

Pre-Anesthetic Administration of Sublingual Buprenorphine for Postoperative Analgesia after Hemorrhoidectomy a Clinical Trial

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Abstract: Buprenorphine is classified as an agonist-antagonist mu opioid agonist, which has a longer half-life compared with other opioids. The objective of this study was, to evaluate the efficacy of pre-anesthetic administration of buprenorphine on postoperative pain intensity, in patients undergoing hemorrhoidectomy. In a prospective, double-blinded, randomized study, 60 ASA I and II subjects with age of 15-65 years scheduled for elective hemorrhoidectomy under general anesthesia were enrolled. They were randomly allocated to receive sublingual buprenorphine (0.4 mg, 30 min before surgery) or placebo. All the patients were anaesthetized with halothane N₂O/O₂ after induction with thiopentone. Pain scores, as assessed by a visual analog scale, were evaluated immediately, 2, 4 and 6 h postoperatively. Total dose of analgesics and time of the first request for an analgesic medication were measured as well. The pain scores in buprenorphine group were similar to that in control group immediately and 2 h postoperatively. The postoperative pain intensities in 4 and 6 h following surgery were significantly lower in patients receiving buprenorphine compared with control group (3.83±2.50 vs. 5.27±2.63 and 1.60±2.63 vs. 4.40±2.59, respectively). Patients in buprenorphine group have a significantly longer time to first analgesic request (3.59±0.82 vs. 1.90±0.64 h); however, groups were comparable regarding total dose of analgesic consumption.

Key words: Buprenorphine, postoperative pain, hemorrhoidectomy, randomized, pre-anesthetic, administration

INTRODUCTION

Buprenorphine is classified as a partial mu-opioid agonist (Pick *et al.*, 1997). It has a high affinity, but low efficacy at the mu receptor, where it yields a partial effect upon binding (Helm *et al.*, 2008). Buprenorphine has a poor bioavailability due to significant first-pass metabolism in the liver after oral administration (Cowan *et al.*, 1977). Conversely, because of high lipid solubility, it has an excellent sublingual bioavailability. Following the sublingual administration of 0.4 or 0.8 mg doses, the time to maximum concentration was variable, ranging from 90-360 min (Bullingham *et al.*, 1981; Watson *et al.*, 1982) and duration of action of 8-12 h (Brodbeck *et al.*, 1997). The average systemic bioavailability was 55%, with large intersubject variability. It is used on a once-a-day dose for maintenance therapy

(Helm *et al.*, 2008). Buprenorphine has been in clinical use for over 25 years (Johnson *et al.*, 2005).

It has been used as an analgesic in several studies, however, 3 are limited studies evaluating the post-surgical analgesic properties of preoperative administration of Buprenorphine. To our knowledge, there is only one study in which the effects of preoperative sublingual buprenorphine have been assessed on postoperative pain, the need for postoperative opioid injections and on time to discharge in human being (Juhlin-Dannfelt *et al.*, 1995). In another study, it has been shown that the preoperative use of buprenorphine jelly is easy to use and causes post-surgical analgesia in rats (Flecknell *et al.*, 1999).

The objective of this study was, to evaluate the efficacy of pre-anesthetic administration of buprenorphine on postoperative pain intensity, in patients undergoing hemorrhoidectomy.

MATERIALS AND METHODS

Sixty adult patients with American Society of Anesthesiologists (ASA) physical status I or II were enrolled in a prospective, randomized, double-blinded study, following approval of ethical committee of Arak University of Medical Sciences and obtaining written informed consent and underwent general anesthesia for elective hemorrhoidectomy. Patients with chronic pain, daily intake of analgesics, suffering from liver disease or treated with antiepileptic drugs, unable to cooperate or with a record of drug or alcohol abuse were excluded from the study.

Using a table of random numbers, patients were randomly assigned to 2 groups of Buprenorphine (Buprenorphine tablet 0.4 mg, manufactured by Darudarman Pars Drug Production and Distribution Company) or control (placebo). Both groups received their tablets sublingually, 30 min before surgery.

All patients were premedicated with fentanyl 2-3 $\mu\text{g kg}^{-1}$ before induction of anesthesia. Under standard monitoring, general anesthesia was induced with thiopentone 4 mg kg^{-1} and additional 50 mg doses until disappearance of the ciliary reflex. Succinylcholine 1 mg kg^{-1} was used for neuromuscular blockade. Anesthesia was maintained with 1-1.5 MAC (inspiratory saturation) of Halothane in O_2 and N_2O (50%) with spontaneous ventilation. Then the subjects were transported to the Post Anesthesia Care Unit (PACU) and next to the ward for the remainder of the study period. After transferring the patient to the PACU and surgery ward, 25 mg of meperidine was administered IV upon each request of the patient for analgesics.

The intensity of the pain was evaluated on a 10 cm Visual Analogue Scale (VAS) (from 0, which means no pain sensation, to 10 as the most intense pain the patient has ever experienced), in the PACU, 2, 4 and 6 h following completion of surgery by a single independent investigator blinded to subject group assignment.

The pain intensity, time to the first request for rescue analgesics and the total dose of it during the first 6 h were recorded and compared between groups.

Data are expressed as mean \pm SD or number of patients. Parametric data were analyzed using independent samples t-test. For categorical data analysis chi-square (χ^2) or Fisher's exact test was utilized as appropriate. Statistical calculations were performed utilizing SPSS (SPSS Inc., Chicago, Illinois, USA) version 12.0. Differences were considered significant at $p < 0.05$.

RESULTS

No patients were excluded. The mean of age was 37.38 \pm 11.69 years and 40% of practitioners

Table 1: Subjects clinical data

	Control	Buprenorphine	p-value
Pain			
PACU†	8.73 \pm 2.210	8.83 \pm 2.57	0.8700
2 h	7.07 \pm 2.300	5.77 \pm 2.80	0.0540
4 h*	5.27 \pm 2.630	3.83 \pm 2.50	0.0300
6 h*	4.40 \pm 2.590	1.60 \pm 2.63	0.0001
Pethidine dose (mg)	35.33 \pm 12.92	32.08 \pm 9.88	0.2800
Time to first analgesic request (h)*	1.90 \pm 0.640	3.59 \pm 0.82	<0.0001

Data are represented as mean \pm SD; †: Post Anesthesia Care Unit; *: Significant difference, t-test

were male. There were no significant differences among groups demographic data.

The pain intensities were comparable among groups in PACU and second hour following surgery. However, its intensity was significantly lower in Buprenorphine group, both in 4th and 6th h postoperatively (Table 1).

While patients in Buprenorphine group have a significantly longer time to first analgesic request, both groups were comparable regarding total dose of analgesic consumption (Table 1). All the patients experienced uneventful recoveries.

DISCUSSION

This study showed that administration of Buprenorphine 0.4 mg sublingually significantly reduced the pain intensities, 4 and 6 h following surgery and lengthened the duration to first time analgesic request. Yet, it did not make any changes in the total dose of postoperative analgesic consumption.

As a supplement to anesthesia, buprenorphine has been used successfully in dosages ranging from 5-40 $\mu\text{g kg}^{-1}$ (Kay, 1980; McQuay *et al.*, 1980; Pedersen *et al.*, 1986). It was as effective as morphine in dogs (Brodbelt *et al.*, 1997), with greater duration of postoperative analgesia and potency than could be achieved with morphine, in human subjects (Bradley, 1984). Compared with meperidine, buprenorphine was shown to be a satisfactory analgesic for preoperative and postoperative use with little difference in the incidence of unwanted effects and much longer duration of action (Khan and Kamal, 1990; Watanabe *et al.*, 1994). There are other studies supporting the analgesic properties of buprenorphine in human subjects (Bradley, 1984; Hannibal *et al.*, 1996; Satoh *et al.*, 1994).

Sublingual application of buprenorphine offers an effective and easy alternative to the parenteral route of prescription, especially for the management of postoperative pain (Gaitini *et al.*, 1996; Lacoste *et al.*, 1997). Despite, the efficacy and safety of sublingual buprenorphine has been demonstrated as an analgesic for postoperative analgesia (Lebedeva *et al.*, 1996), there are limited studies in which buprenorphine given by this route

of administration have been studied as premedication. Risbo *et al.* (1985) revealed that sublingually administered buprenorphine is as good as intramuscular morphine for premedication. In consistence with the results of Juhlin-Dannfelt (1995), the results of the present study revealed that premedication with sublingual buprenorphine reduces the pain intensities postoperatively and the need for postoperative injections of pethidine. Consequently, it should be recommended to patients who wish to avoid injections. These effects are derived from its mu-opioid agonist's activities. However, unlike full mu-opioid agonists, at higher doses, buprenorphine's physiological and subjective effects, including euphoria, reach a plateau. This ceiling may result in a wider safety margin (Johnson *et al.*, 2005).

Although, a precise explanation for this phenomenon is lacking, its analgesic activity is not directly related to its dosage. In one trial undertaken on patients undergoing biliary surgery (Pedersen *et al.*, 1986), while none of the patients receiving 10-20 $\mu\text{g kg}^{-1}$ needed an analgesic within 1 h of the operation, half of the patients who received 30-40 $\mu\text{g kg}^{-1}$ buprenorphine requested an analgesic within 5 min of extubation. To a certain extent, these findings are consistent with the presence of a bell-shaped dose-response curve for buprenorphine in humans.

Only minor and unimportant side effects were seen (Risbo *et al.*, 1985). Usual adverse effects following buprenorphine administration may include sedation, nausea and/or vomiting, dizziness, headache and respiratory depression (Helm *et al.*, 2008). Among them, nausea and vomiting may prolong the recovery time. The higher incidence of nausea was the main reason that Juhlin-Dannfelt *et al.* (1995) did not recommend sublingual buprenorphine for out-patient arthroscopy. Unfortunately, we were not able to compare the nausea, vomiting and other adverse effects between groups. Respiratory depression may occur and may not be responsive to treatment with naloxone; however, as a mu-opioid partial agonist with a demonstrated ceiling on respiratory depression, buprenorphine may have a better safety profile compared to full mu agonists (Johnson *et al.*, 2005).

CONCLUSION

In conclusion, it seems that sublingually administered buprenorphine significantly reduces the postoperative pain intensities and increases time to first time analgesic request; however, no changes in consumption of postoperative analgesics are observed.

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