www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Comparison between Intravenous Fentanyl Alone and Intravenous Fentanyl plus Intravenous Ketorolac for Late Intraoperative and Immediate Postoperative Analgesia during Laparoscopic Cholecystectomy

Authors
S A Mannan[1], Rabiaarifa[2], Sajad Hamid[3]
[1]Consultant, Anesthsiology SKIMS Medical College, Bemina
[2]Medical officer JK Health Services
[3]Lecturer Anatomy, SKIMS Medical College, Bemina
Corresponding Author
S A Mannan
Consultant, Anesthsiology SKIMS Medical College, Bemina
Email: *medicalacademy@rediffmail.com*

ABSTRACT

Objective*: Our study compared the effect of fentanyl alone with fentanyl plus intravenous ketorolac for analgesic efficacy, opioid sparing effects, and opioid-related side effects after laparoscopic cholecystectomy.*

Materials and Methods: Sixty patients undergoing laparoscopic cholecystectomy were randomized into two groups. Both groups received fentanyl during induction. First group of patients received IV placebo before the end of surgery while second group received 0.5mg of I.V. ketorolac just before the end of surgery. The postoperative pain relief was evaluated by a visual analog scale (VAS) using a 100-mm visual analog scale adverse effects, as well as vital signs were recorded every 15 min for 150 min or until discharge from the postanesthesia care unit.

Results: *The mean VAS score in first and second hour after surgery was less in the group receiving I.V. ketorolac (3.4± 0.2 vs5.4±0.5./ 3.3±0.4 vs4.7 ±0.2.); the rescue analgesia consumption over first 24 h was also less in the group receiving I.V. ketorolac (40±25.9 vs. 102±20.7). The time requirement of first dose of rescue analgesic in the postoperative period was also significantly prolonged in the group receiving I.V. ketorolac (240±24.9 vs. 55±12.3). There was no difference in the sedation scores and in the incidence of PONV in the two groups.*

Conclusion: *The study demonstrates the usefulness of intravenous ketorolac as supplementary analgesic in the treatment of postoperative pain after laparoscopic cholecystectomy.*

Keywords: *Intravenous ketorolac, pain after laparoscopic cholecystectomy, postoperative analgesia.*

INTRODUCTION

Pain is the most common complaint after laparoscopic cholecystectomy.[1,2] resulting in the use of rescue opioid analgesics in up to 80% patients.[3] Furthermore the pattern of pain after laparoscopic cholecystectomy is complex and unlikely to benefit always from identical analgesic treatment.[4]

Ketorolac or ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) in the family of heterocyclic acetic acid derivatives, that inhibits both cyclo-oxygenase and lipo-oxygenase enzymes, thereby, preventing the synthesis of both prostaglandins and leukotrienes[5], and may also release endogenous opioids [6]. Parenteral NSAIDs (e.g., ketorolac) are being used increasingly for postoperative pain as sole analgesic agents and in conjunction with opioids as opioid-sparing agents (Cepeda et al. 2005). The efficacy of ketorolac has been well established with 30 mg being equianalgesic with 10 mg of parenteral morphine for acute pain (Cepeda et al. 2005). When used together, there was a significant reduction of adverse side effects of opioids due to a significant reduction in morphine requirements. While ketorolac can reduce opioid requirements, it is not potent enough to be used as a sole analgesic after major surgery such as intra-abdominal surgery (Cepeda et al. 1995). Peak analgesia from ketorolac is typically seen 1–2 h after administration, and the half-life is approximately 6 h, although it may be prolonged in patients with reduced renal function or in the elderly. The manufacturer's recommended dose for elderly individuals or those with renal insufficiency is 15 mg every 6 h following a 30 mg loading dose, and doses as low as 10 mg have been found to significantly reduce opioid requirements and provide analgesia equivalent to 10 mg of intravenous morphine (Ready et al. 1994).

The aim of this randomized study was to compare the analgesic efficacy of intravenous fentanyl alone versus intravenous fentanyl plus ketorolac for postoperative pain relief after laparoscopic cholecystectomy

METHODS

After informed consent a total 0f 60 patients of either sex weighing between 56-80 kg and age between 30- 60 years belonging to ASA-I and ASA-II presenting for elective laproscopic cholecystecomy were included in the study. Patients with diagnostic laparoscopy, those having contraindications to ketamine or to nonsteroidal anti-inflammatory drugs (NSAIDs) (esophago-gastroduodenal disease, renal insufficiency, and abnormal coagulation) were excluded, as were those on treatment by steroids, NSAIDs, or opioids before surgery.

The patients were randomly divided into two groups.

Group I: 30 patients in whom fentanyl was used as sole intravenous analgesia.

Group II: 30 patients in whom fentanyl plus ketorolac was used as an intravenous analgesia.

The study design was randomized and unblinded.

Patients were premedicated with tab. Alprazolam 0.25mg on night before surgery. On arrival to the operating room, after establishing i/v line all

standard monitoring techniques were used and crystalloid infusion was started.

After the administration of oxygen, anesthesia was induced in both the groups with IV propofol (2 mg/kg), fentanyl (2 μg/ kg), and rocuronium (0.6 mg/kg). Anesthesia was maintained by 1–2% isoflurane in nitrous oxide and oxygen (ratio 2:1). The lungs were mechanically ventilated, and ventilation was adjusted to maintain end-expiratory CO2 between 34–36 mm Hg depending on the different stages of laparoscopy. ketorolac was given in the dose of 0.5mg/kg intraoperatively 15 minutes before the end of surgery. After tracheal extubation, patients were transferred to the PACU. Postoperative pain was assessed using a visual analog scale (VAS; 0cm "no pain" and 10cm "worst pain imaginable"). Postoperative analgesia was provided routinely to all patients by intramuscular diclofenac at 8 h interval and intravenous fentanyl 1 μg/kg was administered as rescue analgesic when the VAS score exceeded 3.

The degree of sedation was determined according to a sedation score ranging from 0 to 2 (0_ alert, 1_ drowsy but rousable to voice, and 2_ very drowsy, but rousable to shaking). The VAS scores and sedation scores were assessed at 1, 2, 4, 6, 8, 12, and 24 h after surgery. Total and incremental fentanyl consumption at these times for both the groups was also recorded. If nausea and/or vomiting occurred, the same was noted and 8 mg of ondansetron was given intravenously. The number of patients receiving antiemetics and their total dosages were noted. Patients were observed for the occurrence of any adverse effects during the first 24 h. After 24 h, patients were assessed for: (a) ability to mobilize and dress, (b) need for any analgesic, and (c) surgical complication, if any. When the patient scored yes on the former and no on the two latter questions, they were assessed ready for discharge from hospital. All measurements were recorded by the anesthesia resident who was blinded to the study drugs administered.

Finally all study observations were documented and tabulated, they were analyzed statistically and results were recorded.

The statistical analysis of the data was done by using statistic student's t-test for difference of means for quantitative data analysis.

For nominal data chi-square test (χ^2-test) and fisher's exact test were used.

All these tests were two sided and were referred for p-values for their significance. Any p-value less than 0.05 i.e. ($p< 0.05$) were taken to be statistically significant.

The analysis of the data was performed on statistical package for social sciences, Chicago, USA for windows.

RESULTS

Both groups were similar in regard to age, weight, sex, ASA physical status, duration of anesthesia and surgery, intraoperative blood loss and the duration of hospital stay [Table 1]. None of the patients in either group required additional dose of fentanyl intraoperatively [Table 2].

Table 1 Patient data and characteristics (mean±SD)

Variable	**fentanyl Group I n=30**	**fentanyl plus ketorolac Group II n=30**
Age (yrs)	58±12.5	59± 12.8
Weight(kg)	65±7.8	62±7.0
ASA physicalstatus(I/II)	19/11	23/7
Sex(m/f)	14/16	18/12
Duration of anaesthesia(min)	47±12.4	45±32.2
Intraoperativeblood loss(ml)	44±17.3	49±20.5
Duration of hospital stay (days)	1.3±o.8	1.3±0.6

Table 2 Postoperative pain relief and side effects

Variable	**fentanyl Group I n=30**	**fentanyl plus ketorolac Group II n=30**	**Significance**
Intraoperative fentanyl(µgm)	0	0	NA
Amount of fentanyl in PACU (min)	102±20.7	40±25.9	p< 0.05
Length of stay in PACU(min)	63±12.6	67±13.9	NS
Incidence of PONV	1/30	1/30	NS
Incidence of sedation	2/30	1/30	NS
Time for ist analgesia(min)	55±12.3	240±24.9	p< 0.05
No. Of patients requiring rescue Analgesia in post operative period	9/30	10/30	NS

p< 0.05 test of significance

Post operative pain relief and side effects

The mean VAS pain score over the 24-h period was similar in both the groups [Table 2]; however, the mean VAS score at 1 and 2 h after surgery was lower in the Group II [Table 3].

Table 3 VAS score

Time(hrs)	**fentanyl Group I n=30**	**fentanyl plus ketorolac Group II n=30**	**Significance**
1	5.4±0.5	3.4± 0.2	p< 0.05
2	4.7 ±0.2	3.3±0.4	p< 0.05
4	3.1±0.4	3.5±0.5	NS
6	2.7±0.6	2.7±0.9	NS
8	2.8±0.5	2.9 ±0.2	NS
12	2.6±0.7	2.7±0.8	NS
24	2.5±0.4	2.4± 0.9	NS

p< 0.05 test of significance

Pain scores (mean±SD)

The total consumption of fentanyl as rescue analgesic in PACU was significantly higher in Group I over Group II [Table 2] and the time for the first dose of rescue analgesic in the PACU was significantly lower in Group I over Group II [Table 2].

However, the number of patients requiring rescue analgesic was similar in both the groups [Table 2].

There was no difference in the length of stay in PACU, incidence of PONV and in the incidence of sedation [Table 2].

The sedation scores were similar in both the groups [Table 4]. No postoperative complications were reported from any of the groups.

Time(hrs)	**fentanyl Group I n=30**	**fentanyl plus ketorolac Group II n=30**
1	1(0-2)	1(0-2)
2	1(0-2)	1(0-2)
4	1(0-2)	0(0-2)
6	0(0-2)	0(0-2)
8	0(0-2)	0(0-2)
12	0(0-2)	0(0-2)
24	0(0-2)	0(0-2)

DISCUSSION

Postoperative pain leads to higher morbidity, increased hospital stay and delayed recovery after major surgical procedure[7]. Failure to recognise the extent of pain and fear of precipitating respiratory depression may lead to analgesia being with held, resulting in irregular administration, fluctuating plasma levels and hence inadequate pain relief[8]. Poor pain control during the intraoperative and early postoperative period leads to complications in both long- and short-term periods. Among these complications, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma etc. can be severe. With a good analgesic treatment plan, the anxiety, morbidity, cost and length of hospital stay in the postoperative period are decreased.

The overall pain after laparoscopic cholecystectomy is a conglomerate of three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain), and shoulder pain (referred to visceral pain). Besides showing individual variation in intensity and duration, the pain is often unpredictable. It may even remain severe throughout the first week in 18% of the patients. [9] The complex nature of

pain after laparoscopic cholecystectomy suggests that effective analgesic treatment should be multimodal.[9,10]

In one study,[11] A single 30 mg dose of ketorolac was administered intravenously just prior to induction of sedation with midazolam. Ketorolac was well tolerated and provided good postoperative analgesia. It was suggested that ketorolac is a useful addition to the analgesic armamentarium and appropriately prescribed, provides good pain relief following day case oral surgery.

In another study [12] For post-operative pain Ketorolac was administration at prearranged times, every 8 hours, it was that it offered greater benefits in respect to its continuous infusion

In another study[13] it was found that Ketorolac exhibits significant opiate-sparing effects in the immediate postoperative period without introducing additional morbidity to pediatric surgical procedures.

In our study, we used intravenous ketorolac0.5mg/kg intraoperatively 15 minutes before the end of surgery in laparoscopic cholecystectomy and assessed its effects on the immediate postoperative analgesic requirement, post-operative analgesic effectiveness, post-operative fentanyl consumption, frequency of side-effects, and hospital stay length. Our study showed that intravenous Ketorolac exhibits significant opiate-sparing effects in the immediate postoperative period when used as part of multimodal analgesic regime, has significant opioid sparing effect.

It has been reported in previous studies that Ketorolac when used as as an adjunct produces a 31–37% decrease in the morphine requirement during the first 24 h after surgery.[14,15] Our study results are consistent all previous findings in this regard.

In our study no differences were observed between the two groups in the adequacy of analgesia as assessed by VAS scores. However, the median pain scores were significantly lower in the ketorolac group (Group II) at two intervals and the time for first analgesic requirement was significantly lower in the fentanyl alone group (Group I).

Clinical studies have also found that 30 mg ketorolac employed alone is just as effective as 1 gm intravenous paracetamol, 75 mg diclofenac or 10 mg morphine.[16,17] Our study did not find any reduction in the opioid related side-effects (PONV, sedation etc.) in the ketorolac group (Group II) as might be expected because of the decrease in total fentanyl dose. This may be because of the lesser number of subjects in our study. Larger studies with adequate power to detect opioid-related side-effects would be able to demonstrate the reduction of dose-dependent side-effects of fentanyl, such as sedation, respiratory depression, urinary retention, or nausea.

Our study demonstrated the additive effect of combining intravenous ketorolac with fentanyl on postoperative analgesia resulting in decreased opioid amount and in slightly improved or similar pain relief. The different sites of action of these drugs in the nervous system may be the cause of better pain relief. Whereas the primary mechanism

of action responsible for ketorolac's anti-inflammatory, antipyretic and analgesic effects is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX). . The analgesic effect of fentanyl is due to its agonist action in the opioid receptors of the central nervous system. The complimentary analgesic actions of the two drugs make them an important component of multimodal pain therapy.

In **Conclusion**, our study demonstrates the usefulness of intravenous ketorolac as supplementary analgesia to fentanyl for the postoperative pain after laparoscopic cholecystectomy. Intravenous ketorolac use is associated with a satisfactory analgesia and smaller opioid consumption. This may be beneficial in the management of pain after laparoscopic cholecystectomy in patients prone to opioid-related complications.

REFERENCES

1. McMohan AJ, Russel IT, Ramsay G, Sunderland G, Baxter JN, Anderson JR, et al. Laparoscopic and minilaparotomy cholecystectomy: A randomized trial comparing postoperative pain and pulmonary function. Surgery. 1994;115:533–9. [PubMed]
2. Troidl H, Spangenberger W, Langen R, al-Jaziri A, Eypasch E, Neugebauer E, et al. Laparoscopic cholecystectomy: technical performance, safety and patient's benefit. Endoscopy. 1992;24:252–61. [PubMed]
3. Madsen MR, Jensen KE. Postoperative pain and nausea after laparoscopic cholecystectomy. Surg Laparosc Endosc. 1992;2:303–5. [PubMed]
4. Mouton WG, Bessell JR, Otten KT, Maddern GJ. Pain after laparoscopy. Surg Endosc. 1999;13:445–8. [PubMed]
5. *HYERS TM, TRICOMI SM, LIAO JJ.* Inhibition of somehuman neutrophil functions by the cyclooxygenasene inhibitor ketorolac tromethamine. J LeukocBiol 1992; 51: 490-495.
6. *DOMER F.* Characterization of the analgesic activity of ketorolac in mice. Eur J Pharmacol 1990; 177: 127-135.
7. The reduction of postoperative chest infection by prophylactic co-trimoxazole (p.464-466) C. Morran, C. S. McArdle Published Online: Dec 7 2005 7:48PM DOI: 10.1002/bjs.1800670704
8. P C Rutter, F Murphy, and H A Dudley Morphine: controlled trial of different methods of administration for postoperative pain relief. Br Med J Jan 1980; 280: 12 - 13; doi:10.1136/bmj.280.6206.12
9. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90:261–9. [PubMed]
10. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory

laparoscopic cholecystectomy. Anesth Analg. 1996;82:44–51. [PubMed]

11. The efficacy of postoperative pain management with ketorolac for day case oral surgery P Coulthard, AT Snowdon, JP Rood Ambulatory Surgery Volume 3, Issue 4, December 1995, Pages199–203
12. Efficacy of scheduled time ketorolac administration compared to continuous infusion for post-operative pain after abdominal surgery A. RUSSO1, E. DI STASIO2, F. BEVILACQUA1, S. CAFAROTTI3, A. SCARANO1, E. MARANA1 European Review for Medical and Pharmacological Sciences 2012; 16: 1675-1679
13. Ketorolac reduces postoperative narcotic requirements ☆ J Pediatr Surg 36:76-79. Copyright © 2001 by W.B. Saunders Company. Presented at the 31st Annual Meeting of the American Pediatric Surgical Association, Orlando, Florida, May 25-29, 2000. David E. Carney, Linda A. Nicolette, Michael H. Ratner, Anita Minerd, Thomas J. Baesl
14. Reuben SS, Connelly NR, Steinberg R. Ketorolac as an adjunct to patient-controlled morphine in postoperative spine surgery patients. Reg Anesth. 1997;22:343–6. [PubMed]
15. Reuben SS, Connelly NR, Lurie S, Klatt S, Gibson CS. Dose-response of Ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal fusion surgery. Anesth Analg. 1998;87:98–102. [PubMed]
16. Flower RJ, Vane JR. Inhibition of prostaglandin synthesis in brain explains the anti-pyretic effect of Paracetamol (4-aminodophenol) Nature. 1972;240:410–1. [PubMed]
17. Tjolsen A, Lund A, Hole K. Antinociceptive effect of Paracetamol in rats in partly dependent on spinal serotonergic systems. Eur J Pharmacol. 1991;193:193–201. [PubMed]