



A Comparative Study Between Pharmacological Efficacy of Meperidine and Oxycodone for Preventing Shivering in Patients who underwent Inguinal Hernia Repair with Spinal Anesthesia

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ABSTRACT

Postoperative shivering control without lengthening recovery time and worsening cardiovascular system is important and necessary. The main objective of the present study was to evaluate the efficiency of Meperidine and Oxycodone in preventing shivering in patients who underwent inguinal hernia repair with spinal anesthesia. The present study consisted of patients with herniorrhaphy in the Fatemi and Imam Hospital of Ardabil who were studied through a double-blind clinical trial. with spinal anesthesia from 2017 through 18. In the study 110 cases with hernia were included. In both studied groups of Meperidine or oxycodone, patients were allocated randomly. Interventions began half an hour before spinal anesthesia in the operating room. Each group had their own structured treatment plan so that the first and the second groups received 5 mg of oxycodone and placebo respectively. After the patients being stable, Meperidine 0.4 mg/kg (2 CC) was injected to the second group following the spinal anesthesia. Normal saline (2 CC) injected to the first group as placebo. Patients were evaluated for shivering, nausea, vomiting and other complications up to 4 hours after surgery. After the operation, an uninformed questioner asked for shivering, nausea and vomiting and other complications of the operation, including dizziness and headache, for up to 4 hours (at intervals of 0, 2 and 4 hours), filling the relevant questionnaire and then the data were entered into SPSSv 21 and analyzed using Chi Square, T test and Fisher exact tests. A significance Level of 0.05 was considered for all the tests. The incidence of shivering in the oxycodone group at zero time (in recovery room) was significantly lower than the Meperidine group. But in other times, oxycodone had no significant effect on shivering compared to Meperidine. In both studied groups, there was not significant differences between rate of nausea and vomiting. We showed that oxycodone pills immediately after surgery may reduce the incidence of shivering significantly and also effective in shivering control as much as Meperidine at the other times of recovery.

Article Information

Received 16 November 2022

Revised 20 November 2022

Accepted 28 November 2022

Available online 20 March 2023
(early access)

Published 03 June 2024

Authors' Contribution

GAA designed the study and help in writing the manuscript. SH and SSA performed data collection and analysis. AG wrote the manuscript and approved it for publication.

Key words

Oxycodone tablets, Meperidine injections, Shivering, Inguinal herniorrhaphy, Spinal anesthesia

INTRODUCTION

One of the most prevalent postoperative complications is postoperative shivering which was reported in about 6.3% to 65% of patients. This complication is known as the involuntary or uncontrollable movement of muscles

(Miller *et al.*, 2014; Pazuki *et al.*, 2016). Analogy to the other side effects of general and local anesthesia, shivering increases morbidities like patients' displeasure, pain and oxygen consumption up to 600%. So, shivering should be reduced by appropriate pre and intraoperative arrangements (Miller *et al.*, 2014).

Except the altering the hypothalamus balance, spinal anesthesia causes peripheral vasodilatation. This complication which is mainly due to sympathetic block makes more heat loss (Miller *et al.*, 2014). Core body hypothermia during surgery especially heart surgeries may lead to post-operative shivering and also coagulopathies, nitrogen imbalance, and other medical problems (Reynolds *et al.*, 2008; Kurz, 2008; Alfonsi, 2003).

Patients who have experienced postoperative shivering believe that it is the worst memory of their

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0030-9923/2024/0004-1693 \$ 9.00/0



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hospitalization period (Gaskell *et al.*, 2009; Modir *et al.*, 2019). The major drugs used to treat postoperative shivering include clonidine, ketanserin, physostigmine, magnesium sulfate, dexamethasone, doxapram and on the top of them meperidine (Modir *et al.*, 2019; Grundmann *et al.*, 1997; Nematshahi *et al.*, 2011; Khan *et al.*, 2011; Hwang *et al.*, 2014; Dabir *et al.*, 2011). Although, there is still controversy about the best of them for post-operative shivering treatment, opioids are accepted to control shivering in various rates (Miller *et al.*, 2014). Oxycodone tablet has fewer side effects than Meperidine for example, less respiratory depression amounts (Miller *et al.*, 2014). The main objective of the present study was to examine the pharmacological efficacy of Oxycodone tablet and Meperidine in postoperative shivering through a comparative study.

MATERIALS AND METHODS

The present study consisted of all the patients of inguinal hernia surgery in Fatemi hospital and Imam Hospital of Ardebil from 2017 to 2018 who were investigated through a double-blind randomized clinical trial.

In our study, the sample size was determined based on a similar study by (Entezariasl and Isazadehfar, 2012). Moreover, the shivering rate was reduced by about 30% using both drugs. In this study, P1=40% in Oxycodone group and P2=60% in Meperidine group with the study power equal 80% and an alpha level equal to 5%. The following formula was used for the study with 55 samples in each group and a total of 110 samples. The participants (110 patients) were divided into two groups through sampling technique of randomized block (6: AABBC).

Inclusion criteria included providing written informed consent, age of 18-65 years, and American Society of Anesthesiologists (ASA I and II).

History of Meperidine or oxycodone sensitivity, peptic ulcer, systemic infection or immune deficiency, monoamine oxidase inhibitor therapy, untreated hypothyroidism, benign prostatic hypertrophy, Addison disease and convulsive disorder and addicted patients was considered as exclusion criteria.

Patients who had significant bleeding during surgery and patients who did general anesthesia rather than spinal anesthesia left the study.

The packages designed for each group was similar in appearance. Given that the method of study was randomized block design; both packages were named separately and with specified codes (first package A and second package B). Drug prescriber (anesthesiology assistant) had no information about the contents of the package (blindness

type 2) and packages were selected based on the patient group that had been pre-identified. The patients with type 1 diabetes were not informed about the type of received medicine. In both studied groups, the medication regimen and the used method of anesthesia were the same.

Before in going to the operating room, patients were explained the method of study. Peripheral vein catheter (G18-20) was provided for the patients. Patients underwent complete and standard monitoring including electrocardiography, non-invasive manometry, and pulse oximetry. Interventions began half an hour before spinal anesthesia in the operating room. A 5 mg of oxycodone was given to patients in the first group, and the one in the second group received placebo. Subsequently, the patient received spinal anesthesia 2.2 to 2.8 ml (by patient height) of Marcaine 0.5% (Marcaine Spinal Heavy Ampule 0.5% AstraZeneca) through the L3-L4 or L4-L5 intervertebral space in a sitting position. The level of sensory block in spinal anesthesia was T6-T10.

The operating room temperature measured by a digital thermometer was about 24 °C. After the patients' stability, Meperidine 0.4 mg/kg (2 CC) was injected to the second group after the spinal anesthesia. Normal saline (2 CC) was injected to the first group as placebo. All patients were oxygenated by mask with a flow rate of 2-3 liters per min.

The amount of water loss and maintenance fluid was supplied with intravenous Ringer's solution with the same Temperature in both groups. Hypotension during surgery (MAP less than 20% baseline) was controlled by slow intravenous injection of 5-10 mg ephedrine.

In a bradycardia situation when heart rate is too slow (heart rate less than 50 beats/min), patients were treated with 0.5 mg Atropine Sulphate. Anesthesia technician who was unaware of patient grouping recorded times of nausea, gagging, vomiting and shivering severity during surgery (blinding type 2). Vomiting with Score 3, 4, in the patients was managed by a slow intravenous injection of 10 mg metoclopramide and shivering with Score 3, 4, was treated by Meperidine 25 mg.

All patients underwent standard surgical procedure (oblique inguinal incision). Patients were evaluated for shivering, nausea, vomiting and other complications up to 4 h after surgery. Nausea and vomiting were assessed using the N and V score table. Score 1 was for those who were without symptoms of vomiting and nausea. Scores 2 and 3 were for those who only had nausea and those having one to two symptoms of nausea and vomiting, respectively. Besides, the score of 4 represents patients who had more than two symptoms of nausea and vomiting. As could be seen from table x, the level of shivering was assessed by grading from 0 to 4. (0, Shivering does not occur; 1,

Piloerection, peripheral vasoconstriction, peripheral cyanosis without other specific reason, but without obvious muscle contraction; 2, Limited contraction (limited to a bunch of muscle contractions); 3, Contraction observed in more than one group of muscles; 4, Whole body clear muscular activity).

All data were recorded in the questionnaire during surgery, recovery time, 2 and 4 h after surgery. Chi Square, T test, and Fisher's exact test were used to analyses the data through SPSS v 21. The significance level for all the tests was considered to be a p-value less than 0.05.

RESULTS

In this study, age, sex, level of education, hernia side, MDBP (mean diastolic blood pressure), MSBP (mean systolic blood pressure), HR (heart rate), RR (respiratory rate) were examined and finally, it was revealed that the two studied groups were not significantly different based on the mentioned parameters. 25 patients (46.3%) in oxycodone group had a high school diploma and 28 patients (50.9%) in Meperidine group had a high school diploma (P=0.133).

Table I. Comparison of groups of patients by age, gender, Level of Education, Hernia side, MDBP, MSBP, HR, RR. values have been expressed as mean±SD.

	Oxycodone group	Meperidine group	P value
Age	44.6±14.96	44.5±16.2	0.976
Sex(M/F)	90.9%(M)-9.1%(F)	83.6%(M)-16.4%(F)	0.149
Level of education	46.3%	50.9%	0.133
Hernia side	60% Right	70% Right	0.268
MDBP	70/74±13/09 mmHg	72/23±10/73 mmHg	0.943
MSBP	120/2±16/69 mmHg	118/95±6/69 mmHg	0.697
HR	70.7±13.62	69.25±10.24	0.528
RR	12.38±1.39	12.14±1.56	0.405

Analyzed by Chi square test and T test.

MSBP, mean systolic blood pressure; MDBP mean diastolic blood pressure; HR, heart rate; RR, respiratory rate.

The differences of two studied groups in terms of history of drug consumption, drug allergy, smoking, hypertension, diabetes mellitus, surgery was not significant. Right inguinal hernia surgery (33 cases (60%) in oxycodone group and 39 cases (70.9%) in Meperidine group) was the most common surgical site (P=0.268). The level of anesthesia in all patients was adequate and a T6 sensory block was achieved (Table I).

Incidence of nausea and vomiting was not significantly different between the two groups (Table II).

Table II. Incidence of nausea and vomiting in study groups at Different times.

		Frequency (%)		P value
		Oxycodone group	Meperidine group	
During operation	No nausea	52 (94.5%)	46 (83.6%)	0.067
	Only nausea	3 (5.5%)	9 (16.4%)	
	Nausea and vomiting < 2 times	0	0	
Hour 0 (Recovery)	No nausea	50(90.9%)	48(87.3%)	0.568
	Only nausea	5(9.1%)	6(10.9%)	
	Nausea and vomiting <2 times	0	1(1.8%)	
	Nausea and vomiting >2 times	0	0	
Hour 2	No nausea	52(94.5%)	53(96.4%)	0.604
	Only nausea	2(3.6%)	2(3.6%)	
	Nausea and vomiting <2 times	1(1.8%)	0	
Hour 4	No nausea	53(96.4%)	55(100%)	0.361
	Only nausea	1(1.8%)	0	
	Nausea and vomiting <2 times	1(1.8%)	0	

Analyzed by Chi square test.

Shivering was also evaluated in two groups. Post spinal anesthesia shivering was evaluated during surgery. Based on the data achieved from this study it was observed that the shivering score could not significantly affect the study groups during surgery (P=0.697) (Table III).

Shivering was also evaluated at hour zero (at recovery time). The results showed that shivering in Meperidine group was significantly more than oxycodone group (P = 0.043) (Table III). Evaluation of shivering amount the studied patients two hours after surgery showed a decrease in the level of shivering and also both groups were not significantly difference (Table III).

Shivering was evaluated up to 4 h after surgery and none of the patients had shivering within 4 h after surgery. Vertigo and epigastric pain were observed in 5 patients however analysis of results showed no significant difference between the groups (P = 0.310).

DISCUSSION

The data from the present study revealed that the incidence of shivering at hour zero (in Wrecovery) in

Meperidine group was significantly higher compared to oxycodone group. But at the other times the oxycodone tablets had no significant difference in the incidence of shivering with Meperidine.

Table III. Incidence of shivering in study groups after spinal anesthesia, and during recovery at 0 h and 2 h.

Score	Oxycodone group Frequency (Percent)	Meperidine group Frequency (Percent)	P value
After spinal anesthesia			
0	47(85.5%)	46(83.6%)	0.697
1	0	1(1.8%)	
2	5(9.1%)	5(9.1%)	
3	3(5.5%)	2(3.6%)	
4	0	1(1.8%)	
At 0 h (recovery)			
0	44(80%)	30(54.5%)	0.043
1	3(5.5%)	12(21.8%)	
2	4(7.3%)	7(12.7%)	
3	1(1.8%)	3(5.5%)	
4	3(5.5%)	3(5.5%)	
At 2 h (recovery)			
0	50(90.9%)	52(94.5%)	0.283
1	2(3.6%)	0	
2	1(1.8%)	3(5.5%)	
3	1(1.8%)	00	
4	1(1.8%)	00	

Analyzed by chi square test.

In a study by *Eydi et al. (2014)*, the results showed that there was no significant difference in incidence of shivering between Meperidine and ketamine. In another study by *(Dabir et al., 2011)*, which compared shivering after Meperidine, fentanyl, and morphine between three studied group, the reported differences were not significant in terms of recurrence rate of shivering, shivering time, and the level of shivering suppression.

In their study, Entezari Asl and Isazadeh study *(Entezariasl and Isazadehfar, 2012)* examined the efficiency of dexamethasone on prevention of postoperative shivering in 120 patients undergoing surgery. In their study, normal saline, dexamethasone, and Meperidine were injected into the three groups of patients after induction of anesthesia. It was observed in this study that 10% of dexamethasone group, 37.5% of Meperidine group and 47.5% of placebo group had postoperative shivering. The results showed that both drugs significantly reduced shivering compared to placebo and there were

significant differences between drugs which shivering was less prevalent among patients which were treated with dexamethasone. A similar study by *Bhatnagar et al. (2001)*, compared patients who received tramadol versus Meperidine recipients. Based on our data, the incidence rate of shivering was 26.6% and 80% in Meperidine group and tramadol groups respectively. So, the difference between these groups was statistically significant.

In their study *Isazadehfar et al. (2018)* compared the effect of the combination of dexamethasone with ondansetron and the combination of metoclopramide with dexamethasone on vomiting, nausea, and shivering in 88 patients in two groups undergoing laparoscopic cholecystectomy under general anesthesia demonstrated that administration of a combination of dexamethasone and ondansetron was not significantly powerful enough in decrement of the incidence of nausea and vomiting after surgery related to a combination therapy of dexamethasone with metoclopramide. However, in none of the patients of both groups shivering was observed *(IsazadeFa et al., 2018)*.

In a prospective study by *Adinehmehr et al. (2018)*, a group of 90 patients were selected and scheduled for surgical procedure of TURP (transurethral resection of prostate) with spinal anesthesia which finally were assigned to 1 of 3 groups randomly (each group 30 participants). 50mg of tramadol was given to one-third of patients about 90 min before spinal anesthesia. In another studied group, 4 mg of oral TI was given to the patients, and finally the third group received placebo as the control group. All the participants experienced spinal anesthesia by being injected with 12.5 mg of bupivacaine at L3-L4 or L4-L5 interspaces. An examiner blind to the drugs, recorded the frequency and the degree of shivering. Oral TI, tramadol, and our data could be compared with each other based on their role in reduction of shivering intensity in TURP patients with spinal anesthesia *(Adinehmehr et al., 2018)*.

Khalili et al. (2014) conducted a study included 64 patients allocated in two equal groups who underwent upper limbs operation with general anesthesia. In the first group a mixture of 15 mg/kg and 1 g paracetamol was infused in 100 cc normal saline within 20 min. However, in the control group, patients were infused with 100 cc normal saline within the same time. The pain, operative shivering, peripheral temperature, and core temperature (Tc) were recorded at the same time. Based on the achieved data, the possibility of shivering in recovery time was significantly lower in patients who received Apotel ($P = 0.014$) *(Khalili et al., 2014)*.

In a similar study by *Hwang et al. (2015)* who divided the patients to two groups, the first group received a combination of nefopam and oxycodone and the second

group combination of ketorolac and oxycodone.

The difference between two groups in terms of incidence of shivering was not significant. The incidence of shivering in the first and second group was 5% and 6.66% respectively. Three studies by [Fanelli et al. \(2008\)](#), [Jokela et al. \(2007\)](#) and [Ho \(2008\)](#) reported that administration of oxycodone to patients undergoing laparoscopic surgery, did reduce the complications like shivering although insignificantly similar to Meperidine. Based on the data from the present study, two groups were not significantly different based on the incidence of nausea and vomiting. Another study by [Yamada et al. \(2015\)](#) revealed that the incidence of vomiting and nausea in recipients of oxycodone and Prechlorhexidine tablets was 18.1% and 5.8%, respectively. It was also reported that female gender could increase the risk of nausea and vomiting.

In a study by [Nishizawa et al. \(2018\)](#), the incidence rate of nausea and vomiting after esophagogastroduodenoscopy (EGD) test was investigated, which reported an incidence rate of 0.49% for vomiting and nausea after EGD test. Besides, they introduced Meperidine and female sex as risk factors of nausea and vomiting after EGD test. In their study, [Shamim et al. \(2006\)](#) also reported that there was no significant difference between the administration of tramadol and Meperidine in term of their role in incidence of nausea and vomiting.

Another study by [Nasiri et al. \(2015\)](#) classified the patients into three groups. Three regimens were introduced such as pre-warmed Ringer serum (38°C), pre-warmed ringer serum (38°C) accompanied by humid-warm oxygen, and intravenous Meperidine routinely for the first, second, and the third group respectively. After the treatment, all the participants went under the assessment of the elapsed time of shivering and some hemodynamic parameters for 20 min in the recovery room. Based on the data, a combination of warming and Meperidine could be more impressive in the controlling and management of the postoperative shivering and body temperature rises ([Nasiri et al., 2015](#)).

[Derakhshan et al. \(2018\)](#) conducted a double-blind, randomized clinical trial. In their study, 105 patients were candidates for lower limb surgery and received the following treatments in three groups; a combination of bupivacaine 15 mg with normal saline 1 mL for B groups, a combination of bupivacaine 15 mg and epinephrine 10 µg for BE group, and a combination if bupivacaine 15 mg and sufentanyl 5 µg for BS group. The start of sensory (pinprick) and somatic motor blockade among the three studied groups were statistically different, while vomiting and nausea were not common among them. Moreover, these groups were not different based on the incidence of pruritus ([Derakhshan et al., 2018](#)).

It seems that the incidence of nausea and vomiting after receiving all opioids is almost similar and statistically insignificant in most studies ([Kim et al., 2016](#); [Chiu et al., 2018](#); [Miller et al., 2014](#); [IsazadeFa et al., 2018](#); [Hwang et al., 2015](#); [Nishizawa et al., 2018](#); [Shamim et al., 2006](#)). While, the incidence rate of vomiting and nausea was significantly different between the patients who used Apotel, Opioids, and other analgesics ([Kim et al., 2016](#); [Chiu et al., 2018](#)). Since the present study was conducted on two opioids, the differences between the studied groups in terms of the incidence of nausea and vomiting were not significant.

CONCLUSION

We showed that administration of oxycodone tablet before surgery significantly decreased the incidence of shivering immediately after surgery and oxycodone tablet was as effective as Meperidine injection in controlling shivering at other times of project. The differences between the studied groups in terms of happening of nausea and vomiting were not significant. Therefore, oxycodone tablet is a good alternative for Meperidine in lessening of shivering in postoperative hernia repair with spinal anesthesia.

Our study also faced some limitations, including the duration of patients follow-up. Other limitations were the temperature of injected serum and also the ambient temperature which could influence the results of the study. It is recommended that future studies be conducted with a larger sample size and more follow-up time, comparison of drug doses and different drug forms in postoperative shivering management.

ACKNOWLEDGMENTS

We appreciate the research deputy of Ardabil University of medical science, faculty of medicine who funded this project. Moreover, we are grateful to the operating room's staff and hospital wards of Fatemi and Imam Khomeini Hospital who helped us in performing the present project.

Funding

The study received no external funds.

IRB approval and ethical statement

Before the study, written informed consent was obtained from all participants. The ethics committee with code IR.ARUMS.REC.1396.158 approved our study and then was registered on the clinical trial website with code IRCT20181006041248N1.

Statement of conflict of interest

The authors have declared no conflict of interest.

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