Post-operative Analgesia in Opioid Dependent Patients: Comparison of Intravenous Morphine and Sublingual Buprenorphine

Shaabanali Alizadeh MD, Ghafar Ali Mahmoudi MD, Hassan Solhi MD, Bahman Sadeghi-Sedeh MD, Reza Behzadi MD, Amir Mohammad Kazemifar MD

Abstract

Background: Acute and chronic pain is prevalent in patients with opioid dependence. Lack of knowledge concerning the complex relationship between pain, opioid use, and withdrawal syndrome can account for the barriers encountered for pain management. This study was designed to evaluate the efficacy of sublingual (SL) buprenorphine for post-operative analgesia, compared with intravenous (IV) morphine.

Methods: A total of 68 patients, aged 20-60 years were randomly selected from whom had been underwent laparotomy due to acute abdomen in a University Teaching Hospital in Arak, Iran, and were also opioid (opium or heroin) abuser according to their history. After end of the surgery and patients’ arousal, the patients were evaluated for abdominal pain and withdrawal syndrome by visual analog scale (VAS) and clinical opioid withdrawal score (COWS), respectively 1, 6, and 24 h after the surgery. They received either morphine 5 mg IV or buprenorphine 2 mg SL, 1 h after end of the surgery, and then every 6 h for 24 h.

Findings: VAS was $4.47 \pm 0.73$ and $2.67 \pm 0.53$ at h 6 and 24 in buprenorphine group, respectively. The corresponding score was $5.88 \pm 0.69$ and $4.59 \pm 0.74$ in morphine group. At the same time, patients in buprenorphine experienced less severe withdrawal syndrome.

Conclusion: The present study confirmed the efficacy of SL buprenorphine as a non-invasive, but effective method for management of post-operative pain in opioid dependent patients. Result of this study showed that physicians can rely on SL buprenorphine for post-operative analgesia.

Keywords: Buprenorphine, Morphine, Post-operative pain, Opioid dependence, Withdrawal syndrome
Introduction

Pain management in the perioperative setting refers to actions before, during, and after a procedure that are intended to reduce or eliminate post-operative pain before discharge. Post-operative pain continues to be a challenge and is often inadequately treated, leading to patient anxiety, stress, and dissatisfaction. Inadequately treated pain can lead to detrimental physiological effects and may also have psychological, economic and social adverse effects.

Perioperative techniques for post-operative pain management include, but are not limited to central regional (i.e., neuraxial) opioid analgesia, patient controlled analgesia with systemic opioids, and peripheral regional analgesic techniques. The choice mainly depends on the strategy favored by the physician and the availability of drugs and equipment.

Opioids are typically used for the management of moderate to severe acute pain, but opioid use is limited by the occurrence of a range of side effects. Opioids exert their analgesic effects primarily through agonistic interactions with µ-opioid receptors in neurons in the pain pathway, which lead to a reduction in neurotransmitter release and associated pain. The underuse of opioid analgesics by health care providers to relieve acute pain may be related to attempts to balance analgesia against concerns about opioid-induced side effects and subsequent deleterious repercussions for patient outcome.

Clinicians must prescribe and monitor currently available opioids based on the best available evidence that takes into account the uniqueness of each patient's pain management issues.

Some patient groups are at special risk for inadequate pain control and require additional analgesic considerations, including patients with drug abuse. Iran has one of the highest rates of opioid abuse in the world. It is not surprising that some patients with acute abdomen also have an opioid dependency. They need perioperative analgesia too. However, their management may complicate with insufficient analgesia, superfluous opioid overdose, and withdrawal syndrome.

Intravenous (IV) or intramuscular (IM) administration is more commonly the route of choice in critically ill patients with acute pain who need opioid analgesia. However, any other route with less pain of IM injections and safer than direct IV injection is encouraged.

The present study was designed to evaluate the efficacy of sublingual (SL) buprenorphine for post-operative analgesia, compared to IV morphine.

Methods

In this single-blinded randomized clinical trial, 68 patients, aged 20-60 years were randomly selected from whom had been underwent laparotomy due to acute abdomen in a university teaching hospital in Arak, Iran and were also opioid (opium or heroin) abuser according to their history. Their induction of anesthesia was similar (fentanyl 2-5 µg/kg, midazolam 0.03 mg/kg, atracurium 0.5 mg/kg, and nesdonal 3-5 mg/kg).

After end of the surgery and patients’ arousal, the patients were evaluated for abdominal pain and withdrawal syndrome by visual analog scale (VAS) and clinical opioid withdrawal score (COWS), respectively by one of the authors 1, 6, and 24 h after the surgery. The patients were randomly divided into two groups. The first group received morphine 5 mg IV 1 h after the end of the surgery, and then every 6 h for 24 h. The second group received buprenorphine 2 mg SL with the same schedule. Moreover, if any patient had VAS score more than 4, or complained from pain at any time, he received meperidine 25 mg IV.

The exclusion criteria were the use of any other analgesic, sedative, or narcotic before or after the surgery, history of head trauma, shock, diabetes mellitus, and neurologic diseases. The study had been approved by Local Ethical Committee of Arak University of Medical Sciences. All the studied patients provided informed consent for participation to the study.

The results were analyzed by SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Differences between the groups were determined by two-way repeated measure or chi-square test, whatever relevant. Statistical significance was set at P < 0.050.

Results

68 patients in two equal groups were participated in the study. All of them completed the study. All
of them except two in the first group, and four in the second group were male. Their age was 30.06 ± 7.95 and 30.68 ± 8.45 years in the first and second groups, respectively. The difference was not statistically significant (P = 0.757). The patients had no significant difference in reason for surgery, too. The groups had comparable pain severity at the start of the study. However, severity of pain reduced more prominently in group 2 during the study, compared to group 1. Meanwhile, the patients in group 2 experienced less severe withdrawal syndrome, too. COWS score and VAS score of the studied groups was demonstrated in table 1.

**Discussion**

The present study was performed to evaluate the efficacy of SL buprenorphine as a non-invasive, but effective method for management of post-operative pain in opioid-dependent patients. The result of this study showed that physicians can rely on SL buprenorphine for post-operative analgesia.

Buprenorphine, synthesized in the late 1960s was used as a parenteral analgesic since 1978. Buprenorphine is also available in the forms of SL tablets or transdermal (TD) patches. It is a partial agonist at µ-opioid receptors, an antagonist at kappa opioid receptors. Buprenorphine partial mu agonist activity may induce a milder withdrawal syndrome than most opioids; thus, discontinuing buprenorphine may be easier. Buprenorphine is also a κ-receptor antagonist and, therefore, less apt to generate dysphoria. Moreover, buprenorphine exhibits ceiling effects on respiratory depression due to its intrinsic agonist/antagonist effects. This exceptional pharmacology offers an enhanced safety profile compared other opioids, when used for analgesia. After SL administration, there is a rapid onset of effect (30-60 min) with a peak effect at about 90-100 min.

According to the Canadian guideline for safe and effective use of opioids for chronic non-cancer pain, buprenorphine can be used for the treatment of opioid addiction in chronic non-cancer pain. Furthermore, it can treat opioid-induced hyperalgesia, which occur with chronic opioid therapy.

Though, we did not found any similar studies to compare them with the present study, there are some studies in the literature about the role of buprenorphine in the management of pain. Study of Bounes et al. showed that acute and chronic pain has a negative impact on the persistence of opioid maintenance treatment, particularly in users of buprenorphine. Neumann et al. have showed that SL buprenorphine can be used for the treatment of chronic pain in patients with co-existent opioid addiction. Wang et al. have performed an in-vitro study. They have suggested that the efficacy of morphine, but not buprenorphine for pain control is reduced, when the cancers cells have P-glycoprotein expression.

Hoflich et al. have focused on peripartum pain management in opioid-dependent women. They have concluded that delivering women who are on opioid maintenance treatment need more analgesic drugs compared to control. Study of Przeklasa-Muszynska and Dobrogowski has confirmed high efficacy and good tolerability of TD buprenorphine in the treatment of moderate to severe pain that cannot be effectively treated with non-opioid analgesics. Zoltie and Cust have suggested that buprenorphine can be used in patients with acute abdominal pain without fear of masking the diagnosis.

Study of Finlay et al. has confirmed the superiority of buprenorphine to Pethidine in control of pain in ureteric colic. Bullingham et al. have evaluated the efficacy of buprenorphine and paracetamol for pain after minor orthopedic surgery with favorable results.

| Groups                  | VAS score       | COWS score       |
|-------------------------|-----------------|------------------|
|                         | Hour 0 | Hour 1 | Hour 6 | Hour 24 | Hour 0 | Hour 1 | Hour 6 | Hour 24 |
| Group 1 (mean ± SD)     |         |        |        |         |        |        |        |         |
|                         | 8.58 ± 0.74   | 7.14 ± 0.31 | 5.88 ± 0.69 | 4.59 ± 0.74 | 16.94 ± 2.71 | 2.91 ± 1.33 | 7.05 ± 1.93 | 12.52 ± 3.29 |
| Group 2 (mean ± SD)     | 8.70 ± 0.93   | 7.22 ± 0.47 | 4.47 ± 0.73 | 2.67 ± 0.53 | 18.26 ± 3.40 | 8.47 ± 2.25 | 3.02 ± 1.16 | 7.00 ± 1.68 |
| P                       | 0.621   | 0.550  | 0.001  | < 0.001 | 0.095  | < 0.001 | < 0.001 | < 0.001 |

COWS: Clinical opioid withdrawal score; VAS: Visual analogue scale; SD: Standard deviation
Study of Conaghan et al. showed that 7 days buprenorphine patches plus oral paracetamol are non-inferior to co-codamol (codeine plus paracetamol) tablets with respect to analgesic efficacy in older adults with osteoarthritis pain in the hip/knee.\textsuperscript{23} The present study also confirmed that SL buprenorphine is more effective than parenteral morphine in control of post-operative pain in opioid-dependent patients. Additionally, it produces less severe withdrawal syndrome in them.

**Conclusion**

Patients with opioid addiction who need analgesia for various reasons present a therapeutic challenge. Increased pain sensitivity and the development of opioid tolerance complicate the treatment of pain experienced by opioid-dependent patients. The present study suggests SL buprenorphine for control of pain and withdrawal syndrome in opioid-dependent patients.

**Conflict of Interests**

The Authors have no conflict of interest.

**Acknowledgements**

The authors would like to appreciate the genuine cooperation of the staff of surgery ward of Valie-Asr Hospital, Arak during conduct of the study.

**References**

1. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 2004; 100(6): 1573-81.
2. Ahmed A, Latif N, Khan R. Post-operative analgesia for major abdominal surgery and its effectiveness in a tertiary care hospital. J Anaesthesiol Clin Pharmacol 2013; 29(4): 472-7.
3. Affilalo M, Stegmann JU, Upmalis D. Tapentadol immediate release: a new treatment option for acute pain management. J Pain Res 2010; 3: 1-9.
4. Erstad BL, Puntillo K, Gilbert HC, Grap MJ, Li D, Medina J, et al. Pain management principles in the critically ill. Chest 2009; 135(4): 1075-86.
5. Solhi H, Salehi B, Alimoradian A, Pazouki S, Taghizadeh M, Saleh AM, et al. Beneficial effects of Rosmarinus officinalis for treatment of opium withdrawal syndrome during addiction treatment programs: a clinical trial. Addict Health 2013; 5(3-4): 90-4.
6. Ahmadi-Nejad M, Jadidi F, Dehghani M, Divsalar K. Studying prevalence and pattern of taking narcotic and ecstasy drugs by patients admitted to special care centers of Shahid Bahonar Hospital, Kerman, Iran. Addict Health 2012; 4(1-2): 57-64.
7. Solhi H, Sadeghi-Sedehe B, Emami P, Jamalian M, Kazemifar AM. Does ingestion of tincture of opium notably raise blood alcohol concentration? Addict Health 2014; 6(3-4): 100-4.
8. Naing C, Yeoh PN, Aung K. A meta-analysis of efficacy and tolerability of buprenorphine for the relief of cancer pain. Springerplus 2014; 3: 87.
9. Douaihy AB, Kelly TM, Sullivan C. Medications for substance use disorders. Soc Work Public Health 2013; 28(3-4): 264-78.
10. Bonhomme J, Shim RS, Gooden R, Tyus D, Rust G. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. J Natl Med Assoc 2012; 104(7-8): 342-50.
11. Colson J, Helm S, Silverman SM. Office-based opioid dependence treatment. Pain Physician 2012; 15(3 Suppl): ES231-ES236.
12. Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician 2012; 58(1): 37-41.
13. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. Clin Interv Aging 2008; 3(3): 421-30.
14. Silverman SM. Opioid induced hyperalgesia: clinical implications for the pain practitioner. Pain Physician 2009; 12(3): 679-84.
15. Bounes V, Palmaro A, Lapeyre-Mestre M, Roussin A. Long-term consequences of acute pain for patients under methadone or buprenorphine maintenance treatment. Pain Physician 2013; 16(6): E739-E747.
16. Neumann AM, Blondell RD, Jaanimagi U, Giambrone AK, Homish GG, Lozano JR, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. J Addict Dis 2013; 32(1): 68-78.
17. Wang J, Cai B, Huang DX, Yang SD, Guo L. Decreased analgesic effect of morphine, but not buprenorphine, in patients with advanced P-glycoprotein (+) cancers. Pharmacol Rep 2012; 64(4): 870-7.
18. Hoflich AS, Langer M, Jagsch R, Bawert A, Winklbaur B, Fischer G, et al. Peripartum pain...
management in opioid dependent women. Eur J Pain 2012; 16(4): 574-84.

19. Przeklasa-Muszynska A, Dobrogowski J. Transdermal buprenorphine in the treatment of cancer and non-cancer pain-the results of multicenter studies in Poland. Pharmacol Rep 2011; 63(4): 935-48.

20. Zoltie N, Cust MP. Analgesia in the acute abdomen. Ann R Coll Surg Engl 1986; 68(4): 209-10.

21. Finlay I, Scott R, McArdle CS. Prospective double-blind comparison of buprenorphine and pethidine in ureteric colic. Br Med J (Clin Res Ed) 1982; 284(6332): 1830-1.

22. Bullingham RE, McQuay HJ, Moore RA, Weir L. An oral buprenorphine and paracetamol combination compared with paracetamol alone: a single dose double-blind post-operative study. Br J Clin Pharmacol 1981; 12(6): 863-7.

23. Conaghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. Osteoarthritis Cartilage 2011; 19(8): 930-8.
درمان در بیماران وابسته به مواد مخدر اپیوپنید پس از جراحی: مقایسه بوپرونورفین

زیرباینی با مرفن وریدی

دکتر شعبانعلی علیزاده ۱، دکتر غفار علی محمودی ۲، دکتر حسن صلی‌یاری ۳، دکتر بهمن صادقی‌صفهانی ۴، دکتر رضا ییزدانی ۵

دکتر امير محمد کاظمی‌فر ۶

مقدمه
درمان و درمان وابسته به مواد مخدر اپیوپنید شایع است. عدم وجود درک کافی از کنش بین درد، مصرف اپیوپنید و سندرم محرومان، موجب ابعاد ماحقی برای مدیریت صحیح در درمان می‌گردد. مطالعه حاضر با هدف مقایسه تأثیر بوپرونورفین/Ziropain با مرفن وریدی در کنار درد بیماران وابسته به مواد پس از عمل جراحی نجات شد.

روش‌ها: ۲۰ سال به طور تصادفی از میان بیماران وابسته به مواد مخدر اپیوپنیدی که به دلیل شکم درد حاد در یک بیمارستان آموزشی دانشگاهی در شرک ارک تحت لایانتوئز قرار گرفته بودند، برای مطالعه حاضر انتخاب گردیدند. پس از اندازه‌گیری و بیان (VAS) یا Visual analog scale (VAS) یا Visual analog scale، مقدار سنگین نظیر درد پس از فاصله ۶، ۴۴ و ۴۴ ساعت پس از عمل جراحی سنگین شد. در (COWS) با شدت کمتر را نیز تشخیص دادند.

یافته‌ها: مقدار سنگی نظیر درد پس از عمل جراحی در گروه بوپرونورفین به ترتیب ۷/۳±۴/۲ و ۷/۴±۵/۸ و ۷/۴±۵/۸ بود. بیماران گروه بوپرونورفین به طور هم‌زمان علاوه سندرم محرومنی با شدت کمتر را نیز تشخیص دادند.

نتیجه‌گیری: مطالعه حاضر نشان داد که بوپرونورفین زیربایینی یک داروی مؤثر و غیر تهاجمی برای کنترل درد پس از عمل در بیماران وابسته به مواد مخدر اپیوپنیدی است. پژوهشگاه می‌تواند با اطمینان حاصل از این دارو جهت درمان درد پس از عمل بهبود بیربیند.

واژگان کلیدی: بوپرونورفین، مرفن، درد پس از عمل، وابستگی به مواد مخدر اپیوپنیدی، سندرم محرومنی

ارجاع;

- علیزاده، علی‌رضا علی‌دغدغه و رضا، رضایی مصطفی. درمان در بیماران وابسته به مواد اپیوپنیدی پس از جراحی: مقایسه بوپرونورفین وریدی با مرفن وریدی. مجله انتخاب و سلامت؛ ۱۳۷۷: ۷ (۲-۳): ۱۰۲-۱۰۵.

تاریخ دریافت: ۹۳/۷/۲

طراحی و دیجیتال: حسین علی‌دغدغه

Email: mahmoudi.gh@lums.ac.ir