Comparison Effect of Local Subcutaneous Tramadol and Methadone in Post-laparotomy Pain Control

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OBJECTIVE: Postoperative pain management is an important part of surgical care. It is commonly known that methadone and tramadol are often administered for pain relief after surgery. In this study, we evaluated the effects of a subcutaneous injection of methadone and tramadol before carrying out a skin suture for postoperative pain following laparotomy.

MATERIALS AND METHODS: In this double-blinded randomized clinical trial, 60 patients who underwent major abdominal surgery were randomly allocated into either subcutaneous methadone or tramadol groups. Tramadol 1.5 mg/kg or methadone 70 μg/kg, both diluted with normal saline to 10 cc, were injected subcutaneously around the patient’s incision site. The patient’s pain severity was measured every 1, 6, 12, 18, and 24 hours after surgery using a visual analog scale (VAS). Pethidine was injected if the patient requested further pain relief. The administered pethidine doses and pain VAS scores were compared between the two groups.

RESULTS: There was no significant difference observed in the duration of hospital stay post surgery between the tramadol and methadone groups. Both drugs were effective in relieving pain in the first 12 hours with no significant difference between groups; afterwards, the pain was aggravated. However, the VAS score was significantly lower in the tramadol group at 18 hours (3.13±0.93 vs. 4.30±0.95, p<0.001) and 24 hours (3.93±0.86 vs. 5.00±1.25, p<0.001). The tramadol group required a significantly lower dose of pethidine (214.01±23.12 mg vs. 243.3±36.72 mg, p=0.01) than the methadone group.

CONCLUSION: Subcutaneous administration of tramadol and methadone was effective in relieving pain in the first 12 hours post surgery, but afterwards, the need for analgesics were increased. The study concluded that tramadol may be more effective than methadone for pain relief in the first day after surgery.

KEYWORDS: Abdominal surgery, postoperative pain, analgesia, tramadol, methadone

INTRODUCTION

Abdominal surgery is often accompanied by significant postoperative pain that requires the use of analgesics (1). Postoperative pain, if not treated well, can lead to longer hospital stay and pain care with increased readmissions (2–4). Uncontrolled postoperative pain can deteriorate a patient’s quality of life and previous studies have shown that the severity of postoperative pain is an important predictor of postoperative chronic pain (2). This pain is also associated with different deleterious organ responses including pulmonary, cardiovascular, digestive, urinary and metabolic, endocrine and mood disorders (5).

Therefore, it is imperative that there be effective pain control after surgery. There are various methods for administering analgesics from intravenous to local injections that have been previously introduced. For example, local anesthesia can reduce pain intensity, while simultaneously preventing general complications of anesthesia and systemic administration of certain drugs (5). Opioids are also common analgesics used after surgery for pain relief and can be administered via different routes including oral, sublingual, rectal, parenteral (subcutaneous, intramuscular, intravenous), neuroaxial, and perineural means (6).

Among the different opioids that exist, tramadol and methadone are common analgesics used for postoperative pain. Tramadol is a codeine analog that has a dual mechanism that stimulates the μ receptor and, by a lower rate, δ and κ receptors. This substance activates the inhibitory spinal cord reflexes by reducing the norepinephrine and serotonin receptors (7). Tramadol is seen as a weak opioid that has local anesthetic effects (8), while methadone is a synthetic analgesic with a long half-life that has good analgesic effects (9). Methadone is a known drug for controlling various pains, especially chronic pain, preventing symptoms of drug withdrawal, and relieving pain after surgery. Methadone has the same strength as morphine, but its duration is longer. Its main application is in the prevention of drug withdrawal symptoms and to treat chronic pain (8, 9).

Both drugs had considerable side effects when used intramuscularly, intravenously and intra-articular to relieve...
postoperative pain (9–12). Tramadol could also reduce pain when used subcutaneously around the wound alone or in combination with ketamine (8). A recent study on women undergoing cesarean sections also showed that subcutaneous methadone was both safe and effective in reducing postoperative pain (13).

Considering the lowest dosage needed for subcutaneous injection and analgesia as well as for preventing general side effects, it is feasible to use these opioids in this route. However, studies evaluating their efficacy are few. Therefore, this study aimed to evaluate the efficacy of subcutaneous tramadol and/or methadone injected at the wound site in patients undergoing major abdominal surgeries.

**MATERIALS and METHODS**

In this randomized double blind clinical trial, sixty patients >18 years old undergoing elective major abdominal surgery in Imam Reza Hospital, Tabriz, Iran between November 2016 and November 2017 were enrolled in the study. Inclusion criteria included all patients >18 years with American Society of Anesthesiologists (ASA) I-II undergoing elective major abdominal surgery with general anesthesia. Those excluded from the study included patients with epidural catheters, those using analgesics for at least 6 hours before surgery or those who were pregnant, diabetic, under drug or substance addiction, had a history of laparotomy, chronic renal, hepatic or heart disease, chronic pain disorder, or a history of seizures. The ethics committee of Tabriz University of Medical Sciences has approved the study protocol (IR.TBZMED.REC.1397.088, IRCT20120605009948N3).

All participants underwent 8 hours of fasting prior to surgery. Preloading was completed with Ringer lactate solution (5 ml/kg body weight). Before intubation, premedication was used with midazolam (300 mcg/kg) and fentanyl (10 mcg/kg). General anesthesia was induced with thiopental 5 mg/kg and 0.1 mg/kg vecuronium intravenously and patients were intubated. To maintain anesthesia, sevoflurane (MAC=2%) and a 50% O₂+50% NO₂ combination gases was used. No additional analgesia was given to any patient during the intraoperative period.

Patients were enrolled in the study using the block randomization method and in accordance with sample size. They were then randomly allocated to either the methadone or tramadol study groups. The patients and the physician evaluating the outcome of the treatments were blinded to the group allocation.

The wound was washed with normal saline before suturing the skin and after closure of the fascia. In the tramadol group, 1.5 mg/kg of tramadol was diluted with normal saline to 10 cc and was injected subcutaneously alongside the wound. In the Methadone group, 70 μg/kg of methadone was diluted with normal saline to 10 cc and was injected using the same method. After injection of the drug, the skin was closed with a nylon 0-3 stitch and the wound was dressed.

The severity of pain in patients was assessed 1, 6, 12, 18, and 24 hours after surgery using the visual analog scale (VAS). If the patients experienced a severe pain (VAS>4) or requested analgesics for pain relief, doses of 1 mg/kg pethidine were injected to help control the pain. In both groups, the pethidine doses were also recorded according to the nursing report. Excluding pethidine, no other analgesics were administered to the patient to equalize and reduce the confounding factors. Oral or rectal analgesics were not prescribed during the course of this study.

**Statistical Analysis**

Data was analyzed using SPSS software (version 23; SPSS Inc., Chicago, IL). The results are expressed as Mean±standard deviations or percentages. Kolmogorov-Smirnov test was used to assess normal distribution of data. Chi square test, Fisher’s exact test, independent t-test, or Mann-Whitney U test were used to compare data between groups. Friedman test was used to analyze the VAS values of groups. Additionally, p-values of less than 0.05 were considered statistically significant.

**RESULTS**

In this study, 60 patients were evaluated in two methadone and tramadol groups. Demographic and postoperative findings between two groups are detailed in Table 1. Both groups were similar in age, gender, weight, height, and ASA. Although the duration of hospital stay after surgery was higher in the methadone group compared to the tramadol group, the difference was not significant (p>0.05).

| Table 1. Demographic and postoperative findings between the two study groups |
|----------------|----------------|----------------|
|                  | Methadone      | Tramadol      | p    |
|----------------|----------------|----------------|------|
| Age (years)     | 46.80±9.84     | 47.33±9.60    | 0.83 |
| Weight (kg)     | 68.48±9.39     | 71.33±7.66    | 0.20 |
| Height (cm)     | 168.66±6.74    | 164.73±5.61   | 0.47 |
| Gender          |                |                |      |
| Male            | 15 50          | 15 50          | –    |
| Female          | 15 50          | 15 50          |      |
| ASA             |                |                |      |
| I               | 17 56.7        | 14 46.7        | 0.43 |
| II              | 13 43.3        | 16 53.3        |      |
| Post-surgery hospital stay (days) | 2.93±0.82 | 2.56±0.62 | 0.05 |
| Pethidine dose (mg) | 243.3±36.72 | 214.01±23.12 | 0.01* |

*: p is two-sided significant; ASA: American Society of Anesthesiologists

| Table 2. Pain severity according to VAS |
|----------------|----------------|----------------|
| VAS             | Methadone      | Tramadol      | p    |
| 1st hour        | 2.33±0.71      | 2.40±0.72     | 0.72 |
| 6th hour        | 2.73±0.69      | 2.66±0.80     | 0.73 |
| 12th hour       | 2.93±0.78      | 2.76±0.77     | 0.41 |
| 18th hour       | 4.30±0.95      | 3.13±0.93     | <0.001* |
| 24th hour       | 5.00±1.25      | 3.93±0.86     | <0.001* |

VAS: Visual analog scale; *: p is two-sided significant
Following the first 12 hours post-operation, all patients requested analgesics for pain relief. The Interestingly, the tramadol group required significantly lower doses of analgesic administrations compared to the methadone group (p<0.05).

The Friedman test demonstrated that the VAS score varies significantly between two groups at different hours. There were no significant differences in the first 12 hours between groups. While both drugs were effective in reducing pain, the analgesic effects of the drugs were diminished 12 hours after injection (Table 2). The increase in VAS and pain severity was significantly less in the tramadol group in 18 and 24 hours after operation.

DISCUSSION

There are multiple ways of administering opioids for postoperative analgesia including intravenous, intramuscular, and subcutaneous (a recently considered method). Local analgesia, both with subcutaneous administration or with an epidural, could provide improvements in pain relief and increase patients' satisfaction. With this approach, the amount of analgesia needed is reduced as well (14).

According to our results, tramadol and methadone subcutaneous injections alongside the wound can reduce postoperative pain severity in its first 12 hours but may be accompanied by a need for analgesia afterwards, which was lower for the tramadol group in this study.

Previous studies have demonstrated that subcutaneous tramadol alongside the wound compared to intravenous infusion may be better at controlling pain and reducing postoperative opioid consumption with lower side effects (15). Multiple studies have been previously performed on patients undergoing appendectomy (16), hernia surgery (17), cesarean section (18), or minor surgeries (19) and compared pain VAS in the first 6 hours or first 12 hours following surgery with acceptable pain control for tramadol, similar to the results of our study. These findings prove that tramadol may be a good choice for postoperative analgesia, if there are no contraindications for its use.

Jabalameli and Kalantari (13) observed that subcutaneous incision site injection of methadone in women who have undergone cesarean section had significantly in the first 24 hours post surgery, but not in the first 6, 12, and 18 hours compared to the control group. In our study, patients receiving subcutaneous methadone had sufficient pain relief in the first 12 hours following surgery but required analgesia afterwards. Subcutaneous tramadol used in previous studies also showcased a lower need for rescue analgesia in the first 24 hours, similar to our findings (15, 16, 20).

To the best of our knowledge, there are no previous studies comparing the efficacy of subcutaneous wound injection of tramadol or methadone in pain control. However, intravenous methadone compared to tramadol in orthopedic surgery in animals had significantly lower rates of need for analgesia and better pain control in the first 4 hours, while in both groups after 4 hours the pain VAS was increased (21). Furthermore, while administering intra-articular after arthroscopic anterior cruciate ligament reconstruction, the methadone group compared to tramadol needed less analgesia in the first 12 hours (11).

The reason for the difference between intravenous and subcutaneous administration of these two drugs could be due to different surgery types. Also, the bioavailability of the subcutaneous administration of tramadol seems to be more than methadone around the surgery wound with a longer duration of pain relief.

Limitations

Although this study was the first clinical trial to compare the subcutaneous use of tramadol and methadone in major abdominal surgeries, it does have its limitations. Firstly, we did not consider the suture type and incision length or patient mobility after operation which may have had an effect on the patient’s pain severity. Secondly, only the presumed time of rescue analgesia was included rather than the exact time. The small sample size could have also been another limitation.

CONCLUSIONS

The results of this study demonstrate that subcutaneous administration of tramadol and methadone were both effective in relieving pain in the first 12 hours post surgery, but afterwards, the need for analgesics are increased. Tramadol seems to be more effective than methadone in controlling pain following the first day after surgery.

Ethics Committee Approval: The ethics committee of Tabriz University of Medical Sciences has approved the study protocol (IR.TBZMED.REC.1397.088, IRCT20120605009948N3).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Türkoğlu Z, Karacaer F, Biricik E, Ilgınel M, Ünlüengen H. Comparison of the Effects of Epidural Levobupivacaine with Tramadol or Morphine Addition on Postoperative Analgesia following Major Abdominal Surgery. Turk J Anaesthesiol Reanim 2019; 47(4): 287–94. [CrossRef]
2. Khansa I, Koogler A, Richards J, Bryant R, Janis JE. Pain Management in Abdominal Wall Reconstruction. Plast Reconstr Surg Glob Open 2017; 5(6): e1400. [CrossRef]
3. Baratta JL, Schwenk ES, Viscusi ER. Clinical consequences of inadequate pain relief: barriers to optimal pain management. Plast Reconstr Surg 2014; 134(4 Suppl 2): 155–215. [CrossRef]
4. Joshi GP, Beck DE, Emerson RH, Halaszynski TM, Jahr JS, Lipman AG, et al. Defining new directions for more effective management of surgical pain in the United States: highlights of the inaugural Surgical Pain Congress™. Am Surg 2014; 80(3): 219–28. [CrossRef]
5. Kelly DJ, Ahmad M, Brull SJ. Preemptive analgesia I: physiological pathways and pharmacological modalities. Can J Anaesth 2001; 48(10): 1000–10. [CrossRef]
6. Cheung CW, Ching Wong SS, Qiu Q, Wang X. Oral Oxycodone for
Acute Postoperative Pain: A Review of Clinical Trials. Pain Physician 2017; 20(2): SE33–SE52. [CrossRef]
7. James MF, Heijke SA, Gordon PC. Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: a placebo-controlled double-blind trial. Anesth Analg 1996; 83(1): 87–91. [CrossRef]
8. Khajavi MR, Navardi M, Shariat Moharari R, Pourfakhr P, Khalili N, et al. Combined Ketamine-Tramadol Subcutaneous Wound Infiltration for Multimodal Postoperative Analgesia: A Double-Blinded, Randomized Controlled Trial after Renal Surgery. Anesth Pain Med 2016; 6(5): e37778. [CrossRef]
9. McNicol ED, Ferguson MC, Schumann R. Methadone for neuropathic pain in adults. Cochrane Database Syst Rev 2017; 5(5): CD012499.
10. Ali S, Sofi K, Dar AQ. Comparison of Intravenous Infusion of Tramadol Alone with Combination of Tramadol and Paracetamol for Postoperative Pain after Major Abdominal Surgery in Children. Anesth Essays Res 2017; 11(2): 472–6. [CrossRef]
11. Arti H, Mehdinasab SA. The comparison effects of intra-articular injection of different opioids on postoperative pain relieve after arthroscopic anterior cruciate ligament reconstruction: A randomized clinical trial study. J Res Med Sci 2011; 16(9): 1176–82.
12. Machado FC, Palmeira CCA, Torres JNL, Vieira JE, Ashmawi HA. Intraperoperative use of methadone improves control of postoperative pain in morbidly obese patients: a randomized controlled study. J Pain Res 2018; 11: 2123–29. [CrossRef]
13. Jabalameli M, Kalantari F. Evaluation of the analgesic effect of subcutaneous methadone after cesarean section. Adv Biomed Res 2014; 3: 197.
14. Mamoochehrian N, Bakhshaei MH. The evaluation of topical and subcutaneous bupivacaine infiltration on postoperative pain in postpartum tubal ligation. Anesthesiology and pain 2011; 1(3): 1–16.
15. Khajavi MR, Aghili SB, Moharari RS, Najafi A, Mohtaram R, Khashayar P, et al. Subcutaneous tramadol infiltration at the wound site versus intravenous administration after pyelolithotomy. Ann Pharmacother 2009; 43(3): 430–5. [CrossRef]
16. Khazaei A, Arbab-Kalati F, Borumand S, Rooshanravan R. The effect of local tramadol injection in post appendectomy pain. Zahedan J Res Med Sci 2012; 13(9): 43–7.
17. Malik AI, Sheikh IA, Qasmi SA, Adnan A. Comparison of Tramadol with Bupivacaine as Local Anaesthetic in Postoperative Pain Control. Journal of Surgery Pakistan (International) 2011; 16(1): 10–3.
18. Behdad S, Sekhavat L, Ayatollahi V, Meshkat F, Mortazavi A. Comparison of postoperative analgesic effect of tramadol and bupivacaine subcutaneous infiltration in patients undergoing cesarean section. Acta Clin Croat 2013; 52(1): 93–7.
19. Altunkaya H, Ozer Y, Kargi E, Ozkocak I, Hosnuter M, Bekir Demirel C, et al. The Postoperative Analgesic Effect of Tramadol When Used as Subcutaneous Local Anesthetic. Anesth Analg 2004; 99(5): 1461–4.
20. Demiraran Y, Ilce Z, Kocaman B, Bozkurt P. Does tramadol wound infiltration offer an advantage over bupivacaine for postoperative analgesia in children following herniotomy? Pediatric Anesthesia 2006; 16(10): 1047–50. [CrossRef]
21. Cardozo LB, Cotes LC, Kahvegian MA, Rizzo MF, Otsuki DA, Ferrigno CR, et al. Evaluation of the effects of methadone and tramadol on postoperative analgesia and serum interleukin-6 in dogs undergoing orthopaedic surgery. BMC Vet Res 2014; 10: 194. [CrossRef]