



Randomised Controlled Trial

The effect of preoperative sublingual buprenorphine on postoperative pain after lumbar discectomy: A randomized controlled trial

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ABSTRACT

Background: Lumbar discectomy is one of the most common surgical procedures performed to manage pain caused by the protrusion of an intervertebral disc. Postoperative pain management can be challenging and might lead to increased intake of opioids. **Objective:** The aim of this study was to determine the effect of preoperative sublingual buprenorphine on severity of pain after lumbar disc surgery and postoperative intake of morphine.

Methods: This Randomized clinical trial study was performed on 78 patients who were selected for lumbar discectomy surgery. Patients were randomly divided into two groups of 39 patients, each. Patients in the buprenorphine and placebo group received 2 mg buprenorphine sublingual, and placebo 1 h before surgery. Severity of pain, nausea, vomiting and pruritus and intake of opioids in the two groups were evaluated and recorded 1, 6, 12 and 24 h after surgery. Data were analyzed using SPSSv21.

Results: There was a significant difference in pain score in buprenorphine group at 1, 6, 12, and compared with placebo ($P < 0.005$). In the control group, the use of analgesics was more than the buprenorphine group. In the first hours after surgery (1–6 h), the incidence of nausea in the buprenorphine group was significantly lower than of the control group ($P < 0.05$). However, at 12 and 24 h, this difference was not observed, $p > 0.05$. There was no significant difference in incidence of side effects (nausea, vomiting, pruritus) in the two groups ($P > 0.05$).

Conclusion: Sublingual buprenorphine in postoperative pain management is an effective and low dose drug. Due to its simpler administration, it is recommended to relieve postoperative pain after lumbar disc surgery.

1. Introduction

Acute postoperative pain is one of the common complaints [1,2]. Its treatment is one of the important health-related issues and a number of guidelines have been recommended to treat the pain [3,4]. After surgery, pain assessment is considered as a fifth vital sign [5]. Inadequate pain management is associated with gastrointestinal and respiratory dysfunction [6]. Increased physiological stress impairs immunity and delays the healing process [7]. Pain following lumbar discectomy is a common complaint in patients, that leads to increased requirement of opioids [8,9], and delayed hospital discharge [10,11]. This procedure is commonly performed in patients presented with radiculopathy or lumbar spine-related presentation that cannot be treatment with conservative therapy [12,13].

Drugs, especially their injectable form, are widely used as the first

line of treatment for pain relief in relieving acute postoperative pain, including lumbar spine surgery [14,15]. Intense pain cannot be managed by single therapy [16]. Furthermore, high dose of analgesics used to manage pain, is likely to be associated with side effects like respiratory depression, nausea, vomiting, urinary retention, pruritus, drowsiness, or postoperative ileus [17,18].

Buprenorphine is a semisynthetic opioid that binds to mu, kappa and delta opioid receptors. In 1981, parenteral buprenorphine was introduced as an analgesic in the United States. Its sublingual form at a dose of 0.2–0.4 mg was then introduced in Europe. Sublingual buprenorphine is used to maintenance therapy to prevent opioid abuse [19,20]. Studies on the use of sublingual buprenorphine in the control of acute postoperative pain and orthopedic injuries (acute bone fractures) in the emergency department have shown that sublingual buprenorphine is therapeutically effective in managing the pain and has few minor

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complications [21,22]. A recent systemic review and meta-analysis concluded that effectiveness of morphine and buprenorphine is same in terms of analgesic effects. Additionally, buprenorphine is likely to be associated with reduced incidence of pruritus [23].

This study is designed to evaluate the effects of sublingual buprenorphine for the management of postoperative pain among lumbar discectomy patients. We hypothesize that intake of buprenorphine is likely to reduce postoperative need of morphine and associated side effects.

2. Methods

This study was a controlled double-blind randomized clinical trial that aimed to determine the effect of preoperative sublingual buprenorphine on postoperative pain intensity among patients undergoing elective discectomy referred to (XXX). These patients underwent discectomy for 1 or 2 lumbar vertebrae and were under class American Society of Anesthesiologists (ASA) physical status I and II. Written consent was obtained from all the patients for the participation in the study. Inclusion criteria for patients was confirmation of the diagnosis by physical examination, CT scan MRI, the patient's desire to participate in the study and gain informed consent, candidate for non-emergency discectomy, aged between 18 and 35 years and insensitivity to buprenorphine. Patients unwilling to continue participation in the study at any time, those need emergency discectomy, involvement of more than two lumbar discs, patients taking narcotic painkillers up to 24 h before the intervention, alcohol or drug abuse patients and those with perioperative and/or postoperative complications were excluded from the study.

Patients meeting inclusion criteria were assigned to the intervention or placebo groups using random allocation software. To determine the sample size, the results of the study by Abdol Hosseinpour et al. were considered with the test power 71%, and confidence level 35%. The study range was determined using the comparison formula between the mean in G-power software which was 71. We included 21 people in the intervention group and 21 people in the buprenorphine group.

Then, the patients who met the inclusion criteria were divided into buprenorphine group A and placebo group B. Prior to surgery, patients were provided with adequate information and training on how to determine the severity of postoperative pain, nausea, vomiting, and pruritus using the Visual Analog Scale (VAS) and how to use a PCA (patient-controlled analgesia) pump.

The patients in the intervention group received one buprenorphine tablet (manufactured by Faran Shimi) sublingually, and the patients in the placebo group received one placebo, sublingually 1 h before the operation. Anesthesia protocol included; premedication with midazolam at a dose of 0.01 mg/kg and fentanyl at a dose of 2 mc/kg, then induction with sodium thiopental at a dose of 4.4 mg/kg/IV and atracurium at a dose of 0.5 mg/kg/IV and intubation was performed with Armod tube No. 5, 7 and 8. During the surgery, at the rate of 0.1 mg/kg morphine was administered intravenously along with atracurium 0.01 mg/kg and nitrous oxide gas and isoflurane or sevoflurane inhalational anesthesia were used as maintenance anesthetics.

After surgery, patients were brought to the recovery ward where PCA pump was provided containing 25 mg of morphine and 1 g of paracetamol and the rest up to a volume of 51 cc of normal saline (total volume of the pump). The amount of narcotics used by patients in the two study groups after recovery was recorded at 2, 4, 6, 12, and 24 postoperative hours. If the pain was more than 5, according to the VAS criteria, the 3 mg of morphine was increased. Pain intensity, nausea, vomiting and itching was also recorded in the two groups. In addition, the amount of fentanyl consumed during anesthesia was recorded. Primary outcomes of the study were the intensity of the pain and the use of analgesia whereas, itching, vomiting and nausea were secondary outcomes. Patients' BMI, age, level of education and gender were also recorded as demographic variables. The evaluation was performed by a nurse who

did not have information about the study groups and received sufficient training in this field. The surgery was performed by a surgeon and placebo was designed at the School of Pharmacy, Sari. The placebo tablet was identical to buprenorphine.

This clinical trial was carried out in Iran at the center of clinical trial registered with a special registration code: (XXX).

The obtained data was entered in SPSS v24 software for statistical analysis. The variables were described using percentage, mean, standard deviation and range. Repeated measurement analysis was used to compare the mean pain intensity between each group and between the two groups. To compare the frequency of nausea, vomiting and pruritus in patients, Cochran and Generalized estimating equations (GEE) were used. $P < 0.05$ was considered to be statistically significant.

This study was approved by the Research Ethics Board of (XXX).

Unique Identifying Number (UIN): researchregistry6526.

The study is reported in accordance with CONSORT 2010 criteria [24].

3. Results

Of 78 patients included in the study, there were 27.8% males and 51.3% females in group A and 51.3% males and 27.8% females in group B. The results of Chi-square test showed that the gender distribution was not significantly different in the two groups, $p = 0.821$, Fig. 1.

Age distribution among the two groups is reported in Fig. 2. In group A, 33.3% patients were under 21 years, 31.7% were 21–51 years, 12.7% were aged 52–61 years and 23.1% were above 61 years of the age. In placebo group, 21.1% were under 21 years, 25.6% were aged 21–51 years, 15.2% were 52–61 years and 18.3% were aged above 61 years. The results of chi-square test showed that the two age groups had the same age distribution, $p = 0.833$. The mean age of the patients in group A and B was 26.73 ± 11.71 years and 25.13 ± 11.31 years, respectively.

On 1st postoperative hour, the mean VAS score in group A and B was 1.64 ± 1.5 and 4.23 ± 1.42 , respectively. The difference in the two groups were statistically significant, $p < 0.001$. On 6th postoperative hour, the mean VAS score in group A and B was 1.09 ± 0.85 and 2.44 ± 1.45 , respectively. The difference in the VAS score at 6th postoperative hour was also significantly different in the two groups, $p < 0.001$. At 12th postoperative hour, the VAS score among the two groups was significantly different, $p = 0.045$ whereas, 24 h after the surgery, the VAS score was not significantly different in the two groups, $p = 0.44$, Table 3 (Table 2). Friedman test showed that over the time, both the groups underwent significant changes in the pain intensity and buprenorphine significantly reduces early postoperative pain, $p < 0.001$ (Table 1).

The intensity of nausea in group A and B, 1 h after the surgery was recorded to be 0.52 ± 0.128 and 1.14 ± 0.41 , which was not significantly different, $p = 0.404$. 6 h after the surgery the intensity of nausea was 0.32 ± 0.051 in group A and 0.16 ± 0.026 in group B. The difference was also not significant at this interval, $p = 0.985$. Similarly, 12 and 24 h after the surgery, the mean intensity of nausea was 0.16 ± 0.026 and 0.16 ± 0.026 , respectively in group A and was 0.00 in group B, respectively. The differences were not seen to be significantly different, $p = 0.317$, respectively. However, overall, there was a significant reduction in the intensity of nausea in both the groups, $p = 0.003$, with the time).

18.3% patients in group A and 2.6% in group B had no incidence of vomiting, throughout the period. In group A, the overall frequency of vomiting was 1.641 ± 0.778 whereas, it was 1.92 ± 0.35 in group B. The frequency of vomiting was not different in the two groups, $p = 0.068$, seen from U-Whitney test.

The intensity of itching in group A and B, 1 h after the surgery was 0.502 ± 0.103 and 0.81 ± 0.23 , respectively. The difference was not significantly different in the two groups, $p = 0.621$. Following 6 h of the surgery, the mean intensity of itching in group A was 0.66 ± 0.13 and 0.27 ± 0.78 , respectively. The two groups were not significantly

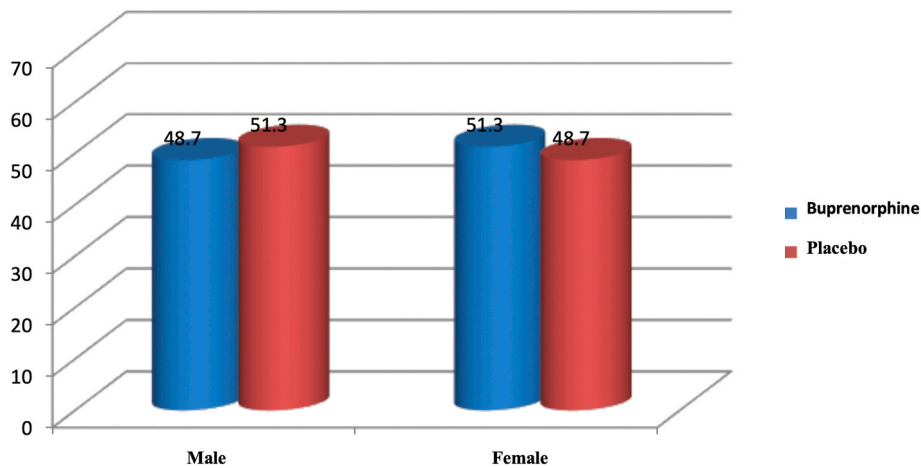


Fig. 1. Distribution of patients' gender percentage in two treatment groups.

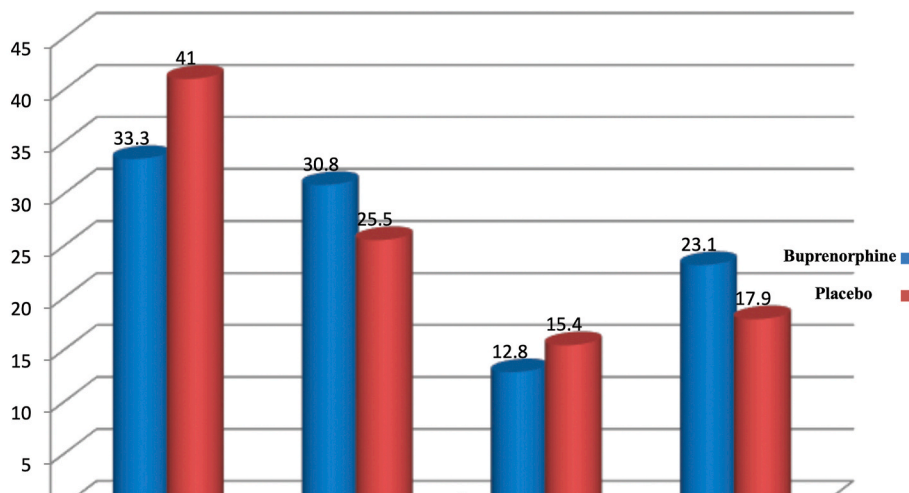


Fig. 2. Evaluation of age distribution of patients in two treatment groups.

different at this time interval, $p = 0.672$. At postoperative 12 and 24 h, the intensity of itching was 0.00 in group B, respectively whereas it was 0.22 ± 0.05 and 0.16 ± 0.03 , respectively. These differences were also not significantly different, $p = 0.155$ and $p = 0.317$, respectively. The overall difference in the intensity of itching at different time interval was not different in group A, $p = 0.801$, however, it was significantly different in group B, $p = 0.029$ (Table 3).

The results showed that in the buprenorphine group 17.9% and in the placebo group 2.6% did not vomit. Among the buprenorphine group among those who felt nausea, 82.1% of the vomiting intensity was equal to the severity of two. In the placebo group 64.9%, the severity of vomiting was two and 2.6% the severity of vomiting was one. The results of comparing Chi-Square

Test in terms of vomiting severity were not significantly different between the two groups and also the results of U-Whitney test showed that the two groups were not significantly different in terms of mean vomiting severity.

The results showed that both buprenorphine and placebo groups received analgesia. In the group A, 2.56% in 6 h and 15.38% group in B received analgesia. At time 6–12 h, 7.69% in buprenorphine group and 12.82% in placebo group received the drug. At 12–24 h 2.56% in group A and 7.69% patients in group B required analgesia. The results of Fisher's exact test did not show difference between the two groups in terms of overall morphine intake $p = 0.66$.

Maximum morphine intake was 3 mg in both groups following 24 h

of the surgery.

4. Discussion

In the study conducted by Azizi et al., there was no significant difference between the sublingual buprenorphine and injectable pethidine groups, in terms of the intensity of the pain. However, the pain intensity was always lower in the sublingual buprenorphine group than pethidine [25]. There was no statistically significant difference in the incidence of side effects in the two groups. Patients' satisfaction in the sublingual buprenorphine group was higher than the injectable pethidine group. In the present study, the severity of pain in the sublingual buprenorphine group was significantly reduced compared to placebo group within 24 h, and the complications including nausea, vomiting and itching, and the need for additional narcotics were similar in the two groups.

In the study by Issazadehfar et al. [26], the efficacy of sublingual buprenorphine (6 and 12 postoperative hours) in controlling pain after cesarean section on 80 patients was evaluated. The amount of analgesic administered in the control group was higher than the buprenorphine group. At 2 and 6 postoperative hours, the incidence of nausea and vomiting in the buprenorphine group was significantly lower than in the control group, but no such difference was observed at other time intervals. There was no significant difference between the sedation score and the incidence of side effects in the two groups. They concluded that buprenorphine is an effective drug in reducing postoperative and due to

Table 1
Determining the severity and mean of pain in the two groups during the study.

Time	Severity	buprenorphine		Placebo		p-value	Buprenorphine		Placebo		p-value
		Frequency	%	Frequency	%		Mean	Standard deviation	Mean	Standard deviation	
1 h	0	15	38.5	0	0	0.000	1.64	1.50	4.23	1.42	0.000
	1	1	2.6	0	0						
	2	11	28.2	2	5.1						
	3	8	20.5	12	30.8						
	4	3	7.7	11	28.2						
	5	1	2.6	7	17.9						
	6	0	0	5	12.8						
	7	0	0	0	0						
6 h	0	22	56.4	2	5.1	0.000	0.85	1.09	2.44	1.54	0.000
	1	4	10.3	8	20.5						
	2	11	28.2	14	35						
	3	1	2.6	6	15.4						
	4	1	2.6	6	15.4						
	5	0	0	1	2.6						
	6	0	0	2	5.1						
	7	0	0	0	0						
12 h	0	26	66.7	16	41	0.032	0.62	1.02	1.05	1.19	0.045
	1	6	15.4	11	28.2						
	2	3	7.7	9	23.1						
	3	4	10.3	1	2.6						
	4	0	0	1	2.6						
	5	0	0	1	2.6						
24 h	0	34	87.2	31	79.5	0.744	0.23	0.67	0.31	0.69	0.44
	1	2	5.1	5	12.8						
	2	2	5.1	2	5.1						
	3	1	2.6	1	2.6						
P-value							0.000		0.000		

- 1.Fisher’s exact test (comparison of pain intensity distribution).
- 2.U Whitney test between groups.
- 3 Friedman (case comparison).

Table 2
Evaluation of nausea in both treatment groups during the study.

Time	Severity	buprenorphine		Placebo		p-value	buprenorphine		Placebo		p-value
		Frequency	%	Frequency	%		Mean	Standard deviation	Mean	Standard deviation	
1 h	0	36	92.3	34	87.2	0.296	0.128	0.52	0.410	1.14	0.404
	1	2	5.1	0	0						
	2	0	0	1	2.6						
	3	1	2.6	3	7.7						
	5	0	0	1	2.6						
6 h	0	38	97.4	38	97.4	1.00	0.51	0.32	0.26	0.16	0.985
	1	0	0	1	2.6						
	2	1	2.6	0	0						
12 h	0	38	97.4	39	100	1.00	0.26	0.16	0.000	0.00	0.317
	1	1	2.6	0	0						
24 h	0	38	97.4	39	100	1.00	0.26	0.16	0.000	0.00	0.317
	1	1	2.6	0	0						
P-value							0.300		0.003		

Table 3
Evaluation of pain itching and group therapy during the study.

Time	Severity	buprenorphine		Placebo		p-value	buprenorphine		Placebo		p-value
		Frequency	%	Frequency	%		Mean	Standard deviation	Mean	Standard deviation	
1 h	0	37	94.9	36	92.3	0.615	0.103	0.502	0.231	0.810	0.621
	1	1	2.6	0	0						
	3	1	2.6	3	7.7						
6 h	0	37	97.4	36	92.3	0.615	0.128	0.656	0.77	0.270	0.672
	1	1	2.6	3	7.7						
	4	1	2.6	0	0						
12 h	0	37	94.9	39	100	0.247	0.051	0.223	0.000	0.00	0.155
	1	2	5.1	0	0						
24 h	0	38	97.4	39	100	0.500	0.026	0.160	0.000	0.00	0.317
	1	1	2.6	0	0						
P-value							0.801		0.029		

fewer side effects, it can be used routinely in patients. Chang KY et al. [27] also reported that the among 50 patients undergoing elective lumbar fusion, buprenorphine and morphine via PCA pump has similar analgesic effects at 6, 24, 48 postoperative hours. In the study by Akbari et al. [28], the efficacy of sublingual buprenorphine (0.4 mg, every 8h hours) with morphine (using PCA) in controlling the pain following orthopedic surgery in 90 patients at 3, 6 and 12 h was reported. The mean pain score was significantly lesser in buprenorphine group. However, the incidence of side effects was not significantly different in the two groups. Studies have also suggested that chronic pain patients undertaking high dose of opioids can be converted to sublingual buprenorphine [29].

Our study is based on a small sample size and effects on hemodynamic parameters such as blood pressure, heart rate and rate of respiration are not involved in the study. Further studies with different dosage, more variables and greater sample size are therefore required to validate these outcomes.

Conclusion

Sublingual buprenorphine is effective for the management of postoperative pain following lumbar discectomy, compared to placebo. It is safe and has lower side-effects.

Provenance and peer review

Not commissioned, externally peer-reviewed

The surgery was performed by a surgeon and placebo was designed at the School of Pharmacy, Sari. The placebo tablet was identical to buprenorphine.

This clinical trial was carried out in Iran at the center of clinical trial registered with a special registration code: **IRCT20201026049147N1**.

This study was approved by the Research Ethics Board of Mazandaran University of Medical Sciences, Sari, Iran (IR.MAZUMS.IMAM-HOSPITAL.REC.1397.007).

<https://ethics.research.ac.ir/ProposalCertificateEn.php?id=19777&Print=true&NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true>

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Human and animal rights

No animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Disclosure

Approval of the research protocol: N/A
Informed Consent: Informed consent was obtained from each participant.

Consent for publication

Informed consent was obtained from each participant.

Availability of data and materials

All relevant data and materials are provided with in manuscript.

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Contributors' statement page

Dr. Farshad Hassanzadeh Kiabi and Dr. Abdolmajid Gholinataj Jelodar: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Seyed Abdollah Emadi and Dr. Hojat Deylami: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr. Misagh Shafizad: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Declaration of competing interest

The authors deny any conflict of interest in any terms or by any means during the study.

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