COMPARISON OF INTRAVENOUS KETOROLAC WITH DICLOFENIC FOR POSTOPERATIVE ANALGESIA

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ABSTRACT

Objective To compare analgesic effect and complications of non - steroidal anti-inflammatory drugs (NASIDs), ketorolac versus diclofenic in prevention of pain after laparoscopic cholecystectomy.

Study design Quasi-experimental study.

Place & Duration of study The Department of Anesthesiology and Surgical Intensive Care Unit, Dow Medical College, Karachi from March 2003 to March 2004.

Patients and Methods Sixty patients, ASA physical status I and II were selected to receive either ketorolac 30 mg intravenous (group A) or diclofenic 75mg intravenous (group B), after general anesthesia induction and before surgical incision. In ketorolac group same dose repeated three times daily for 24 hours. The diclofenic group received diclofenic 75mg 12 hourly for 24 hours. Analgesic effect assessed by intensity of pain postoperatively using visual analogue scale, 0 mean no pain and 10 most severe pain. Rescue analgesic nalbuphine was administered if needed.

Results Both groups required rescue analgesic 0.1mg/kg nalbuphine boluses postoperatively. Higher nalbuphine consumption was noted compared to diclofenic group until 12 hours, which is statistically significant (P value < 0.05). Side effects were almost similar in both groups.

Conclusions Ketorolac and diclofenic are insufficient alone for analgesia after laparoscopic cholecystectomy. The total nalbuphine consumption was less in ketorolac group.

Key words Ketorolac, Diclofenic, Postoperative pain.

INTRODUCTION:

Systemic opiods are used commonly for postoperative pain but they are a potential cause of respiratory depression. Non-steroidal anti-inflammatory drugs have been shown to be effective in the treatment of pain and in reducing opioids consumption, thus reducing the risk of opioids related side effects. The non steroidal anti inflammatory drugs do not cause respiratory depression, but other adverse events may occur. These include increased bleeding time caused by decrease platelet function, gastrointestinal symptoms, and renal dysfunction. The mechanism of action of non-steroidal anti-inflammatory drugs is inhibition of prostaglandin synthesis (cycloxygenase activity). This enzyme exists in two different isoform (COX 1 and COX 2) and nonsteriodal anti-inflammatory drugs may differ in their inhibition of both COX 1 and COX2 isoenzymes. The analgesic efficacy relative

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to side effect may vary from agent to agent. Diclofenic is a sodium salt of aminophenyl acetic acid. It was developed as an analgesic, but it also has anti-inflammatory and antipyretic properties.

The most recent parenteral non-steroidal anti-inflammatory drug available for control of postoperative pain is ketorolac, a pyrrolizine carboxylic acid derivative, structurally related to indomethacin. Ketorolac inhibit both cyclo-oxygenase and lipo-oxygenase enzyme thereby preventing synthesis of both prostaglandin and leukotrienes, and may release endogenous opioids. These properties of ketorolac make it more potent than other non-steroidal anti-inflammatory drugs. The analgesic potency of ketorolac 30mg intramuscular (I/M) has shown to be comparable with morphine 10- 12 mg I/M.[1]

Comparative studies between the analgesic efficacy of intravenous ketorolac and diclofenic are few. The type of surgery may influence the analgesic efficacy of individual non steroidal anti inflammatory drug on postoperative pain. Laparoscopic cholecystectomy is less invasive and causes less tissue damage compared with open cholecystectomy. Therefore it is assumed that it also cause less postoperative pain. We found it worthwhile to investigate if there was any difference in postoperative analgesia between ketorolac and diclofenic after intravenous administration at time of induction of anesthesia and during postoperative period in laparoscopic cholecystectomy. In addition, to determine adverse events like bleeding from surgical site, gastrointestinal bleeding, acute renal failure and severe allergic reactions.

PATIENTS AND METHODS

Study was carried out after informed consent and approval from institutional ethics committee, from March 2003 to March 2004 at the department of Anesthesiology and Surgical Intensive Care Unit, Civil Hospital Karachi.

Sixty patients ASA physical status I and II, age ranged 45 – 50 years, undergoing elective laparoscopy surgery were selected using sealed envelopes to be opened by anesthesia resident, who was involved in anesthetic management to receive, ketorolac 30mg intravenous in group A, and diclofenic 75mg intravenous in-group B, before induction of anesthesia.

Patients with history of allergic reaction to non-steroidal anti-inflammatory drugs, bronchial asthma, gastrointestinal ulceration, bleeding disorder and patients with cardiac, renal, hepatic dysfunction were excluded from study.

All patients were anesthetized using balanced anesthetic technique. Injection nalbuphine 0.1mg/kg was administered as a part of induction agent along with thiopentone sodium (5mg/kg) and atracurium (0.5mg/kg). Patients were intubated, and anesthesia was maintained on oxygen, nitrous oxide and supplemental dose of muscle relaxant (atracurium) along with inhalation agent (halothane).

Non-invasive blood pressure assessment, oximetry, ECG and end tidal CO2 were monitored during the anesthesia. The patients were extubated and after spending about 30 minutes in recovery room shifted to ICU and studied for 24 hours postoperatively. During postoperative period group A received ketorolac 30mg intravenous 8 hourly and group B received diclofenic 75mg intravenous 12 hourly. Monitoring included heart rate, respiratory rate, blood pressure, oxygen saturation half hourly. Patients were given supplemental oxygen, if it was less than 90%. Urine output measured for forty-eight hours.

Pain assessment done by visual analogue scale ranging 0 to 10, where 0 mean no pain, while 10 signify the most severe pain. All the patient were explained about the method of assessment of pain on a horizontal 10 cm visual analogue scale (Table I). Pain assessment was done at period of 1, 2, 3 and 4 hours then four hourly for twenty-four hours postoperatively. Rescue analgesic medication consisting of nalbuphine 0.1mg/kg was administered to patients if pain persistently remained above two on visual analogue scale. The number of doses and time of administration were noted.

Any adverse event likes nausea, vomiting, bleeding from wound were noted and coagulation profile including PT, APTT, platelet count, bleeding time and serum creatinine were done on first and second postoperative days. All results were expressed as mean ± SD (standard deviation). Statistical analysis was performed using a statistical soft ware package (SPSS) version 10. Independent sample t-test was used for comparison of age and weight in two groups. One-way analysis of variance (ANOVA) was used for inter group change in rescue analgesic consumption. The P value less than 0.05 considered as significant.

RESULTS:

Both groups were comparable with regard to age and weight. Male to female ratio was 6/24 in-group A, and 25/5 in group B. Regarding ASA physical status, twenty six patients in group A and twenty five patients in group B were in ASA physical status class I, and four patients in group A and five patients in group B were ASA physical status class II (Table II). Almost all procedures concluded in thirty to sixty minutes, which clearly depicts the degree of surgical trauma that the patients had to sustain. After surgery local anesthetic bupivacaine 0.25% was infiltered at incisional sites and peritoneal cavity.

Pain assessment done by visual analogue scale at hourly interval upto four hours then four hourly till twenty four hour. In our study pain assessment by visual analogue scoring showed that during first four hours 16.6% patients in-group A and 66.6% patient's in group B experienced pain. During 8th hour 36.6% patients in group A and 66.6% in group B experienced pain. During 12th hour 26.6% patients in group A and 40% patients in group B experienced pain, but during 16 and 20th hour there was no difference in visual analogue score as16.6% and 3.3% patients experienced pain respectively (Table III). Statistically significant difference in rescue analgesic consumption in two groups noted upto 12 hours period (Table IV).

Frequency of side effects were non-significant in two groups, except vomiting which occurred in five (16.6 %) in group A, and two (6.6%) in-group B. Two patients in ketorolac group andthree

in diclofenic group experienced local venous pain during administration. There was no significant difference between two groups in creatinine concentration, urine output and coagulation profile during first and second postoperative day (Table V).

Table I: Visual analogue scale

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

Table II: Patients characteristic

	Group A (n=30)	Group B (n=30)
Age (years)	44.17 ± 12.05	43.50 ± 12.56
Weight (Kg)	66.00 ± 13.03	61 72 ± 16.02
Sex (M/F)	6/24	5/25
ASA (1/11)	26/4	25/5

Group A = Ketorolac, Group B = Diclofenic
Values are expressed as Mean ± (SD) standard deviation, Significant (P < 0.05)

Table III: Visual analogue score in postoperative period

	1 -4 hrs		8th hr		12th hr		16th hr		20th hr		24th hr	
VAS score	A	B	A	B	A	B	A	B	A	B	A	B
0	25	10	19	10	22	18	25	25	29	29	30	30
1 -2	2	5	4	9	3	4	1	2	1	1	0	0
3 -4 -5	1	7	2	3	2	3	3	2	0	0	0	0
6 -7	1	5	5	8	3	5	1	1	0	0	0	0
8 -9	1	3	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0

Ketorolac group = A, Diclofenic group = B, 30 patients in each group

Table IV: Nalbuphine consumption in mg/kg

Time Period	Ketorolac Group	Diclofenic Group	P value
0 - 4 hrs	1.30 ± 3.01	2.57 ± 3.77	.000
4 - 8hrs	2.80 ± 3.83	5.13 ± 3.82	.003
8 -12hrs	2.10 ± 3.58	2.77 ± 3.78	0.14
12 -16hrs	1.27 ± 2.91	1.40 ± 3.21	.299
16 -20	0.27 ± 1.46	0.27 ± 1.46	ns
20 -24hrs	0	0	ns

Dose of Nalbuphine expressed in (mean ± SD) in both groups over 24 hours period postoperatively. P value < 0.05 significant, ns = not significant

Table V: Side effects and monitoring

	Group A	Group B
Nausea and vomiting	5(16.6%)	2(6.6%)
Itching	None	None
Pain on injection	2	3
Gastrointestinal bleeding	None	None
Urine output (hourly)	57.97 ± 97	59 13 ± 19.29
Serum creatinine	Unchanged	Unchanged
Coagulation profile (PT, APTT, Platelet count, bleeding time)	N	N

DISCUSSION

The intensity of postoperative pain varies with the individual patient and largely depends upon the site and nature of tissue trauma.[1] Abdominal pain is more severe and is aggravated by movement or coughing. Adequate administration of an analgesic can reduce the intensity and duration of postoperative pain.[2,3] The provision of analgesia is important, as it determines the physiological and psychological outcome of the patient.[4,5] An analgesic drug having prompt and lasting action, with minimum adverse effects still to be found.[6] No single analgesic technique has so far been developed to provide sufficient pain relief without untoward effects.[7,8] Postoperative pain relief is currently being achieved with drugs of two main categories, non-steroidal anti – inflammatory drugs (NASIDS) and narcotic analgesic.[8]

In our study the NSAIDS did not provide complete analgesia as patients experienced pain in immediate postoperative period after laparoscopic cholecystectomy, even though it is considered as less traumatic procedure than conventional open cholecystectomy.[9]

The dosing interval and doses were chosen on basis of current recommendations, although elimination half-life of diclofenac is only 1.1 hour. It has long therapeutic effect, probably because of active metabolites and accumulation in inflamed tissue. The elimination half-life of ketorolac is 5 – 6 hour and repeated doses are recommended at 6– 8 hour interval.[10] We administered nalbuphine as rescue analgesic when pain persistently remained above 2 on visual analogue scale, in order to keep patients pain free. The NSAIDs are not as effective for immediate postoperative pain as are opioid, and appear to be ineffective for shoulder pain related to stimulation of phrenic nerve after laparoscopic cholecystectomy.[11]

The ketorolac and diclofenic were equally effective in reducing pain and opioids requirement after laparoscopy and faciomaxillary surgery, and reduces opioid requirement (mean 32%) but did not provide complete analgesia.[12,13] Various studies[14,15] conclude that both ketorolac and diclofenic administered in infusion were equally effective in reducing morphine consumption as rescue analgesic postoperatively.

In our study where total consumption of nalbuphine as rescue analgesic was significantly lower in ketorolac group compared to diclofenic group. The reason probably is that we administered NSAIDS in boluses rather than by infusion, and used nalbuphine rather than morphine, which is less potent. No significant difference in adverse effects like was nausea, vomiting and pain on injection was noted in both groups. Acute renal failure is potential complication, associated with the use of NSAIDs during and after surgery, especially in patients with preexisting renal disease, or with hypovolemia and receiving loop diuretic. [16,17] In our study I.V crystalloid fluid volume were administered as recommended for surgical patients, with monitoring of volume status. The short term use of NSAIDs for surgical patient does not seem to induce renal failure however, prospective controlled studies with large population are required to study the incidence of renal side effect after administration of NSAIDs. [18]

There have been controversial results regarding postoperative bleeding with parentral ketorolac.[19,20] Gallagher et al.[21] demonstrated five fold increase in postoperative hemorrhage, in patients who had received ketorolac in postoperative period for tonsillectomy and adenoidectomy Niemi et al. [22] conclude that ketorolac and diclofenic cause reversible platelet dysfunction, diclofenic had the mildest effect, while platelet dysfunction was still seen 24hour after administration of ketorolac.

In our study, we assessed bleeding at incision site and coagulation profile on first and second postoperative days. Besides these patients were also monitored in the ward throughout their stay in hospital, but there were no clinical problems like oozing from surgical wound, which is known to be due to NSAIDS induced platelet dysfunction. It should be noted, however that our patients did not receive prophylaxis for deep vein thrombosis, which could potentially increase the risk of haemostatic complications of NSAIDs

CONCLUSIONS:

We conclude that ketorolac and diclofenic in laparoscopic cholecystectomy are insufficient alone for analgesia postoperatively and need additional rescue opioid nalbuphine. The total nalbuphine consumption was less in ketorolac group. There was no marked difference between the drugs with respect to side effects.

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