Anaesthesia, Pain & Intensive Care
2004; 8/2:12-17

A COMPARISON OF ANALGESIC EFFICACY OF KETOROLAC AND PIROXICAM FOR POSTOPERATIVE PAIN RELIEF AFTER CHOLECYSTECTOMY

AMANAT KHAN, MCPS, FCPS*, TARIQ MEHMOOD MUFTI MCPS, FCPS**

ABSTRACT:

OBJECTIVE

This prospective randomized single blind study was designed to evaluate the analgesic efficacy of ketorolac and compare its effectiveness with the analgesic efficacy of piroxicam for postoperative pain management after cholecystectomy.

SETTINGS:

Department of Anaesthesiology and Intensive Care, PNS SHIFA, KARACHI.

METHODOLOGY:

In this study, fifty patients who had to undergo cholecystectomy were randomized in two groups. The patients were monitored for 72 hours post operatively. The patients were ASA physical status of I and II, of both the sexes and aged between 30 to 60 years. A balanced anaesthetic technique was used for all the patients during the conduct of procedure. All the patients were operated through a standard subcostal incision (3 to 4 inches in length). First dose of both the drugs was given immediately after induction (15 mg Ketorolac I/V or 20 mg Piroxicam I/M). Postoperatively, group I patients received injection Ketorolac 15mg I/V 8 hourly, group II patients were given injection Piroxicam 20mg I/M once daily. If pain persistently remained above 5 on VAS, injection Pethidine 50mg I/V p.r.n. was used as rescue analgesia for both the groups. In group I (ketorolac group) 7 patients (28%) required rescue analgesia whereas in group II, eight patients (32%) required it. The effect of both the drugs on pulse rate, blood pressure, and respiratory rate and oxygen saturation were monitored and recorded. The frequency of postoperative complications was recorded. Relevant laboratory data (bleeding time, platelet count, serum creatinine and liver function tests) was monitored.

RESULTS:

Both the drugs were found effective in controlling post operative pain. Ketorolac was found to be as effective an analgesic as piroxicam. Both drugs had similar side-effects spectrum.

CONCLUSION

Both drugs Ketorolac and Piroxicam provided adequate pain relief.

KEY WORDS: post-operative pain, ketorolac, piroxicam

* **Lt Col Amanat Khan**
MCPS, FCPS
Anaesthesiologist, 9 Field Ambulance, Dera Nawab Cantt
** **Brig Tariq Mehmood Mufti**
MCPS, FCPS**
Head Department of Anaesthesiology & Intensive Care, Military Hospital, Rawalpindi
For Correspondence:
* **Lt Col Amanat Khan**

INTRODUCTION

Postoperative pain remains a high concern for the patients undergoing surgery. Best postoperative pain management begins preoperatively or at the least intra operatively. Numerous methods / techniques and a number of analgesics have so far been used for this purpose with variable results.

The severity of postoperative pain may remain under-assessed due to various reasons, for example, a non conversant patient in immediate postoperative period, or an under treated patient due to unfound fear

of side effects of the drugs like respiratory depression due to traditional narcotic analgesics. The most important side effects of narcotics analgesics are respiratory depression, excessive sedation, itching and higher incidence of nausea and vomiting.

A lot of work has been done in the past in management of postoperative pain and still, a lot needs to be done. Ketorolac (injection 'Toradal' brand by Roche) and Piroxicam (Injection 'Feldene' by Pfizer) both belong to a group of drugs called NSAID's and being used as analgesics in the management of different types of pain. Piroxicam is an old NSAID but Ketorolac is relatively a newer agent. These agents are devoid of serious side effects like respiratory depression, though these drugs have their own side effects / complications.

We are presenting a randomized, single blind standardized trial, conducted in the department of Anaesthesiology and Intensive care PNS Shifa Karachi.

PURPOSE

The objective of the study was to compare the analgesic efficacy of Ketorolac and Piroxicam in ASA-I and ASA-II patients coming for cholecystectomy, who fulfilled the inclusion / exclusion criteria.

MATERIAL AND METHODS

This study, designed to compare the analgesic effects of Ketorolac and Piroxicam for relief of postoperative pain was approved by the ethical committee of PNS Shifa, Karachi. A total of fifty patients who had to undergo cholecystectomy were randomized in two groups.

Informed consent was obtained from the patients. All the patients were operated through a standard subcostal incision (3 to 4 inches in length).

Following were the inclusion criteria:

- ASA-I and ASA-II patients (Figure 1)
- Both sexes
- Age 30-60 years

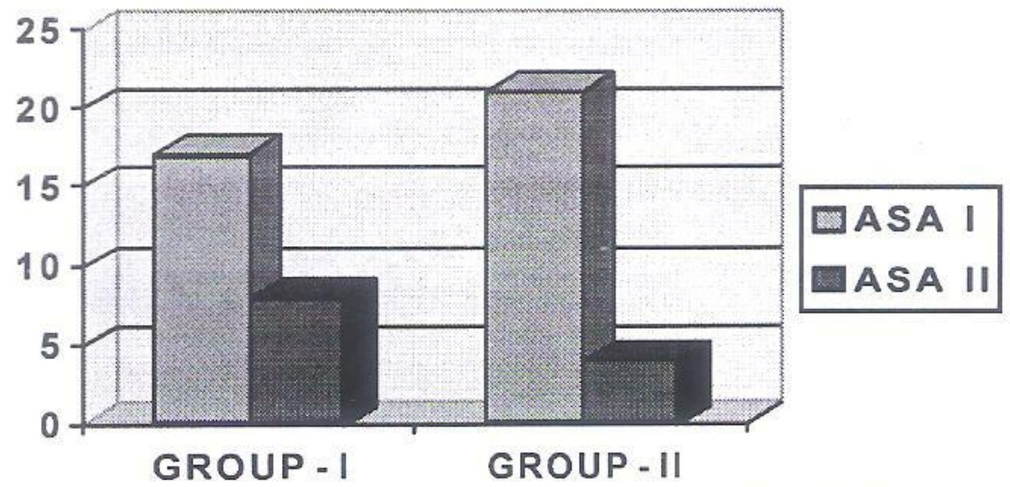

Fig 1: Distribution of Patients According To ASA Status

Following were the exclusion criteria:

1. History of gastrointestinal bleeding
2. History of allergy to NSAIDs
3. Bleeding disorders
4. Renal insufficiency
5. Morbid obesity
6. Patients with history of bronchial asthma
7. Pregnancy
8. History of jaundice

Pre anaesthetic assessment was made by taking detailed history and clinical examination and all the patients were evaluated to fulfill inclusion / exclusion criteria.

Following investigations were performed on all the patients in addition to complete picture of blood and routine urinalysis.

Bleeding / clotting time

Liver function tests (Serum bilirubin, ALP and ALT)

Serum creatinine

Prothrombin time

All the above-mentioned investigations were repeated once after 48 hours postoperatively for comparison with preoperative values.

All the patients were explained about the method of assessment of pain on a horizontal 10 cm Visual Analogue Scale. (Figure 2)

0 No pain	1 - 2 Mild pain	3 - 4 - 5 Moderate pain	6 - 7 Severe pain	8 - 9 very severe pain	10 Worst pain

Fig 2: Visual Analogue Scale

Drugs used

Inj Ketorolac
Inj Piroxicam

Patients on ketorolac were placed in group I and those on piroxicam were placed in group II.

First dose of both the drugs was given immediately after induction (15mg Ketorolac I/V or 20mg Piroxicam I/M).

ANAESTHETIC TECHNIQUE

After securing I/V line, all the patients were anaesthetized using balanced anaesthetic induction technique. Injection Pethidine 50mg was administered as a part of induction agent along with thiopentone sodium (5mg/kg) and suxamethonium (1.5mg/kg). The patients were intubated and inj. atracurium besylate (0.5mg/kg) was used as a non-depolarising muscle relaxant. Anaesthesia was maintained on oxygen, nitrous oxide and supplemental doses of muscle relaxant along with inhalational agent (halothane or isoflurane).

Almost all the procedures were concluded in an average time of 70 10 minutes.
The patients were extubated fully awake and after spending about 30 minutes in recovery room, were shifted to postoperative wards.

Non-invasive blood pressure, pulse rate, respiratory rate, oxygen saturation and urine output were monitored during and after surgery (Table 2&3). Intravenous fluids were replaced by calculating the fasting period and duration of surgery.

Postoperatively, group I patients received injection Ketorolac 15mg I/V 8 hourly, group II patients were given injection Piroxicam 20mg I/M once daily. Injection Pethidine 30mg I/V p.r.n. was used as rescue analgesia for both the groups. The number of demand boluses of Pethidine used was documented.

The intensity of pain was estimated by using horizontal visual analogue scale (VAS) (Figure 2). The assessment of pain was done every hour for initial six hours, and 2 hourly for the next six hours. Thereafter, the assessment was made four hourly.

The frequency of postoperative complications was recorded.

The entire data was recorded on a Performa and at the end of study the results were analyzed, p-value calculated and Z score obtained after comparison of both the groups.

RESULTS

Since the patients in both these groups were comparable as regards to their age, physical status, ASA grade, the type and duration of surgery (Table 1), the assessment of postoperative pain was made objectively.

Description	Group I	Group II
Number of patients	25	25
Male to female ratio	4:19	3:22
Average age (in years)	38.13	39.99
Average weight (in kg)	60.9	63.7
Average duration of surger (in minutes)	70±10	70±10
ASA-I	17	21
ASA-II	8	4
Education status (Under-matric / over-matric)	19/6	16/9

Table 1 Demographic Data

Group-I (Ketorolac group),

1-4 hours: The assessment of pain with horizontal VAS scale showed VAS score zero for the first four hours.

After 5th hour: Five patients had VAS score 1-2 (Mild pain), 2 patients had a VAS score of 3-5 (moderate pain), and one patient had VAS score of 6-7 (severe pain) in this group. None of the patients had VAS score beyond 7 in this hour.

After 6th hour: Three patients had VAS score 1-2 (mild pain), one had VAS score 3-5 (moderate pain) and another one had VAS score 6-7 (severe pain).

After 8th hour: Two patients had VAS score of 1-2 (mild pain), another two had VAS score 3-5 (moderate pain). No patient had VAS score more than 5 during this period.

After 12 hours: Only two patients had a VAS score of 1-2 (mild pain) and no patient had VAS score more than 2 during this period.

After 14 hours: Only one patient had VAS score of 1-2 (mild pain).

After 16 hours: Only one patient had VAS score of 1-2 (mild pain).

After 18 hours: Only one patient had VAS score of 1-2 (mild pain).

After 20 hours: VAS score of all the patients remained zero.

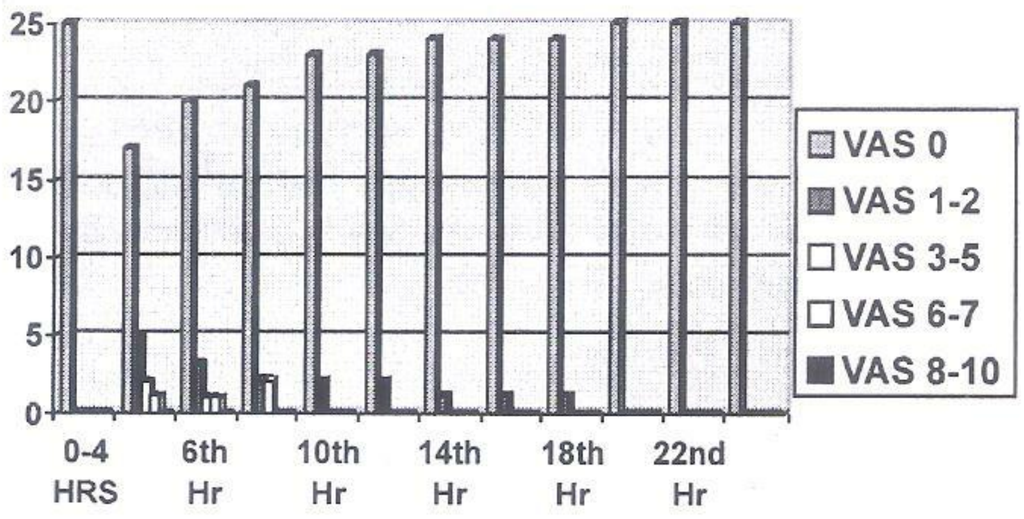

Figure 3: Vas Score In Post Operative Period Group I (Ketorolac Group)

Group II: Piroxicam group

1-12 hours: VAS score zero for the first twelve hours.

After12 hours: Four patients had VAS score 1-2 mild pain, 2 patients had VAS score 3-5 (moderate pain), 2 patients had VAS score 6-7 (severe pain).

After 14 hours: Three patients had VAS score 1-2 (mild pain), 2 patients had VAS score 3-5 (moderate pain), one patient had VAS score 6-7 (severe pain).

After 16 hours: Two patients had VAS score of 1-2 (mild pain), one patient had VAS score of 3-5 (moderate pain).

After 18 hours: One patient had VAS score of 1-2 (mild pain), one patient had VAS score of 3-5 (moderate pain).

After 20 hours: One patient had VAS score of 1-2 (mild pain).

After 22 hours: One patient had VAS score of 1-2 (mild pain).

After 24 hours: VAS score of all the patients remained zero.

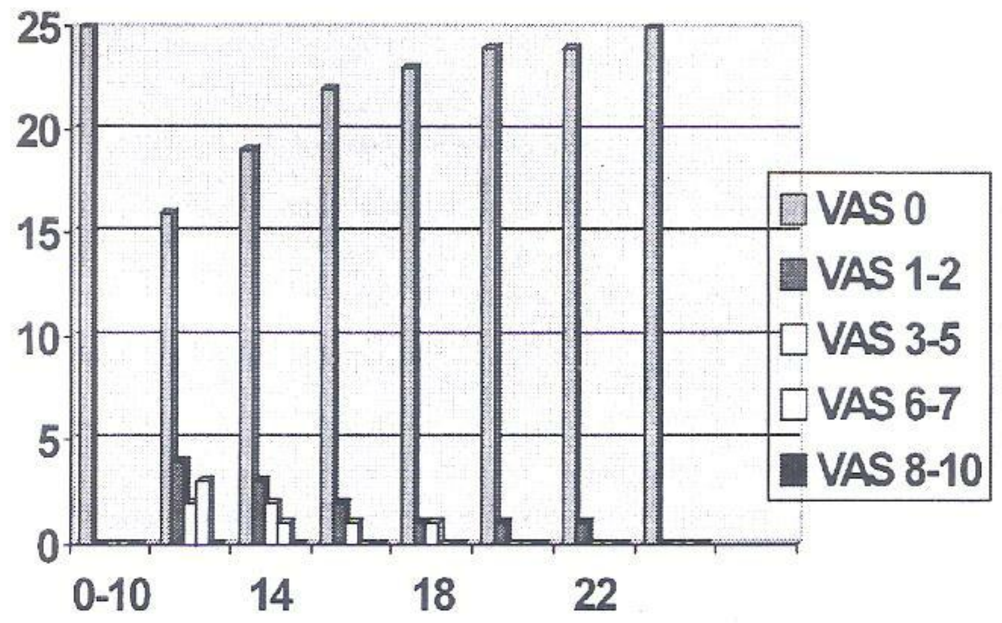

Figure 4: Vas Score In Post Operative Period Group Ii (Piroxicam Group)

Rescue analgesia (Injection Pethidine 30mg I/V) was administered to 7 patients in-group I and to 8 patients in-group II. Furthermore, none of the patients demanded more than one dose of rescue analgesia (Table 2). In GROUP II the VAS score remained zero for a relatively longer duration that is, up to 12 hours and after that the VAS score pattern remained comparable to group I.

	Group-I	Group-II
PONV#	4	3
Rescue analgesia	7	8
Hypersensitivity reaction	Nil	Nil
Increase in bleeding time*	5	0

Table 2: Comparison of different parameters in Group-I and Group-II patients

#Post operative nausea and vomiting.

* 1. Bleeding time still remained in normal range.

2. No significant postoperative bleeding observed.

No clinically significant change in pulse rate and blood pressure was noted in both the groups (Table 3).

Time in hours	Group I (Ketorolac) MAP	HR	Group II (Piroxicam) MAP	HR
0 hours	88±6	76±4	89±5	75±6
1 hours	90±4	83±3	93±5	85±3
2 hours	89±3	83±2	90±3	85±5
3 hours	87±4	74±6	88±4	75±5
4 hours	88±2	85±3	89±3	84±3
6 hours	98±6	84±3	100±7	88±4
12 hours	103±3	92±3	104±4	94±3
24 hours	94±3	84±4	92±4	81±6
36 hours	99±4	87±2	101±3	89±3
48 hours	90±5	80±5	92±4	81±6
72 hours	89±4	89±3	94±4	80±5

Table 3: Comparison of Mean Arterial Blood Pressure (Map) and Heart Rate (HR)

P<0.05 compared with the base line value (0 hour) for each group.

No statistically significant difference between both the groups.

There was also no significant variation in respiratory rate and oxygen saturation in both the groups (Table 4). All the other investigations were repeated after 48 hours and no significant derangements were found in liver function test and serum creatinine levels.

Parameters / Time in	Group I (Ketorolac) SpO_2	PR	Group II (Piroxicam) SpO_2	PR
0 hours	97±0.3	19±0.8	97±0.2	19±0.8
1 hours	97±0.3	19±0.5	97±0.4	10±0.4
2 hours	97±0.2	19±0.9	97±0.2	19±0.7
3 hours	97±0.5	19±0.6	97±0.5	19±0.5
4 hours	94±0.7	18±0.8	95±0.6	18±0.9
6 hours	97±0.9	20±0.9	97±0.8	20±0.7
12 hours	96±0.5	18±0.7	96±0.2	18±0.5
24 hours	97±0.7	20±0.8	97±0.6	20±0.6
36 hours	94±0.9	18±0.7	95±0.8	18±0.4
48 hours	95±0.6	18±0.6	96±0.4	18±0.4
72 hours	95±0.7	18±0.6	96±0.4	18±0.5

Table 4: Comparison of Oxygen Saturation (Spo_2) And Respiratory Rate (R.R)

P<0.05 compared with the base line value (0 hour) for each group.

No statistically significant difference between both the groups.

Discussion

Like all other types of pain, the postoperative pain is a subjective feeling. The intensity of postoperative pain varies with the individual patient and largely depends upon the site and nature of operation and constitution of the patient. Upper abdominal pain, for example, is more severe than lower abdominal pain and is aggravated by movements or coughing. Adequate administration of an analgesic can reduce the intensity and duration of postoperative pain. The provision of analgesia is important, as it determines the physiological and psychological outcome of the patient.

The objective of providing good pain control has led researchers to invent various methodologies and modalities. An analgesic drug having prompt and lasting action, with minimum adverse effects still remains to be found. No single analgesic technique has so far been developed to provide sufficient pain relief without untoward effects.[1]

Postoperative pain relief is currently being achieved with drugs of two main categories, non-steroidal anti-inflammatory drugs (NSAID's) and narcotic analgesics.[1,2] A similar research has led to the development of Ketorolac tromethamine. A standard dose of Ketorolac (15-30mg) provides analgesia equivalent to 6-12 mg of morphine administered by same route. Its time of onset is similar to morphine, but ketorolac has a longer duration of action (6-8 hours).[3,4]

Piroxicam too, has intense analgesic activity, comparable or superior to other drugs (aspirin, codeine and many other NSAID's) and a prolonged duration of action (distribution half life 50 minutes). This seems to be the reason that the patients in group II remained pain free in initial post operative period. The incidence of untoward effects remained negligible.

Both the drugs are free from side effects of respiratory depression, nausea and vomiting, which are so commonly observed with opioids. The present study provided a comparison between these two drugs as far as their pain control and side effects are concerned.

The results are not significantly different for both the drugs. Ketorolac appeared to be marginally superior agent as far as its pain control is concerned. The

number of patients who required the dose of rescue analgesia was almost same with ketorolac as with piroxicam (7 versus 8). However, the quality of analgesia in both the groups was almost similar.

There was no significant effect on heart rate, mean arterial pressure and respiratory rate in either group (Table 3&4). Also there was no significant postoperative nausea and vomiting in both the groups.

Several clinical studies have established the ability of Ketorolac and Piroxicam for relief of postoperative pain after different procedures. On the review of the literature we could find studies in which Ketorolac and Piroxicam were comparable as far as their analgesic potency is concerned.[5] These drugs have also been found to produce effective analgesia after orthopedic surgery, laparoscopy, day case procedures and cholecystectomy.[6]

In one study intramuscular Ketorolac, Piroxicam and diclofenac sodium were compared for relief of postoperative pain after laparoscopy with similar results ($P<0.05$). A few of the patients, in all the three drugs in comparison in that study, also required further analgesia (rescue analgesia) but the difference between the individual groups was not of statistical significance.

In our study, there was no report of increased bleeding at operation site, bronchospasm, bleeding from gastrointestinal tract, renal impairment or pain at the site of injection. This study showed that there is no significant difference in results in providing postoperative analgesia by both these drugs. However, in the patients with upper gastrointestinal bleeding, renal impairment and patient having allergies to NSAID's, one should resort to other modalities for pain relief.

It is seen in our study that both these agents can be used effectively to control postoperative pain up to acceptable levels. However, still better results might be achieved with combining one of the agents of this study (i.e. Ketorolac or Piroxicam) and a narcotic analgesic (in the form of balanced analgesia).[7]

Out of the two drugs in our study, Piroxicam was found to be cost effective.

LIMITATIONS OF THE STUDY

Following pitfalls were observed in our study.

1. The route of administration of both the drugs was not same.
2. The drugs under study had different half-lives and therefore, the frequency of doses remained different.
3. Rescue analgesia with injection pethidine had to be administered to a few patients in both the groups.

Despite the above-mentioned shortcomings the control of postoperative pain remained in acceptable limits.

CONCLUSION

We conclude that both Ketorolac and Piroxicam provide adequate pain relief. By using these drugs we can prevent untoward effects of traditional narcotic analgesics (nausea, vomiting, respiratory and cardiovascular depression etc.). Our patients can remain pain free and at the same time fully awake. These drugs can make good choice for day care surgery as well and these can effectively be used for short-term control of postoperative pain.

REFERENCES

1. Reissine T, Pasternac G. Opioid analgesics and antagonists: Goodman Gilman A.Ruddon RW, Molinoff PB, eds. The Pharmacological Basis of Therapeutics: 10th ed. New York, McGraw Hill; 1996: 521-555.
2. Szabo S, Spill WF , Rainsford KD. Non-steroidal anti-inflammatory drugs induced gastropathy. Mechanism and management. Med toxicol Adverse Drug Exp.1989;4:77-94.
3. Benedetti C. Acute pain: Physiopathology and consequences. ALGOS 1991; 8: 34- 44.
4. Morgan GE, Makhail MS. Clinical Anaesthesiology. Appleton and Lange, USA.1996: 204-5.
5. Whaetley RG. Analgesic efficacy of ketorolac. Acta Anaesthesiol Belg 1996; 47(3): 135-42.
6. O' Hanlon JJ, Beers H, Huss BK, Malligan KR, A comparison of the effect of intramuscular diclofenac, ketorolac and piroxicam on postoperative pain following laparoscopy. Eur J Anaesthesiol 1996 Jul 12(4): 404-7.
7. Lysk SZ, Andeson PT, Carlthers RA, DeVane GG, smith ML, Bates GW. Postoperative effects of fentanyl, ketorolac, and piroxicam as analgesic for out patient laparoscopic procedures. Obstet Gynaecol 1994 feb; 83(2): 270-5.