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Effectiveness of Sublingual Buprenorphine and Fentanyl Pump in Controlling Pain After Open Cholecystectomy

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Abstract

Background: The proper management of postoperative pain improves patients' quality of life, accelerates early postoperative recovery, shortens hospitalization period, and reduces medical costs. This study aimed to compare the effectiveness of intravenous fentanyl pump and sublingual buprenorphine tablet in controlling pain after open cholecystectomy.
Objectives: Evaluating the effectiveness of sublingual buprenorphine in reducing postoperative pain and complications after open cholecystectomy.
Methods: This study was a double-blind, randomized clinical trial. The study population encompassed those candidates undergoing open cholecystectomy, patients with ASA class I and II, individuals undergoing no other concomitant surgery, and patients in the age range of 20 - 50 years. The first group received sublingual buprenorphine 6, 12, and 18 hours after the first administration. The second group received fentanyl as patient-controlled analgesia (PCA) for 24 hours. Then nausea, vomiting, sedation, and Visual Analog Scale (VAS) scores were evaluated at the beginning, 2, 6, 12, 18, and 24 hours after surgery. The collected data were analyzed using SPSS software version 20.
Results: The mean age of the patients in the buprenorphine and fentanyl groups were 44.8 $\pm$ 5.5 and 42.8 $\pm$ 7.1 years, respectively. In this study, 22.5% of the patients in the buprenorphine group and 35.5% of the patients in the fentanyl group were male. During 6 and 24 hours after surgery, the pain level regarding the VAS scores was significantly lower in the buprenorphine group than in the fentanyl group; however, analgesic consumption was higher in the fentanyl group. In the early hours after surgery (2 and 6 hours), nausea and vomiting were lower in the buprenorphine group than in the fentanyl group even though the difference was not significant.
Conclusions: This study suggests buprenorphine as an effective drug for patients to reduce postoperative pain because of its limited complications, inexpensiveness, and more convenient administration method.

Keywords: Postoperative Pain, Sublingual, Buprenorphine, Fentanyl, Visual Analog Scale, Patient-Controlled Analgesia

1. Background

The management of postoperative pain requires multi-specialized teams. Awareness of analgesics and their various applications allows us to select the most appropriate medicine to control postoperative pain. In this regard, an ideal medicine to control postoperative pain should be easily accessible and inexpensive, with minimal complications and no need for prescription by professionals. Moreover, since these drugs are available in different forms and doses, an ideal painkiller should not reveal a remarkable interaction to be used in critically-ill patients, including male and female patients with underlying diseases in different age groups (1, 2).

Postoperative pain is among the patients' best-known difficulties, which arouses dissatisfaction, increases medical costs, and prolongs the hospitalization period. The postoperative phase can also be associated with other problems such as nausea, vomiting, hypotension, and chills; hence, the pain management and control are of great importance (3, 4). Bearing painful upper abdominal incisions increases the abdominal muscles' tone during exhalation and decreases diaphragm function and pulmonary efficiency. This would, in turn, reduce deep breathing power, leading to strong cough and hypoxemia, secretion retention, atelectasis, and pneumonia (5, 6). Different treatment modalities, including analgesics (opioids and NSAIDs), anesthetics, acupuncture, and so forth (3, 4, 7-10), are proposed to manage accompanied compli-

cations. The most commonly used treatment is opioids administration because of its remarkable pain management effects. Although opioids are the most commonly prescribed painkillers, there has been a great attempt to replace them with an effective alternative or adjunctive drugs to shrink the side effects (11). Some example alternative are dexmedetomidine, ketamine, paracetamol, gabapentin, pregabalin, clonidine, amantadine, lidocaine, ketorolac, melatonin, and magnesium sulfate, whose role in postoperative pain management has been already examined (12-16). Although the intravenous administration of opioids provokes the rapid onset of high-quality analgesics and is less expensive than PCA pain control pump, the plasma level of this drug is highly fluctuated, and its analgesic efficiency decreased over a long period. Continuous opioid infusion induces an appropriate painless period with the lowest serum level of the drug. It should be pointed out that the high plasma levels of the drug have not been observed for the opioid treatment.

On the other hand, its prescription requires additional equipment and is time-consuming. However, there are highly effective analgesic drugs, which are easy to use and have been successfully implemented (17). An example is buprenorphine, which is the partial agonist of opioid receptors and not only is used sublingually but also has exhibited acceptable analgesic effects in some surgeries (18, 19).

2. Objectives

This comparative study aimed to assess the effectiveness of intravenous fentanyl pump and sublingual buprenorphine tablet in controlling pain after open cholecystectomy.

3. Methods

The statistical population of the study encompassed patients referred to Fatemi and Imam Khomeini Teaching Medical centers in Ardabil, Iran, during 2019 - 2020. The study population was limited to those candidates undergoing open cholecystectomy, patients with ASA class I and II, individuals undergoing no other concomitant surgery, and patients in the age range of 20 - 50 years. Patients with opium consumption records, the records of neurological drugs, active asthma, ASA $\geq$ 3, and records of other concomitant surgeries, which were prolonged and complicated, were excluded from this study. Herein, the error type I, study power, and mean difference were considered 5, 80, and 0.7%, respectively, according to which the sample size in each group was 40 persons.

$$N = \frac{2 \times \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times P\,(1-P)}{(P_1 - P_2)^2}$$

$$P = P_1 + \frac{P_2}{2}$$

$\alpha = 0.05$; $\beta = 80\%$

To observe the principles of medical ethics, the collected data was kept confidential, and the results were reported anonymously. Moreover, the patients' written informed consent was obtained before the study. The study proposal was submitted to the Ethics Committee of the Ardabil University of Medical Sciences, and they confirmed the study (code: R.Arums.REC.1398.103). The study was also registered in the Iranian Clinical Trial Center (No. IRCT20190901044665N1).

Upon patients' agreement, 80 patients were selected using the convenient sampling method and were then assigned to two groups using the random block method with four blocks (AABB). The same method was used for anesthesia in all patients. The general anesthesia program in the patients was as follows: (1) ringer infusion (5 - 10 mL/kg); (2) midazolam (20 ug/kg); (3) lidocaine (1 mg/kg); and (4) fentanyl (2 ug/kg) were injected as pre-anesthetic drugs. Then anesthesia induction was performed using propofol (2 - 3 mg/kg) and atracurium (0.5 mg/kg). N_2O was used, and 5 mg of morphine was intravenous injected during the surgery to maintain the anesthesia with isoflurane 1.2 Mac with oxygen.

Given that the study was randomly blocked, buprenorphine and placebo tablets, fentanyl pumps, and placebo pumps were separately placed in two different packs (containing one pump and one tablet) as pack A and pack B. The pack A included sublingual buprenorphine tablets and placebo pump, and the pack B encompassed placebo tablets and fentanyl pumps. None of the patients were aware of the taken drugs (type 1 blindness), and the drug injector (anesthesia technician) also had no knowledge of the content of the packs (type II blindness). Regarding the research groups, either the pack A or pack B was distributed. The administration of the packs was initiated after cholecystectomy and during the recovery stage. In the first group, in the recovery stage, a sublingual buprenorphine tablet (0.4 mg) was administered and repeated 6, 12, and 18 hours after the first dose. The intravenous placebo pump, containing 50 cc of normal saline, was also installed during recovery and continued for 24 hours. In the second group, a sublingual placebo tablet was administered in the recovery stage, and an intravenous fentanyl pump, containing 40 cc of fentanyl and 10 cc of normal saline, was injected for 0.5 cc (20 mg) STAT and pumped up to 24 hours. In the fentanyl pump treatment case, PCA (half cc:

20 mg/time injection) was injected every other fifteen minutes, and the placebo tablets were repeated 6, 12, and 18 hours after the first dose. In both groups, the pain score was then assessed regarding the visual analog scale (VAS), nausea and vomiting scores, and Ramsey sedation scale during the recovery stage 2, 6, 12, 18, and 24 hours after surgery. Regarding the uncontrolled pain and the need for analgesics, 3 $\geq$ VAS diclofenac suppository (100 mg) was used every 6h and recorded in both groups.

Nausea and vomiting in the patients were scored using the N&V Scale (1: no nausea and vomiting; 2: nausea; 3: nausea and vomiting once or twice; 4: nausea and vomiting for more than twice) (18). The patients' pain was rated based on the Verbal Rating Scale ranging from zero to five regarding pain intensity. In this scale, "painless" was at one end of the continuum and "the most severe pain" at the other end. The scores zero, one, two, three, four, and five represent no pain, mild pain, moderate pain, severe tolerable pain, severe but unbearable pain, and the most severe pain, respectively (18, 19). Furthermore, sedation and sleep issues were recorded based on Ramsey scoring scale ranging from 0 to 5, where we have 0: restless; 1: calm and alert; 2: sleepy; 3: confused but responding to verbal commands; 4: no response to verbal commands; and 5: failure to respond to painful stimulations (15). Meanwhile, a checklist containing patients' demographic information, pain score, nausea and vomiting rate, sedation score, and drug side effects were used immediately after the surgery and 2, 6, 12, 18, and 24 hours after surgery for all patients. After completing the checklists, the data were imported into SPSS software (version 20). The relationship between qualitative and quantitative analyses was respectively examined using the chi-square test and *t*-test. The statistical significance was set as $P < 0.05$. The descriptive results are presented as mean $\pm$ standard deviation.

4. Results

Patients with the mean age of 44.8 $\pm$ 5.5 years in the fentanyl pump group and 42.8 $\pm$ 7.1 years in the buprenorphine group were included in this study(P = 0.17). Regarding the age intervals, 26 patients in the fentanyl group (65.0%) and 19 patients (47.5%) in the buprenorphine group were 45 years and above (P = 0.171). The evaluation of the patients' gender revealed an insignificant difference between the study groups, wherein 35.5% (n = 14) of the fentanyl group were male, and 22.5% (n = 9) of the buprenorphine group were female (P = 0.162).

A majority of the patients in both groups were residing in Ardabil, Iran, and the difference in terms of the place of resident was not statistically significant (P = 0.321). The patients' record was also examined. IN this regard, 28 patients (30%) in the buprenorphine group and 32 patients (80%) in the fentanyl group had negative records of the disease and no previous records (P = 0.220). The patients' level of the education was checked, and no significant difference was observed between the studied groups in this regard (P = 0.459).

Class ASA I and Class ASA II were 80 and 20% in the fentanyl group and 67.5 and 32.5% in the buprenorphine group, respectively (P = 0.155), revealing no significant difference between the two groups. Considering complications, no headache was reported among the studied groups (P = 0.179). In terms of dizziness, 38 patients (95.5%) in the first group and 40 patients (100%) in the second group reported no dizziness, and the difference between the two groups was non-significant in this regard (P = 0.308). Regarding the drug side effects and pruritus, 39 patients in the first group (97.5%) and 37 patients (92.5%) in the second group reported no pruritus, indicating a non-significant change between the two groups (P = 0.308). The results of the continued VAS score in the patients showed that pain was at a lower intensity in patients receiving buprenorphine compared to those in the fentanyl group 6 hours after surgery (P = 0.005). Moreover, the pain in the buprenorphine group was of lower intensity compared to the fentanyl group (P = 0.002) (Table 1). No significant difference was noticed between the two groups at other studied hours.

Nausea and vomiting scores were evaluated 2, 6, 12, 18, and 24 hours after surgery. The results showed that the frequency of nausea and vomiting was lower in the buprenorphine group during the early hours after surgery (2 and 6 hours) compared to the fentanyl group; however, the difference was not significant. The sedation score of the patients was also checked. In this regard, there was no significant difference between the two groups (Table 2).

Another factor evaluated in the patients was the amount of analgesic consumption. The consumption rate of analgesics in the group receiving fentanyl pumps was significantly higher than that of the buprenorphine group. This difference was statistically significant (P = 0.013), wherein 17.5% of the total samples in the buprenorphine group received diclofenac once (Table 3).

5. Discussion

In the present study, 80 patients were assigned to two groups. The first group received sublingual buprenorphine tablets and placebo pumps, and the second group received fentanyl pump and placebo. Regarding the pain scores based on the VAS index, the pain levels were significantly lower in the buprenorphine group than in the fen-

Table 1. Comparison of VAS Scores Between the Research Groups by Hours of Recovery [a]

Hours of Recovery	Buprenorphine Group	Fentanyl Group	VAS Score	P-Value
0	45 (18)	5.53 (21)	0	0.24
	25 (10)	5.7 (3)	1	
	20 (8)	5.32 (13)	2	
	5 (2)	5.2 (1)	3	
	5 (2)	5 (2)	4	
	0 (0)	0 (0)	5	
2	50.0 (20)	37.5 (15)	0	0.435
	22.5 (9)	15 (6)	1	
	20 (8)	32.5 (13)	2	
	5 (2)	12.5 (5)	3	
	2.5 (1)	2.5 (1)	4	
	0 (0)	0 (0)	5	
6	47.5 (19)	47.5 (19)	0	0.005
	37.5 (15)	7.5 (3)	1	
	10 (4)	27.5 (11)	2	
	5 (2)	10 (4)	3	
	0 (0)	7.5 (3)	4	
	0 (0)	0 (0)	5	
12	52.5 (21)	40 (16)	0	0.103
	25 (10)	17.5 (7)	1	
	20 (8)	20 (8)	2	
	2.5 (1)	17.5 (7)	3	
	0 (0)	5 (2)	4	
	0 (0)	0 (0)	5	
18	67.5 (27)	52.5 (21)	0	0.391
	20 (8)	20 (8)	1	
	10 (4)	22.5 (9)	2	
	2.5 (1)	5 (2)	3	
	0 (0)	0 (0)	4	
	0 (0)	0 (0)	5	
24	87.5 (35)	17.5 (19)	0	0.002
	10 (4)	30 (12)	1	
	2.5 (1)	20 (8)	2	
	0 (0)	2.5 (1)	3	
	0 (0)	0 (0)	4	
	0 (0)	0 (0)	5	

[a] Values are expressed as No. (%) unless otherwise indicated.

tanyl group (P = 0.002, P = 0.005) 6 and 24 hours after surgery. Although the analgesic consumption in the fentanyl group was higher than its consumption in another group, buprenorphine was as effective as fentanyl pump in pain control during the other hours of recovery.

Hemati et al. (20) assessed the effectiveness of fentanyl transdermal patches in managing the pain accompanying chronic soft tissue sarcoma. No significant difference was noticed between the patients' characteristics and the VAS scores before the treatment (P > 0.05). According to findings of this study, the pain intensity significantly reduced after the treatment (P = 0.001). However, the rate of negative effects was relatively high (72%) in the patients. The more frequent problems reported were sleepiness (30.2%) and nausea and vomiting (18.6%). Accordingly, a transdermal fentanyl patch was proposed as a safe and effective painkiller in patients suffering from the soft tissue cancer. Moreover, despite its high adverse effects (about 72%), it was recognized as a means to promote well-being among the patients (20).

In another study by Imani et al. (21), the effect of adding ketamine to fentanyl plus acetaminophen on controlling

Table 2. Relationship Between Nausea and Vomiting Scores by Hours of Recovery [a]

Hours of Recovery	Buprenorphine Group	Fentanyl Group	VAS Score	P-Value
0	77.5 (31)	85 (34)	1	0.41
	20 (8)	10 (4)	2	
	2.5 (1)	5 (2)	3	
	0 (0)	0 (0)	4	
2	87.5 (35)	82.5 (33)	1	0.788
	10 (4)	12.5 (5)	2	
	2.5 (1)	5 (2)	3	
	0 (0)	0 (0)	4	
6	90 (36)	90 (36)	1	0.766
	5 (2)	7.5 (3)	2	
	5 (2)	2.5 (1)	3	
	0 (0)	0 (0)	4	
12	87.5 (35)	82.5 (33)	1	0.756
	7.5 (3)	12.5 (5)	2	
	5 (2)	5 (2)	3	
	0 (0)	0 (0)	4	
18	97.5 (39)	95 (38)	1	0.558
	2.5 (1)	5 (2)	2	
	0 (0)	0 (0)	3	
	0 (0)	0 (0)	4	
24	100 (40)	97.5 (39)	1	0.314
	0 (0)	2.5 (1)	2	
	0 (0)	0 (0)	3	
	0 (0)	0 (0)	4	

[a] Values are expressed as No. (%) unless otherwise indicated.

Table 3. Comparing the Consumption of Diclofenac Suppository by the Research Groups [a]

Variable/Number Used	Buprenorphine Group	Fentanyl Group	P-Value
Diclofenac suppository			0.001
0	82.5 (33)	42.5 (17)	
1	17.5 (7)	47.5 (19)	
2	0 (0)	5 (4)	

[a] Values are expressed as No. (%) unless otherwise indicated.

postoperative pain was examined and compared with that of the patients with controlled analgesia after abdominal surgery. According to the findings on the pain scores, a non-significant difference was noticed between the studied groups during the first two days of recovery in resting, movement, and coughing (P = 0.361, P = 0.367, and P = 0.204, respectively). Nevertheless, the ketamine group showed significantly lower nausea scores (P = 0.026). Furthermore, the ketamine supplementation to intravenous fentanyl plus acetaminophen PCA had no additional effect on comforting the postoperative pain (21).

Alizadeh et al. (22) performed a comparative study to assess the pain-relief effects of intravenous morphine and sublingual buprenorphine after laparotomy surgery in opioid-dependent patients. In this study, the sublingual buprenorphine group experienced a significantly lower pain intensity during the first postoperative day. Soltani et al. (23) conducted a similar comparative study to examine the effectiveness of sublingual buprenorphine supplemented intravenous morphine in the postoperative pain management in patients undergoing closed reduction orthopedic surgery. Their study showed that sublingual buprenorphine was more effective than intravenous morphine in pain controlling.

Similar findings proposed that patients who received sublingual buprenorphine endured substantially lower

pain intensity 12 hours after surgery in comparison to the intravenous morphine group. For example, Alijanpour et al.'s (24) comparative study revealed that pain intensity 24 hours after surgery was lower in the patients who received sublingual buprenorphine, compared to those receiving intravenous morphine.

In line with the present findings, Niyogi et al. (25) observed that the consumption of tramadol was significantly lower in buprenorphine recipients than in the placebo group. In another study by Likar et al. (26), the tolerability and usefulness of transdermal buprenorphine were investigated in an elderly group and compared with two other younger patients, all of whom underwent analgesic treatment to deal with moderate to severe pain. The comparative findings revealed that transdermal buprenorphine had the least efficiency, safety, and tolerability effects on chronic pain in elderly patients aged 65 years and above.

In Khandeparker et al.'s (27) study, 50 patients who underwent major cardiovascular surgery were randomly divided into two groups undergoing buprenorphine and pethidine treatments. Their study showed that the buprenorphine effect was more prolonged than pethidine, and that the time intervals for requesting the next dose of the drug were longer in the buprenorphine group. Although the pain intensity in the two groups was almost the same before the first dose administration, at the end of the four-hour research period, the pain intensity in the patients receiving buprenorphine was much lower than that of the patients in the pethidine group. Moreover, more patients the buprenorphine group expressed a decrease in pain intensity after receiving the drug. Nonetheless, the mean duration of pain discontinuation after receiving the drugs was almost the same in the two groups, indicating no significant statistical difference.

Given its potential liver damage, buprenorphine is taken orally and is mainly used sublingually or in a patch form. Regarding the analgesic effects of this drug compared to other drugs, its effectiveness is as high as other known analgesic drugs. This finding can be deduced from the literature and the findings of the present study. Accordingly, buprenorphine can be introduced as an alternative to opioids for postoperative pain control. Notwithstanding, the superiority of buprenorphine to other opioids has not been proved in some other studies. For example, Chang et al. (18) reported no significant statistical difference between the VAS pain scores of buprenorphine and morphine recipients. According to Oifa et al. (28), the pain management functions of morphine and buprenorphine were not significantly different.

In Arshad et al.'s (29) study on 60 patients, transdermal fentanyl and transdermal buprenorphine were prescribed to the two groups. The results showed that VAS scores were 4.47 and 4.48 in the buprenorphine and fentanyl groups at the beginning of the study, respectively. During the three follow-up days, fentanyl showed higher effectiveness in reducing pain than buprenorphine. The effect could be associated with the transdermal route of buprenorphine administration. Troster et al. (30) compared the pain reduction effectiveness of fentanyl (1.5 mg per kg of body weight), buprenorphine (1.5 mg per kg of body weight), and the combination of the two drugs (0.75 + 0.75 mg per kg of body weight). The mean pain reduction was 43.9% in the fentanyl group, 35% in the buprenorphine group, and 39.4% in the mixed group. Desai et al. (31) reported no significant difference between the efficacy and safety of buprenorphine and tramadol in the postoperative pain treatment after femoral neck surgery regarding the mean VAS before surgery and 4 and 12 hours after surgery. However, the mean VAS score was significantly lower in the buprenorphine group than the tramadol group 24 hours and seven days after the surgery. It was also noticed that all patients receiving tramadol needed additional drugs during treatment; however, in the buprenorphine group, 68% of patients received painkillers ($P < 0.001$).

The inconsistencies between the findings of the aforementioned studies and those reported in this study can be explained as follows: (1) difference in the injected doses; (2) genetic variations among different statistical populations; (3) differences in liver enzyme levels caused by the high liver metabolism of buprenorphine; (4) administration time of the drug and its subsequent dosages.

In this study, nausea and vomiting were observed at different intervals, indicating insignificant differences between the two groups treated by buprenorphine and fentanyl. However, in the Niyogi et al.'s (25) study, none of the patients receiving buprenorphine experienced nausea, and only three patients in the placebo group experienced nausea; however, the difference was not statistically significant. In Desai et al.'s (31) study, the nausea and vomiting scores were significantly higher in tramadol recipients than in the buprenorphine group ($P < 0.001$). Consistent with the present findings, the incidence of nausea and vomiting has been reported as non-significant in the aforementioned studies on buprenorphine.

Likewise, the difference between the sedation scores of buprenorphine and fentanyl was not also significant. In a study by Arshad et al. (29), the mean scores of sedation were reported to be 1.57 in the buprenorphine group and 1.41 in the fentanyl group ($P = 0.19$), suggesting no significant difference between the fentanyl and buprenorphine groups. A similar finding on the sedation score was reported by Niyogi et al. (25). The non- significant sedation scores in these studies was in line with the findings of the present study, suggesting the ineffectiveness of buprenor-

phine in the patients' sedation.

Moreover, some complications were also observed in the two studied groups in this study; however, the differences were not significant. In a study by Arshad et al. (29), the incidence rates of nausea and urinary retention were similar in their study groups, with statistically negligible difference in the observed side-effects. Troster et al. (30) reported no significant difference in the incidence of drug complications in the groups receiving fentanyl, buprenorphine, or a combination of the two drugs. The most common complications were nausea and vomiting in the three groups. Similar findings were reported in Khandeparker et al.'s (27) study, in which the incidence rates of the side-effects such as nausea were similar in the two groups. Hypotension occurred only in one of the patients receiving pethidine but not in the buprenorphine group. Niyogi et al. (25) also reported the absence of hypoxia, respiratory arrest, bradycardia, and hypotension, and no complaint of nausea in patients receiving buprenorphine after surgery. In Desai et al.'s (31) study, the incidence rate of the drug-related complications was significantly lower in the buprenorphine group than in the tramadol group. According to the literature, the side-effects of buprenorphine are extremely low, as in the present study; hence, buprenorphine can be used more safely than those of opioid drugs used in operating rooms and surgical wards.

Further, the study groups receiving intravenous morphine and sublingual buprenorphine showed no difference regarding the frequency of nausea and vomiting, as reported by Soltani et al. (23). However, in contrast to the present findings, the incidence rate of pruritus was much lower in the sublingual buprenorphine group than in the morphine group. The findings reported by Payandemehr et al. (32) on the frequency of nausea, vomiting, or pruritus in patients receiving sublingual buprenorphine and intravenous morphine were in agreement with those of the present study. Some other studies reached findings in line with our findings, indicating no difference between the studied drugs with respect to the incidence rate of postoperative nausea and vomiting (28, 33).

5.1. Conclusion

The study findings reveal the effectiveness of buprenorphine in reducing postoperative pain and suggests it as a desirable alternative to opioids because of their minimal complications, affordability, and more convenient administration route.

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Footnotes

Authors' Contribution: Study concept and design, V. Norouzi, and A. Ghazi; Data analysis and interpretation, V. Norouzi, and A. Ghazi; Manuscript drafting, A. Ghazi; Critical revision of the manuscript for important intellectual content, V. Norouzi, A. Ghazi, and P. Bakhshpoori; Statistical analysis, F. Amani.

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Conflict of Interests: None to declare.

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Informed Consent: All the patients submitted their written informed consent before the study.

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