study aimed to compare the effectiveness of ondansetron, low dose of propofol, metoclopramide and magnesium sulfate on PIP. Based on current evidence, the efficacy of selected drugs for this purpose has been proved with varying degrees of success. The chosen doses were based on previous studies (8,9) and a well-known method of pain relief by which administration of low-dose of the drug as stimulants resulted in less sensitivity to the main dose of the drug and thus higher pain threshold are achieved (14). The order of efficacy of the studied drugs was: metoclopramide > ondansetron > low doses of propofol > magnesium sulfate basis of mitigation in the severity of PIP. Factors affecting PIP, including the site and speed of injection, vein size, and drug temperature was the same in all patients (15).The results of this study were in line with Richard et al study, which did not support magnesium sulfate as a suitable premedication for PIP(16). In addition, in the magnesium sulfate group, even in slow and diluted drug infusion, 10 patients experienced flushing and palpitation and were excluded from the survey. Furthermore, magnesium sulfate prolongs the effects of muscle relaxants (17,18). In the low-dose propofol group, six patients even complained of pain from low doses of propofol as pretreatment. Metoclopramide as a pro-kinetic agent with antiemetic properties is a safe and effective option used before induction of anesthesia. Based on the available literature, it can lessen PIP alone or in combination with other drugs (19).

So the main obtained result of this paper was that, among studied drugs, metoclopramide could be the preferred option (20). These results are consistent with another article (21). The pain-relieving properties of metoclopramide could be explained by the fact that serotonin 5-hydroxytryptamine (5-HT3) is a biological amine in the brain, and spinal cord (22). Studies indicate that 5-HT3 antagonists have sodium channel blocking action, 15 times greater than that of lidocaine. Furthermore, the ability to bind to the μ receptor is also found (23). In addition to the safety and efficacy, metoclopramide is cost effective as the cheapest 5- HT3 antagonist (24). Based on the evidence, a practical and clinical consequence of this paper could be in CS under GA as this drug has been administrated in the standard protocol of CS. It should be noted that PIP is much more prominent in these cases because pretreatment with benzodiazepines and opioids are avoided due to the concern of fetus harm(25). By the way propofol has also been the drug of choice among various anesthesia induction drugs in CS due to its safe properties, smooth induction and rapid clearance from neonate circulation. Till now most scientific literature on CS and metoclopramide has focused on the prevention of post-operative nausea and vomiting but not its effectiveness on PIP. In addition, as mentioned above it has other benefits such as prevention of esophageal reflux and ileus which are common complications in CS (26, 27).

It is worth noting that according to the results of this study poly-pharmacy which could be harmful to the patients would be somewhat avoided. Indeed, standard protocol of CS under GA is followed and to prevent PIP just the easy method described in this work should be performed. Thus in addition to reducing PIP, earlier post-CS recovery would be achieved due to the lower risk of postoperative complications (26).

Conclusions

We found that metoclopramide was the most effective one to prevent PIP among the studied drugs. By the way, in addition to PIP reduction, this drug provides other advantages. It should be noted that metoclopramide is administrated as the standard protocol of CS anesthesia management. Future well-planned studies are welcomed to clarify some unresolved aspects of the issue.

Authors' Contribution

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: GB, SGT and MH. Acquisition, analysis, or interpretation of data: AY, LM, and AC. Drafting of the manuscript: MH and FF. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: RSR and MKS. Supervision: FF and GB.

Conflict of Interests

None of the authors declared any conflicts of interest.

Ethical Issues

The study proposal was approved by the ethics committee of Guilan University of Medical Sciences, Rasht, Iran (Code: IR.GUMS.REC.1395.357). It was also registered at the Iranian Registry of Clinical Trials (IRCT) (identifier: IRCT2017031433069N1). The written informed consent was obtained from all participants.

Funding Support

This study was supported by Guilan University of Medical Sciences.

Acknowledgments

The authors wish to thank the members of the Anesthesiology Research Center of Guilan University of Medical Sciences for their collaboration in this study.

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