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Comparison of the Effect of Sublingual Buprenorphine and Intravenous Fentanyl on Pain Control after Cesarean Surgery

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Authors' contributions

This work was carried out in collaboration between all authors. Author AG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KIF and MEA managed the analyses of the study. Author AV managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: One of the major challenges in women's surgery, including cesarean section, is postoperative pain control. Postoperative pain is one of the most common problems in the postoperative period that can lead to a significant reduction in the quality of surgical operations. Other problems may be associated with postoperative pains such as nausea and vomiting,

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hypotension and shivering. Therefore, the present study aimed to compare the effect of sublingual buprenorphine and intravenous fentanyl pump on postoperative cesarean section pain control and its effect among patients.

Methods: The present study is a randomised, double-blind clinical trial. Patients are 18-45 years old and all candidates for cesarean section at Alavi Hospital in Ardabil in 2017 -2018. After obtaining consent from patients for inclusion in the study, 80 patients were selected using simple sampling method and divided into two groups with 40 members in each group. In the first group, 40 patients received fentanyl and placebo tablets, and the pump was used to inject intravenous fentanyl and infusion lasted for up to 24 hours. The second group (40 patients) received normal saline pump and sublingual buprenorphine which repeated 6 and 12 hours after the first dose and continued up to 24 hours. Then, VRS (Verbal Rating Scale) pain score, vomiting-nausea, quantity of sedation (from ramsay sedation scale), and the amount of analgesia need for pain control at 2, 6, 12, and 24 hours, and postoperative analgesia (time of the first need to pain killer) were evaluated. Finally, all patient information was entered into a pre-designed checklist and all data were analysed using the SPSS(statistical package for the social sciences) v20 statistical analysis program.

Results: In this study, 80 patients were evaluated in two groups. The results of VRS pain score in patients showed that, except for the 24 hours after surgery, in no other postoperative time of study, the pain score in the two groups didn't show any significant difference. In the fentanyl group, the use of analgesics was higher than the buprenorphine group. During the postoperative time (hours 2 and 6), the incidence of nausea and vomiting was significantly lower in the buprenorphine group than the fentanyl group, but during the other hours, no such difference was observed. The sedation score was also evaluated, but no significant difference was observed between the two groups. Also, the incidence of other side effects in the two groups did not differ significantly.

Conclusion: The results of this study showed that buprenorphine is an effective drug in reducing postoperative pain in patients and, due to its very low side effects, it can be used routinely in patients.

Keywords: Regional anaesthesia; Caesarean section; buprenorphine; fentanyl; Ardabil City.

1. INTRODUCTION

Childbirth is a completely natural process requiring prevention and supportive actions. Natural delivery is effective in mothers who are able to do so. Otherwise, cesarean section may be used in cases where delivery is unlikely or if there are risks for mother and infant [1,2,3,4,5]. One of the problems of cesarean delivery is acute postoperative pain. Pain is a completely mental experience [6] that generates adverse hemodynamic and metabolic responses in patients [7,8]. Pain also causes undesirable psychological responses such as anxiety, sadness, aggression, insomnia, and lack of logical connection by the physician and nurse, and possibly by the newborn. Pain decreases milk secretion and reduces the mother's tolerance for breastfeeding [4,9]. Postoperative pain is one of the most common problems in the postoperative period that can significantly reduce the quality of surgical procedures. It can also be associated with other problems such as nausea and vomiting, hypotension and shivering [10,11,12]. Therefore, prevention of this problem is of great importance [2,11]. Several therapies are available for the treatment of these pains and prevention of these complications. They include analgesics (narcotics and NSAIDs), ansesthetics, acupuncture, method of anaesthesia and etc [4,10,11,12,13,14,15,16,17]. The most commonly used treatment is intravenous opioids that are commonly used during and after surgery. Since injectable drugs have many side effects such as cardiovascular and respiratory side effects, and on the other hand, in some cases, they are not effective, using more controllable & effective drugs are more desirable [18,19]. Effective management of postoperative pain is part of the surgical process and involves a multi-faceted approach in which different drugs are used with different mechanisms and methods of Administration [4,7,8,14,15,20]. Administration of non-opioid analgesic drugs is an essential component of multidisciplinary pain management programs [4,14,15]. Today, fentanyl is widely used for anaesthetic and pain relief. An appropriate drug for controlling postoperative pain should have the following characteristics: easily accessible and affordable, does not impose a high cost for the patient, hospital and the healthcare system of the country. The form of use be in a way that cause least complication, it does not need professional people for

prescription and preferably be usable by the patient himself, take less time from the medical staff, and different forms of drug with different doses of the drug be available to be used base on patient's body weight. Such drugs include buprenorphine, a relative agonist of opioid receptors that has agonist and antagonistic effects on receptors. It is currently used globally and has injectable, sublingual and transdermal forms [11,21]. This drug has been used in many studies to control pain [19,22,23,24]. The aim of this study is to compare the effect of sublingual buprenorphine and intravenous fentanyl pump on postoperative pain control in cesarean section and to investigate its effects among patients.

2. MATERIALS AND METHODS

This study was a randomised, double-blind and controlled clinical trial. The statistical population of this study included patients referring to the Alavi education at medical center of Ardabil city in 2017 -2018 underwent cesarean section with spinal anaesthesia. Patients were in the age ranged from18 to 45 years and classified according to the physical conditions with ASA(American Society of Anaesthesiologist) I or II and gravid I or II. The present study was carried out by obtaining the introduction letter and permission from the research deputy of Ardabil medical science university and confirmation of the ethics committee from the research ward of university and registered in the IRCT system with the IRCT 2017010923559N14 number. The patients participated in the research and consent forms completed, we received and stored consent form by each patient. All provided information and responses of the questionnaire were confidential. Patients with heart failure, with contraindication of fentanyl and buprenorphine, with dissatisfaction to participate in the study, and those who required more intervention or general anaesthesia during the procedure excluded from the study. All patients received 2 mg midazolam after the baby's birth. Patients were excluded from the study in cases requiring more sedation or intervention. Also, patients with unusual bleeding and other complication during surgery were excluded from the study. The duration of operation in all patients was 1 - 1.5 hours due to cesarean delivery by obstetric assistant. After obtaining patients consent 80 patients were selected by simple sampling method and selected patients were divided in two groups by random 4 block method (AABB). Blocking was done by the implementer and anaesthesiologists were not aware of block type. The first group was 40 patients receiving fentanyl pump (product of Pouyan Tajhiz) and a placebo tablet, the second group was 40 patients receiving normal saline pump and buprenorphine pill. The operating room temperature and other influential factors were identical. All patients had spinal anaesthesia with 0.5% bupivacaine (2.5 ml) and patients who needed more intervention to control pain excluded from study. The level of spinal anaesthesia was up to nipple level and the surgery was done by Pfannenstiel incision. Given that this study is blocked randomly, two drugs: fentanyl (product of daroupakhsh) and buprenorphine(product of faman chemie sirang co.ltd), each with a placebo, in the other group, drugs are individually and in packs (containing a pump and a pill) with specific codes (A and B) and the drug injector(anaesthesiologist), had no information about contents of the package (type II blindness). The package A contained the fentanyl pump and the placebo pill, package B contained a placebo pump and buprenorphine pill, and the choice of A or B pack were according to the pre-specified patient group, and each day were set aside preoperative according to the number of the surgeries listed in the daily sheet and patients were uninformed about the type of the received drugs (blindness type I).

In the first group, the pain control pump was used to inject intravenous fentanyl (1000 micrograms or 20 ml fentanyl in 80 ml normal saline) and placebo tablets (at recovery and 6 and 12 hours after recovery) and intravenous pump was continued for up to 24 hours at a rate of 4 ml/h. In the second group (buprenorphine group), buprenorphine 0.4 mg sublingually with placebo pain control pump contained 100 ml normal saline and buprenorphine pills were repeated 6 and 12 hours after the first dose. The placebo pump was infused at a rate of 4 ml/h for up to 24 hours. Patients who received intervention weren't excluded from the study. Patients' pain was assessed by VRS (Verbal Rating Scale) at 2, 6, 12, and 24 hours after surgery. The VRS score in this study was graded from 0 to 3 points. If the patient had no pain, the score was zero, score 1 for mild and minor pain, score 2 for moderate pain, score 3 for severe pain. The nausea and vomiting was assessed by N & V score table, score 1: without nausea and vomiting, score 2: only nausea, score 3: one to two episodes of nausea and vomiting, score 4: more than 2 episodes of nausea and vomiting, and sedation of the patients was assessed by Ramsay sedation score (0 to 5): Score 0:

Restless, Score 1: Quiet and Attentive, Score 2: Sleepy, Score 3: confused but responsive to verbal orders, Score 4: No Response to verbal Orders , Score 5: No response to painful stimuli that evaluated and registered at 2, 6, 12, and 24 hours, as well as the need for additional analgesic at 2, 6, 12, and 24 hours, and the number of needed times. Additional injection drugs were 25 mg intravenous meperidine (product of Caspian tamin) or suppository diclofenac (product of pharma chemie) for each patient. In this study, the number of received drugs was evaluated. meperidine (25 mg) was prescribed in patients when the pain score was severe (3) or moderate (2). In milder cases, we used diclofenac suppositories (100 mg), and evaluated set time of the postoperative analgesia (time of the first administration).

2.1 Statistical Analysis

In this study, counting the first type error of 5% and the study strength of 80% and mean difference: 0.7. Sample size was estimated 80 patients who were candidates for cesarean section and were randomly assigned into two groups of 40 subjects using a simple randomised allocation method. After collecting the data from the review and arranging the relevant tables and charts, in order to analyse descriptive information, the central indices (mean, median) and dispersion indices (standard deviation, variance, etc.) were used. After completing the checklist, the obtained information entered to SPSS v20 software and the chi-square test was used to examine the relationship between qualitative variables and t-test was used to analyse the quantitative variables. P value less than 0.05 was considered statistically significant. The results were displayed as ± mean ± SD where possible.

3. RESULTS

In this study, 80 patients were divided into two groups. The first group received fentanyl pump & placebo pill; the second group received normal saline pump with buprenorphine pill.

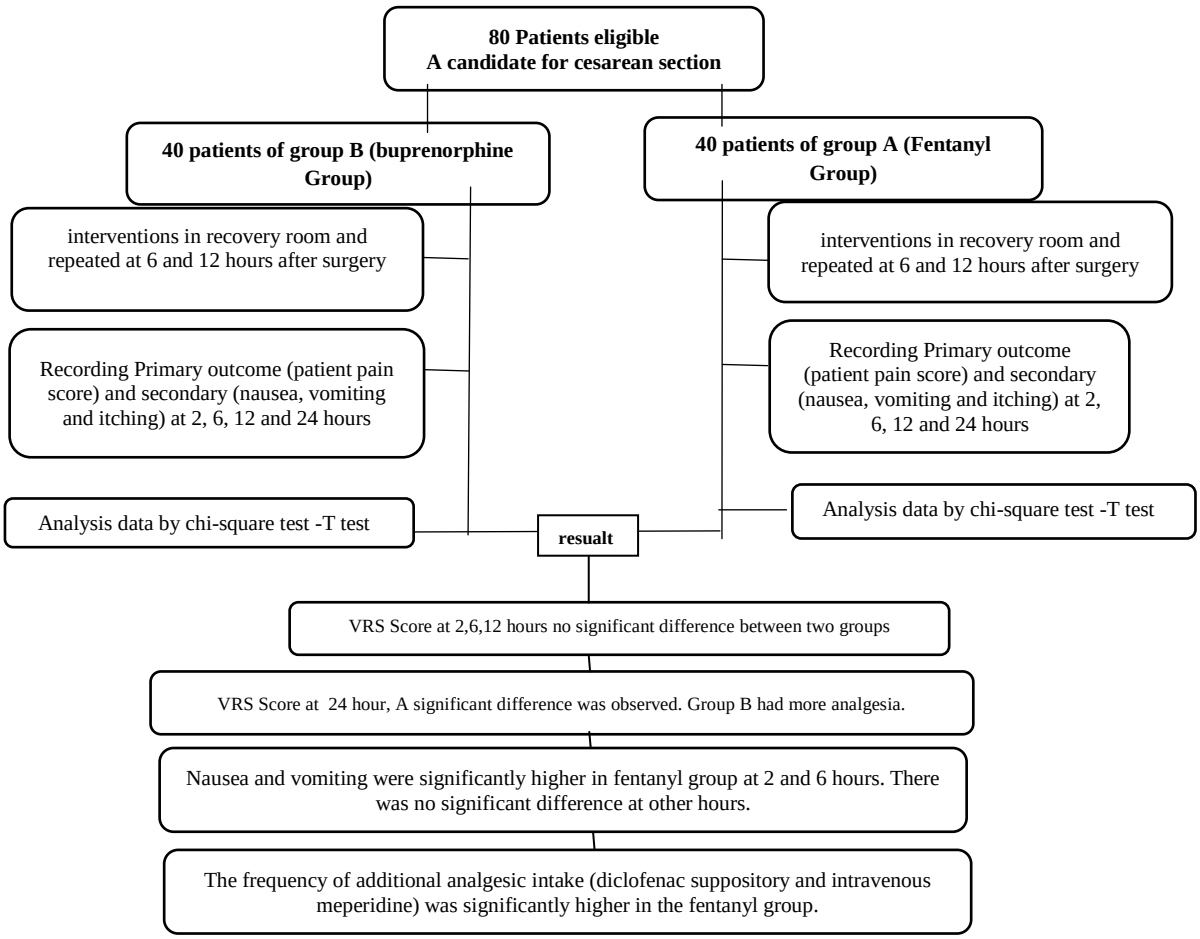

Diagram 1. Flow chart

It was observed that the mean age of patients in the fentanyl pump group was 29.2 ± 5.92 years and 28.3 ± 5.94 years in the buprenorphine group (P = 0.500), the mean weight of the mothers in the fentanyl group was 7 67.74 ± 77.7 and in the buprenorphine, group was 62.75 ± 8.8 kg (P value = 0/81). After age distribution, we observed that 17 patients in the fentanyl group (42.5%) and 16 patients (40%) in the buprenorphine group were at the age of 30 -26 years (P = 0.449) and the level of education was evaluated. It was observed that there was no significant difference between education and study groups (P = 0.617). In the study of the residential area, the majority of both groups was living in the city and this difference was not statistically significant (P = 0.775). Surgery history was also one of the other questions asked from patients. The results showed that 17 patients (42.5%) in first group and 24 patients (60%) in the second group had a history of previous surgery (P = 0.117). In the study of smoking and narcotic use in patients (habits), we observed that neither of patients in both groups had any previous history of smoking and opiate abuse in the past.

Patients' pain was evaluated based on VRS score. The results showed that, except at 24 hours after surgery, at other hours of study, VRS levels in the patients receiving buprenorphine did not significantly differ from the fentanyl group. However, at 24 hours after surgery, pain was significantly lower in the buprenorphine group than the fentanyl group (P = 0.002).

Nausea and vomiting score was evaluated at 2, 6, 12, and 24 hours after surgery. The results showed that the incidence of nausea and vomiting in the buprenorphine group was significantly lower than the fentanyl group at the initial postoperative hour (hours 2 and 6), but as the incidence of nausea and vomiting was decreased in the fentanyl group at 12 hours & 24 hours after surgery; it was observed that there is no significant difference between the two groups.

In this study, the sedation score of patients was also evaluated. The results showed that the sedation score in patients measured was from 1 to 5 did not show significant difference between 2 groups. The frequency of analgesic usage was evaluated in patients. In the results of the study, it was observed that the consumption of analgesics was significantly higher in the fentanyl group than the buprenorphine group, and this difference was statistically significant (P = 0.013).

The time of receiving the first postoperative drug was also evaluated in patients. The results showed that in both groups, the majority of patients receiving the additional pain drug relief received the first dose 2-3 hours after surgery. The results showed that there was no significant difference in the time of first dose of pain relief in two groups (P = 0.681).

Studying the side effect during the first 24 hours after surgery, 7 patients (17.5%) of fentanyl group and 3 patients (7.5%) in buprenorphine group had side effects but no significant side effect was observed in the incidence of adverse effects between the study groups. (P = 0.176).

Table 1. VRS mean pain score of patients in different times after surgery

Time of study (postoperative hours)	Buprenorphine group		Fentanyl group		Score VRS	P value
	Percent	Frequency	Percent	Frequency		
2	15	6	20	8	0	0.517
	40	16	37.5	15	1	
	27.5	11	35	14	2	
	17.5	7	7.5	3	3	
6	47.5	19	25	10	0	0.079
	42.5	17	52.5	21	1	
	7.5	3	7.5	3	2	
	2.5	1	15	6	3	
12	70	28	47.5	19	0	0.115
	30	12	45	18	1	
	0	0	5	2	2	
	0	0	2.5	1	3	
24	97.5	39	72.5	29	0	0.002
	2.5	1	27.5	11	1	
	0	0	0	0	2	
	0	0	0	0	3	

Table 2. Frequency of nausea and vomiting among studied patients in two groups in different times after surgery

Time of study (postoperative hours)	Buprenorphine group		Fentanyl group		Score VRS	P value
	Percent	Frequency	Percent	Frequency		
2	100	40	82.5	33	1	0.022
	0	0	10	4	2	
	0	0	7.5	3	3	
6	100	40	87.5	35	1	0.021
	0	0	12.5	5	2	
	0	0	0	0	3	
12	95	38	87.5	35	1	0.409
	5	2	10	4	2	
	0	0	2.5	1	3	
24	100	40	95	38	1	0.152
	0	0	5	2	2	
	0	0	0	0	3	

Table 3. The number of additional admissions by patients in the both groups

Variable	Number	Buprenorphine group		fentanyl group		P value
		Percent	Frequency	Percent	Frequency	
Drug use	No use	42.5	17	40	16	0.013
	First time	32.5	13	55	22	
	Second time	25	10	2.5	1	
	Third time	0	0	2.5	1	

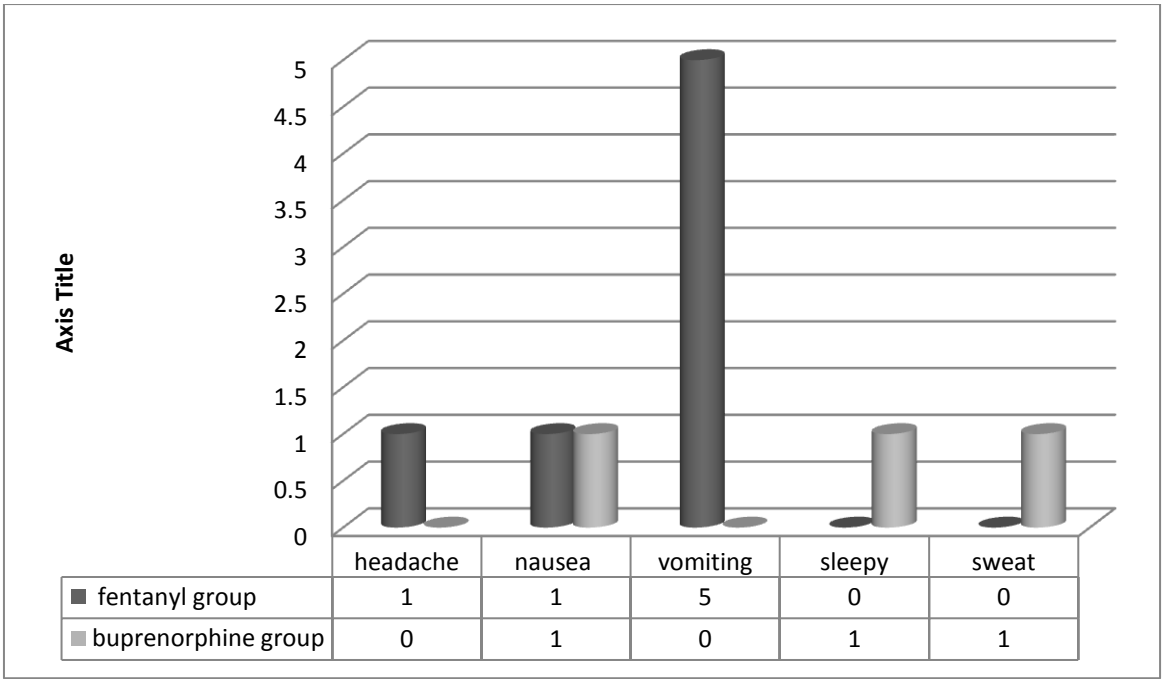

Diagram 2. Frequency of patients by incidence of side effects

In this study, all infants in both groups were evaluated within 24 hours and no adverse effects were observed in neonates. In many studies, the blood levels of drugs during breast feeding following the material use of fentanyl & buprenorphine, are negligible in the neonate and have no side effects [25,5]. One of the limitations of the study is the lack of measurement of the opiate blood concentration the infant.

4. DISCUSSION

In this study, 80 patients were evaluated in two groups (the first group receiving fentanyl pumps & placebo pill, the second group receiving the normal saline pump and buprenorphine (0.4 mg pill). The results showed that only 24 hours after surgery, pain was significantly lower in the buprenorphine group than the fentanyl group (P <0.05), and the level of pain in the fentanyl group was higher than the other group. In a study by Arshad et al. [26], conducted on 60 patients, patients were divided into two groups, the first group administered transdermal buprenorphine and the second group administered transdermal fentanyl. The results showed that, at the beginning of the study, the visual analogue scale of the buprenorphine group was 4.47 and 4.80 in the fentanyl group. Patients followed up within 3 days and observed that in the buprenorphine group, VAS of patients was decreased while the score was increased in the fentanyl group. A study by Chang et al. [27], in Taiwan states that there is no statistically significant difference between the VAS pain score in recipients of buprenorphine and morphine. In study by Akhavan Akbari et al. [19], that conducted in Ardebil, Lower limb orthopedic patients were divided into two groups. One group received morphine and another group received sublingual buprenorphine pill. Patients' pain score at 1, 8, 16 and 24 hours, amont of meperidine usage, and side effects including nausea and vomiting, sedition, and itching were recorded in the first 24 hours after surgery. The mean pain severity in the sublingual buprenorphine group was significantly lower than morphine group. The mean of consumed meperidine at 24 hours postoperatively in the sublingual buprenorphine group was significantly less than morphine group. Another study by OIFA et al. [28], compared buprenorphine and morphine and found that there was no significant difference in the anti-nociceptive effect of the two drugs. In a study by Niyogi et al. [29], the rate of receiving tramadol in buprenorphine was significantly less than the placebo group. In other study by Azizi et al. [30], comparing the effect of injectable meperidine and sublingual buprenorphine on pain relief after colorectal surgery in Rasool Akram Hospital, the results showed that the deference pain intensity in recovery room between the 2 groups was not significant, but in subsequent measurements, pain in the buprenorphine recipient group was always less than the injectable meperidine group. In a study by Tröster et al. [31], comparing pain relief in both buprenorphine (1.5 µg / kg) and fentanyl (1.5 µg / kg) and their combination (0.75 ± 0.75 µg / kg), the analysis of the results showed that the combination of the two drugs had increased pain reduction.

In a study by Desai et al. [24], that evaluated the efficacy and safety of buprenorphine and tramadol in the treatment of pain after femoral neck surgery, it was observed that the mean of VAS score before surgery and at 4 and 12 hours postoperatively had no significant difference between the two groups. However, at 24 hours after surgery, up to 7 days after surgery, the mean VAS score in the buprenorphine group showed a significant decrease compared to tramadol. It was also observed that all patients receiving tramadol needed to receive another analgesic drug during treatment but in the buprenorphine group, only 68% of patients (P <0.001) received other analgesic drug. In a study by Khandeparker et al. [32], 50 patients undergoing cardiovascular major surgery were enrolled and randomly divided into buprenorphine and meperidine groups. The results showed that the duration of buprenorphine is longer than meperidine. In the buprenorphine group, 68% of patients needed single dose of buprenorphine to control their pain after surgery. In the meperidine group, only 36% of the patients received single dose of meperidine after surgery. In the buprenorphine group, the time interval of the next dose was longer. Before the first dose, the severity of pain in both groups was similar, but after the first dose at the end of the 4-hour period, the severity of pain in the buprenorphine group was Less than meperidine group. Comparing the analgesic effects of buprenorphine with other drugs, its efficacy is as strong as other opiates. In the study by Desai et al. [24], the score of nausea and vomiting in tramadol recipients was significantly higher than the buprenorphine group (P <0.001) In the study of nausea and vomiting at different hours, it was observed that the incidence of nausea and vomiting in the buprenorphine group was significantly lower than the fentanyl group in 2^{nd} and 6^{th} hours after surgery, but at the other hours no such difference was observed. In a study by Niyogi et al. [29], none of the patients receiving buprenorphine were nauseous, but 3 patients were nauseous in the placebo group, which was not statistically significant. In the study of Akhavan Akbari and colleagues [19], the incidence of nausea and vomiting was not significantly different between the two groups. Therefore, this drug seems to

have very little effect on the incidence of nausea and vomiting in patients. In assessing the sedation score after evaluation, there was no significant difference between the two groups. In the study of Arshad et al. [26], there was no significant difference between the two groups. In this study, the change in sedation score of the fentanyl group did not show a significant difference from that of the buprenorphine group. In the study of Akhavan Akbari and colleagues, there was no significant difference in terms of sedation score between the two groups [19].

Studying the side effect in both groups receiving fentanyl and buprenorphine, adverse events were no significantly different between the two groups.In the study of Tröster et al. [31], the incidence of drug side effects was not significant in the three groups of fentanyl, buprenorphine and the combination of these two, and the most common side effects was nausea and vomiting in all three groups. In a study by Niyogi et al. [29], hypoxia, respiratory depression, Arrythmia, and hypotension accrued in none of the patients receiving buprenorphine, and no one complained of nausea. In a study by Desai et al. [24], the incidence of side effects in the buprenorphine recipient group was significantly lower than the tramadol recipient group. Studying side effects of other narcotics and buprenorphine, it was observed that the side effect of buprenorphine was very low and there was no significant difference. This result was observed in the present study as well.

5. CONCLUSION

The results of this study showed that sublingual buprenorphine is an effective medication for reducing postoperative pain in patients. Due to its low cost and easy administration, it can be used routinely in patients. Limitations of study include the lack of pain relief follow up after 24 hours, and the lack of control group due to ethical considerations. It is recommended that another study on the analgesic effects of these drugs be performed in a long-term spectrum of time as well as studies on other surgeries and with different anaesthetic techniques and if possible, the blood concentration of opiates be measured in the following studies.

CONSENT

The patients participated in the research and consent forms completed, we received and stored consent form by each patient. All provided information and responses of the questionnaire were confidential.

ETHICAL APPROVAL

The present study was carried out by obtaining the introduction letter and permission from the research deputy of Ardabil medical science university and confirmation of the ethics committee from the research ward of university and registered in the IRCT system with the IRCT 2017010923559N14 number.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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