Original Article

Comparison of the Postoperative Analgesic Effects of Morphine, Paracetamol and Ketorolac in Patient-Controlled Analgesia (PCA) in Patients undergoing Open Cholecystectomy

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ABSTRACT

Objectives: Effective post-operative pain management in abdominal surgeries which are painful procedures, plays an important role in reducing post-operative complications and increasing patient's satisfaction. There are many techniques for pain control, one of which is patient-controlled analgesia (PCA). The aim of this study was to compare the analgesic effects of morphine, paracetamol and ketorolac in patients undergoing open cholecystectomy, using PCA method.
Design: Randomized controlled trial
Setting: Department of anesthesiology, Shahid Rajaee Hospital, Qazvin, Iran
Subjects: Three hundred and thirty ASA (American Society of Anesthesiology) I-II patients (three equal groups of n = 110) who were scheduled for elective open cholecystectomy.
Intervention: The control group received morphine with maximum dose of 0.02 mg/kg/h, the paracetamol group received paracetamol with maximum dose of 1 mg/kg/h, and the ketorolac group received ketorolac with maximum daily dose of 60 mg using IV-PCA method.
Main outcome measure: Post-operative pain
Results: There were no significant differences in demographic data between the three groups. There was a statistically significant difference with regard to the mean pain score at all times between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups ($p < 0.001$). The mean level of pain in ketorolac group was less than that in the other two groups ($p < 0.001$) at all times.
Conclusion: According to the results of this study, ketorolac is more effective than morphine and paracetamol in post-operative pain control.

KEYWORDS: analgesia, cholecystectomy, ketorolac, morphine, paracetamol

INTRODUCTION

Post-operative pain is the most common surgical complication, and is experienced by more than 70% of patients after surgery[1]. It is essential to control post-operative pain. It is often difficult to achieve an acceptable analgesia following a surgery with minimal side effects[2]. Various studies have described several undesirable effects of pain with maximum physiological effects on the body systems which include adrenal sympathetic activity, reduced blood flow to coronary arteries, deep vein thrombosis, inadequate depth of breathing, atelectasis, increased heart rate and blood pressure. Post-operative pain management leads to reduced mortality, length of hospital stay and costs, as well as early ambulation. Accordingly, management and control of pain is always regarded as a professional challenge[3-5]. There are several post-operative analgesic techniques, including local injection of anesthetics, nerve blocks, administration of systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs), intrathecal methods, epidural and patient-controlled analgesia (PCA)[6-8]. Intravenous PCA is a highly effective pain-reducing method with minimal side effects. Today, IV-PCA with

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morphine is recognized as an essential component of post-operative analgesia. In this method, morphine is the drug of choice. Some studies have shown that infusion dose of opioids causes respiratory depression, drowsiness and sedation, nausea and vomiting, pruritus, urinary retention, ileus and constipation and because of the respiratory events it is vital to monitor the patients[9-12]. These undesirable side effects urged investigators to search for some other analgesic drugs. Intravenous acetaminophen (paracetamol) is one of the new strategies used for post-operative pain management. It is used for managing mild to moderate pain[13,14]. NSAIDs are another class of analgesics used in some studies[15]. Ketorolac and other NSAIDs have a powerful anti-inflammatory, analgesic, and antipyretic effect by inhibiting cyclooxygenase I and cyclooxygenase II and effectively control mild to moderate post-operative pain[16,17]. Since ketorolac can be administrated intravenously, and serious complications such as respiratory and cardiovascular suppression was not seen, it has been used for post-operative pain control, alone or by mixing it with opioids through the PCA method[18,19] .

In recent years, several studies have compared the analgesic efficacy of patient-controlled morphine with paracetamol, but no such comparision has been performed with ketorolac. Considering the importance of post-operative pain control, IV-PCA as a beneficial method, and morphine's complications described above, we compared the analgesic efficacy and side effects of morphine, paracetamol and ketorolac administered by PCA method for post-operative pain management after open cholecystectomy in this study.

SUBJECTS AND METHODS

This randomized controlled clinical trial was registered in Iranian Registry of Clinical Trials (IRCT) with number 2014031717048N1. Written informed consent was obtained from all patients and they were informed about the visual analog scale (VAS) and PCA during the pre-operative visits. The study was performed on 330 patients in Shahid Rajaee Hospital of Qazvin, Iran from August 2013 until September 2015.

Inclusion criteria were patients aged between 20 and 50 years, ASA (American Society of Anesthesiology) class I-II and elective open cholecystectomy with Kokher incision. Exclusion criteria were inability to be trained to use the PCA pump, psychiatric illnesses, bronchial asthma, renal or hepatic disease, BMI ≥ 30, addiction, allergic reactions to opioids or paracetamol or other NSAIDs, cardiovascular disease, history of peptic ulcer and gastrointestinal bleeding, and routine analgesic consumption.

The technique of general anesthesia was similar in three groups. After standard monitoring including electrocardiography, pulse oximetry and non-invasive blood pressure monitoring, all patients were pre-medicated with midazolam (0.02 mg/kg) and fentanyl (2 μg/kg). Anesthesia was induced with propofol (2 mg/kg) and atracurium (0.5 mg/kg) and maintained with propofol (100 μg/kg/min) and remifentanil (0.4 μg/kg/min) and atracurium (0.15 mg/kg) was injected every 30 minutes. At the end of the surgery, the effects of the muscle relaxant were reversed using atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg). After transfer to post-anesthesia care unit and achieving full consciousness, patients were randomly divided into three groups of 110 patients each to receive morphine (control group) and paracetamol or ketorolac (intervention groups). Assignment of patients into three groups was implemented using blocked randomization. One group received morphine sulphate (Daroupakhsh, Iran) with maximum dose of 0.02 mg/kg/h, another group received paracetamol (Unipharma, Greece) with maximum dose of 1 mg/kg/h, and the last group received ketorolac (Sinadauro, Iran) with maximum daily dose of 60 mg using IV-PCA method. The level of pain was assessed by VAS (0 = no pain, 10 = the most intense pain). Simultaneously with pain intensity, the presence and severity of nausea, patient's satisfaction (VAS), heart rate (HR) and blood pressure (BP) changes, subsequent itching and respiratory problems after using morphine, paracetamol, and ketorolac were recorded by a third person (trained colleague) every 2 hours for 8 hours post-operatively. Changes in HR and BP < 20% baseline were considered as low, 20 - 40% moderate and > 40% were considered as high. Data were analyzed using SPSS 17 software. Demographic data were analyzed by one way ANOVA, and for comparison of group differences, we used the Kruskal-Wallis test. P-value < 0.05 was considered statistically significant.

RESULTS

We followed the CONSORT (Consolidated Standards of Reporting Trials) guidance for reporting results (Fig 1).

Table 1: Demographic characteristics in the three groups (mean ± standard deviation)

Drug	Age	Gender (Female/Male)
Morphine (n = 110)	37.15 ± 5.42	58/52
Paracetamol (n = 110)	39.27 ± 7.57	58/52
Ketorolac (n = 110)	37.21 ± 8.99	48/62
P-value	0.112	0.162

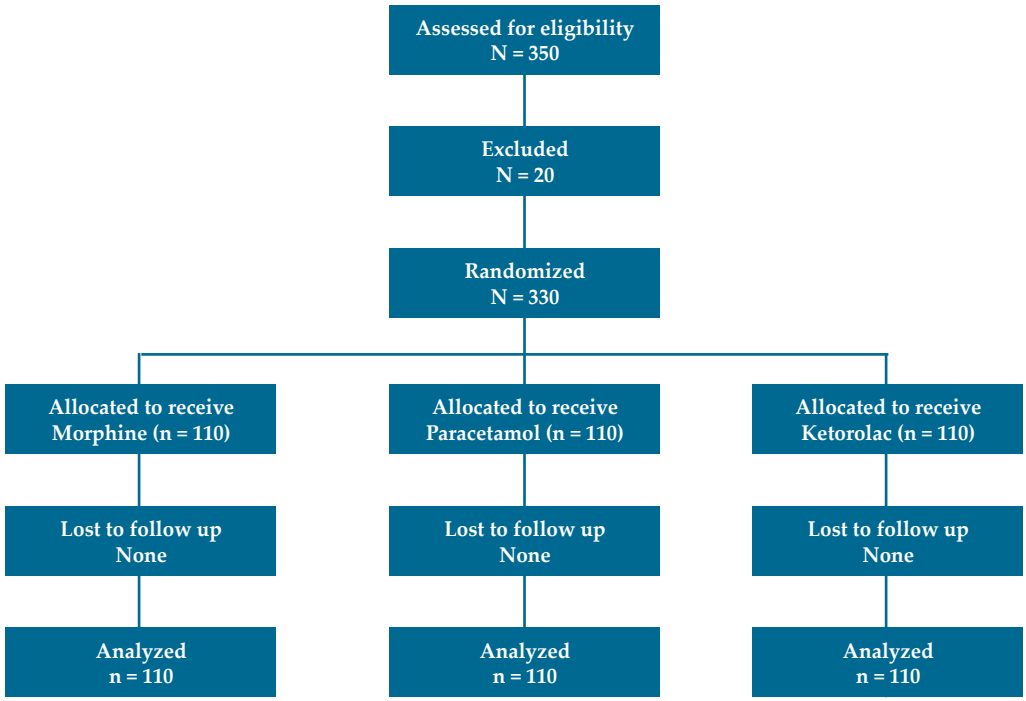

Fig 1: CONSORT Flow Diagram

Table 2: Mean pain score in three groups according to VAS at different hours (mean ± standard deviation)

Drug	After 2 hours	After 4 hours	After 6 hours	After 8 hours
Morphine (n = 110)	4 ± 0.13	3.98 ± 0.23	3.50 ± 0.52	3.13 ± 0.43
Paracetamol (n = 110)	3.37 ± 0.48	2.70 ± 0.51	2.28 ± 0.45	2.00 ± 0.00
Ketorolac (n = 110)	2.50 ± 0.58	1.46 ± 0.50	1.08 ± 0.27	1.00 ± 0.09
P-value	<0.001	<0.001	<0.001	<0.001

In this study, data obtained from 330 patients (110 in each group), aged 20 to 50 years, undergoing elective open cholecystectomy were analyzed. There were no significant differences in demographic data between the groups (Table 1).

As can be seen from Table 2, according to VAS, there was a statistically significant difference regarding the mean pain score at all hours between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups ($p < 0.001$). Post-operative pain scores decreased significantly with time in all three groups. At all times, the mean level of pain in ketorolac group was less than that in the other two groups.

According to Table 3, there were significant differences in changes in level of nausea at all hours between morphine and paracetamol and morphine and ketorolac groups ($p < 0.001$). In addition, there were significant differences between paracetamol and ketorolac groups only after 2 and 4 hours ($p < 0.001$).

As shown in Table 4, there were significant differences in patient's satisfaction at all hours between morphine and paracetamol, morphine and ketorolac, and paracetamol and ketorolac groups ($p < 0.001$). Mean satisfaction in all three groups increased with time, and at all 4 data collection times, mean satisfaction was greater in ketorolac group.

Table 3: Mean nausea score in three groups according to VAS at different hours (mean ± standard deviation)

Drug	After 2 hours	After 4 hours	After 6 hours	After 8 hours
Morphine (n = 110)	4.77 ± 2.19	4.01 ± 2.18	3.39 ± 1.86	2.90 ±1.68
Paracetamol (n = 110)	2.90 ± 1.31	1.75 ± 0.75	1.18 ± 0.47	1.06 ± 0.31
Ketorolac (n = 110)	1.57 ± 0.79	1.04 ± 0.24	1.00 ± 0.00	1.00 ± 0.00
P-value	< 0.001	< 0.001	< 0.001	< 0.001

Table 4: Mean patient's satisfaction in three groups according to VAS at different hours (mean ± standard deviation)

Drug	After 2 hours	After 4 hours	After 6 hours	After 8 hours
Morphine (n = 110)	5 ± 1.07	4.96 ± 0.95	5.04 ± 0.99	5.10 ± 1.01
Paracetamol (n = 110)	5.77 ± 0.99	6.99 ± 0.59	7.35 ± 0.6 7	7.53 ± 0.7 1
Ketorolac (n = 110)	7.26 ± 0.8 9	8.13 ± 0.77	8.59 ± 0.63	8.72 ± 0.58
P-value	< 0.001	< 0.001	< 0.001	< 0.001

Table 5: Changes in heart rate in the three groups

Drug	After 2 hours		After 4 hours		After 6 hours		After 8 hours	
	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)
Morphine (n = 110)	14 (12.7)	95 (86.4)	76 (69.1)	34 (30.9)	99 (90)	11 (10)	110 (100)	0 (0)
Paracetamol (n = 110)	77 (70)	33 (30)	110 (100)	0 (0)	110 (100)	0 (0)	110 (100)	0 (0)
Ketorolac (n = 110)	104 (94.5)	6 (5.5)	109 (99.1)	1 (0.9)	110 (100)	0 (0)	110 (100)	0 (0)

According to Table 5, there were significant differences in changes in HR at all times between morphine and paracetamol and morphine and ketorolac groups ($p < 0.001$). Moreover, there were significant differences between paracetamol and ketorolac groups only after 2 and 8 hours ($p < 0.001$).

It can be seen from Table 6 that there were significant differences in changes in BP at all times between morphine and paracetamol and morphine and ketorolac groups ($p < 0.001$). In addition, there were significant differences between the paracetamol and ketorolac groups only after 6 and 8 hours ($p < 0.001$).

High changes in BP and HR were seen only in one patient in morphine group after 2 hours and not seen in other groups and times.

In this study, patients were also examined for presence of itching after 2, 4, 6, and 8 hours, and only one patient in morphine group complained of itching after 2 hours (2.9%). Furthermore, the three groups were assessed in terms of arterial oxygen desaturation using pulse-oximetery, and no arterial oxygen desaturation below 90% was reported.

DISCUSSION

Effective post-operative pain management is a major concern for anesthesiologists. Use of opioids for post-operative pain control has several side effects such as respiratory depression, nausea and vomiting, pruritus and urinary retention[20]. Therefore, the use of non-opioids such as NSAIDs has become more popular to avoid these side effects[21]. NSAIDs and acetaminophen (paracetamol) are commonly used in the management of mild to moderate pain alone or in combination with opioids[22]. In the current study, comparision of analgesic effects of morphine, paracetamol and ketorolac infusion after elective cholecystectomy was performed and the efficacy of ketorolac was approved. There have been many studies conducted in recent years on post-operative analgesia using various drugs and methods. Various studies have compared ketorolac with opioids. The findings range from ketorolac being more effective than opioids to being equally effective or to being less effective than opioids[23]. According to the study of Taghavi Gilani, intravenous paracetamol added to morphine PCA for post-operative pain management decreases morphine intake and leads to better consciousness level without further complications[24]. In the study of Alimian where analgesic effects of paracetamol and morphine after elective laparotomy surgeries were compared, significant difference in pain score was found between the two groups in the first 8 hours[25]. In the other study, Yaghoubi showed that morphine had superior analgesic effect than paracetamol 2 and

Table 6: Changes in BP in the three groups

Drug	After 2 hours		After 4 hours		After 6 hours		After 8 hours	
	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)	Low n (%)	Moderate n (%)
Morphine (n = 110)	17 (15.5)	92 (83.6)	93 (84.5)	17 (15.5)	99 (90)	11 (10)	110 (100)	0 (0)
Paracetamol (n = 110)	107 (97.3)	3 (2.7)	110 (100)	0 (0)	110 (100)	11 (10)	110 (100)	0 (0)
Ketorolac (n = 110)	110 (100)	0 (0)	110 (100)	0 (0)	110 (100)	11 (10)	110 (100)	0 (0)

4 hours after laparotomy, but after 6 and 8 hours they had similar effects[26]. In another study, morphine was a more efficacious analgesic than ketorolac for post-operative pain[23]. In the research conducted by Unlugenc, the analgesic effect and side effects of IV patient-controlled morphine, pethidine, and tramadol for post-operative pain management were compared and all the three drugs resulted in equivalent pain scores and side effects[27]. The reason for these discrepant results could have been related to the sample size, the moment of evaluation, the duration of follow-up, genetic variations and different responses to drugs and non equianalgesic dose used for drugs. The results of the present study showed that PCA-induced analgesia in ketorolac group was superior than paracetamol and morphine groups. Every factor studied, including nausea, patient's satisfaction and hemodynamic changes, favored ketorolac compared with other groups.

CONCLUSION

According to the results of this study, we can explain that ketorolac provides superior analgesia compared to morphine and paracetamol for post-operative pain management.

REFERENCES

1. Nikolajsen L, Haroutiunian S. Intravenous patient-controlled analgesia for acute postoperative pain. Eur J Pain Suppl 2011; 5(S2):453-456.
2. Elseify ZA, El-Khattab SO, Khattab AM, Atta EM, Ajjoub LF. Combined parecoxib and I.V paracetamol provides additional analgesic effect with better postoperative satisfaction in patients undergoing anterior cruciate ligament reconstruction. Saudi J Anaesth 2011; 5(1):45-49.
3. Imani F , Aleboye MR, Farahini H, Tavvaf H, Sakhaei M. Comparison of patient controlled intravenous analgesia and patient controlled regional analgesia through femoral catheter after anterior cruciate ligamentum repair. Razi Journal of Medical Sciences 2010; 17:16-22.
4. Baltali S, Turkoz A, Bozdogan N, Demirturk OS, Baltali M, Turkoz R, *et al*. The efficacy of intravenous patient-controlled remifentanil versus morphine anesthesia after coronary artery surgery. J Cardiothorac Vasc Anesth 2009; 23:170-174.
5. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995; 62:259–274.
6. Chen WH, Liu K, Tan PH, Chia YY. Effects of postoperative background PCA morphine infusion on pain management and related side effects in patients undergoing abdominal hysterectomy. J Clin Anesth 2011; 23(2):124-129.
7. Albrecht S, Schuttler J, Yarmush J. Postoperative pain management after intraoperative remifentanil. Anesth Analg 1999; 89:540-545.
8. Munoz HR, Guerrero ME, Brandes V, Cortinez LI. Effect of timing of morphine administration during remifentanil-based anesthesia on early recovery from anesthesia and postoperative pain. Br J Anesth 2002; 88(6):814-818.
9. Ghahiri AA, Fereidoni F, Abdi F, Ghasemi M, Sadr OK. Comparison study on effect of intramuscular petidin injection against intra venues patient control analgesia (PCA) after elective cesarean section. Journal of Isfahan Medical School 2011; 29(130):215-221.
10. Mercadante S. Intravenous patient-controlled analgesia and management of pain in post-surgical elderly with cancer. Surg Oncol 2010; 19(3):173-177.
11. Imani F. Postoperative pain management. Anesth Pain Med 2011;1(1):6-7
12. Hurley RW, Wu CL. Acute postoperative pain. Ronald D. Miller, Anesthesia. 7th edition, Philadelphia, Churchil Livingstone. 2010:2758–2759.
13. Kolahdouzan K, Eydi M, Anvari HM, Golzari SEJ, Abri R, Ghojazadeh M, *et al*. Comparing the efficacy of intravenous acetaminophen and intravenous meperidine in pain relief after outpatient urological surgery. Anesth Pain Med 2014; 4(5):e30788.
14. Schug SA, Sidebotham DA, McGuinnety M, Thomas J, Fox L. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesth Analg 1998; 87:368-372.
15. Van Aken H, Thys L, Veekman L, Buerkle H. Assessing analgesia in single and repeated administrations of propacetamol for postoperative pain: comparison with morphine after dental surgery. Anesth Analg 2004; 98(1):159–165.
16. Moote C. Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain. Drugs 1992; 44(Suppl 5):14–29.
17. Fredman B, Olsfanger D, Jedeikin R. A comparative study of ketorolac and diclofenac on post-laparoscopic cholecystectomy pain. Eur J Anaesthesiol 1995; 12:501-504.
18. Buckley MM, Brogden RN. Ketorolac: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1990; 39:86-109.
19. Kenny GN, McArdle CS, Aitken HH. Parenteral ketorolac: opiate-sparing effect and lack of cardiorespiratory depression in the perioperative patient. Pharmacotherapy 1990; 10:127S–131S.
20. Hashemi SM, Esmaeelijah A, Golzari S, Keyhani S, Maserrat A, Mohseni G, *et al*. Intravenous paracetamol versus patient-controlled analgesia with morphine for the pain management following diagnostic knee arthroscopy in trauma patients: a randomized clinical trial. Arch Trauma Res 2015; 4(4):e30788.
21. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth 2002; 88(2):199–214.

22. Moller PL, Juhl GI, Payen-Champenois C, Skoglund LA. Intravenous acetaminophen (paracetamol): comparable analgesic efficacy, but better local safety than its prodrug, propacetamol, for postoperative pain after third molar surgery. Anesth Analg 2005; 101:90-96.
23. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O. Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial. Anesthesiology 2005; 103:1225-1232.
24. Gilani MT, Bameshki A, Yazdi AP, Hasanzadeh R. Comparison of patient-controlled analgesia using morphine with and without paracetamol in postoperative pain control. Patient Saf Qual Improv 2016; 4:375-378. http://psj.mums.ac.ir/article_6689_5c6d0252c07393bb74a6d41737d595de.pdf
25. Alimian M, Pournajafian A, Kholdebarin A, Ghodraty M, Rokhtabnak F, Yazdkhasti P. Analgesic effects of paracetamol and morphine after elective laparotomy surgeries. Anesth Pain Med 2014; 4(2):e12912.
26. Yaghoubi S, Pourfallah R, Barikani A, Kayalha H. The postoperative analgesic effect of morphine and paracetamol in the patients undergoing laparotomy, using PCA method. Glob J Health Sci 2013; 6(1):207-214.
27. Unlugenc Hakki, Vardar MA, Tetiker S. A comparative study of the analgesic effect of patient-controlled morphine, pethidine, and tramadol for postoperative pain management after abdominal hysterectomy. Anesthesia & Analgesia 2008; 106:309-312.