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Comparison of Pre-emptive *vs* Post-operative Parecoxib for Post-operative Pain Relief in Patients Undergoing Elective General Surgeries

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Abstract

Background: Parecoxib has been previously evaluated in various doses to reduce post-operative pain relief. *Aim of the Study:* Parecoxib was evaluated as a pre-emptive agent in patients undergoing surgery under general anesthesia and hemodynamic effects and side effects. *Settings and Design:* This study design was a double blind prospective randomized controlled trial. *Patients and Methods:* 100 patients in age group 20–45 *years* undergoing surgery under general anesthesia were randomly divided into two Groups. Group I received 40 *mg* of Parecoxib I.V. 1 *hour* before induction of anesthesia and 2 *ml* normal saline I.V. at the end of surgery and Group II was given the same vice versa. Hemodynamic parameters i.e., blood pressure and pulse rate, intensity of pain and number of patients requiring rescue analgesia in two groups at baseline and post-operatively at the end of surgery and henceforth at 30 *minutes*, 1, 2, 4, 6, 8, 12 *hours* were noted in addition to adverse effects in two Groups. *Results:* Demographic profile and hemodynamic parameters were comparable at baseline in two Groups. The mean time weighted score of pain intensity was significantly higher in Group II (1.92 ± 0.10) as compared to Group I (1.61 ± 0.34). Pain relief score was significantly lower in Group II (1.13 ± 0.18) as compared to one (1.72 ± 0.56). They demanded rescue analgesia at a relatively early time 125.40 ± 111.87 *min* as compared to Group I patients 357.24 ± 231.37 *min* (t:6.379, p:0.000). Post-operatively the mean of hemodynamic parameters over varied time intervals was slightly higher in Group II as compared to Group I. *Conclusion:* Pre-operative parecoxib has an effective pre-emptive analgesic effect by decreasing the post-operative pain and delaying the time to demand of rescue analgesia as compared to its use post-operatively.

Keywords: Parecoxib; Pre-emptive; Analgesia; Post-operative pain; Rescue analgesia.

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Introduction

The relief of post-operative pain is one the cardinal principles of modern anesthetic practice. Pain leads to increased post-operative morbidity in form of ileus, nausea, vomiting, pulmonary dysfunction, hypoxemia and cognitive impairment which causes agony and suffering. Treatment of post-operative pain is provided not only for humanitarian reasons but also for faster recovery of patients.[1] This reduces length of stay in hospitals and decreases both the psychological and economic costs of diseases.[1–3]

Pre-emptive analgesia may be defined as an anti-nociceptive treatment that prevents establishment

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of altered central processing of afferent input from sites of injury. For this most important is establishment of effective level of anti-nociceptive before injury and continuation of analgesia post-injury period to prevent central sensitization during the inflammatory phase. Sensory signals generated by tissue damage during surgery can trigger a prolonged state of increased excitability in central nervous system.[4] This has encouraged clinical studies to test whether pre-operative opioids, regional anesthesia, local anesthesia, or NSAIDs can pre-empt post-operative pain by preventing the establishment of central and peripheral sensitization. Further the non-analgesic benefits of pre-emptive analgesia are early mobilization, decreased hospital stay, attenuation of intra-operative hemodynamic response and a reduction in respiratory complications.[5]

Opioids, regional anesthesia, local analgesia and conventional NSAIDs have been used adjunctively in management of post-operative pain after surgical procedure. But opioids produce acute tolerance, narcotic addiction, nausea, vomiting, respiratory depression, lethargy rash and itching.[6,7] Regional and local anesthetics may produce systemic toxicity and pneumothorax and are suitable in particular situations only.[8,9] Traditional NSAIDs prolong bleeding time, inhibit wound healing, bone fusion, causes gastrointestinal ulceration and acute renal failure, thereby limiting their use in the peri-operative period.[10] The risk of excessive intra-operative or post-operative bleeding may preclude the use of NSAIDs during surgical procedures in which optimum hemostasis is critical.[10]

Parecoxib, chemically is N-[(5-Methyl-3-phenyl isoxazol-4-yl)-phenylsulfonyl]propanamidesodium is a prodrug of Valdecoxib. It undergoes complete and rapid biotransformation in liver to valdecoxib. Valdecoxib is a non-steroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic and anti-pyretic properties.[12] The mechanism of action is due to inhibition of prostaglandin synthesis primarily through inhibition of COX-2 Half-life is *15–50 minutes* after IM or I.V. use. The dose of valdecoxib required to inhibit enzymatic activity by 50% was *0.005 µmol/l* compared with *140 µmol/l* against COX-1 isoforms.[11-13] Renal excretion is negligible. The elimination half-life is *8 hours* approximately. I.V. parecoxib is given as bolus over at least *15 minutes*. The dose of parecoxib is *40 mg* I.V. or IM every *6–12 hours*, but not to exceed *80 mg/day*.

At therapeutic plasma concentration in humans valdecoxib does not inhibit cyclooxygenase–1 (COX-1). The analgesic effect of parecoxib starts in *7–13 minutes* with clinically meaningful analgesia demonstrated in *23–29 minutes*. Platelet aggregation in response to arachidonate was not significantly altered from baseline with parecoxib *40 mg* twice daily for *8 days* in contrast to ketorolac and ibuprofen.[13–15] Contraindications to its use are previous hypersensitivity to parecoxib and valdecoxib, acute peptic ulcer disease or GI bleeding, patient with history of bronchospasm, urticarial, anaphylaxis with NSAIDS.

Side effects are tachycardia, peripheral edema, headache, dizziness, nausea, vomiting, and somnolence in 5% of patients. Dyspepsia, flatulence, fever, pharyngitis, pruritus, oliguria are also reported. Rare side effects are thrombocytopenia. Ecchymosis, increased blood urea nitrogen, gastroduodenal ulceration, anaphylaxis, hepatitis, acute renal failure. Parecoxib has no interaction with midazolam, propofol and does not affect unfractionated heparin regulated blood coagulation.

Though there are many studies which evaluated parecoxib as pre-emptive anesthetic agents pre-operatively few have compared the efficacy of pre-operative with post-operative parecoxib.[16–20] In our study, we analyzed difference in its effect if it is given before surgery and after surgery in patients undergoing elective general surgery. The pain relief was compared and the side effects of parecoxib, if any, in post-operative period were also evaluated.

Materials and Methods

This prospective double blind randomized study was performed on 100 patients undergoing elective general surgery under general anesthesia at Indira Gandhi Medical College (Shimla, Himachal Pradesh, India). The study was conducted after approval from institution review board and ethics committee. Informed consent was taken from all patients a day prior to surgery. Patient in the age group of *20–45 years* belonging to either gender and with weight between *40–70 kg*, undergoing elective general surgery of less than *1 hour* duration were included in study. Persons with history of peptic ulcer, ulcerative colitis, smoking, alcohol abuse, chronic uncontrolled systemic disease (such as diabetes mellitus, hypertension, asthma, COPD, collagen disease), bleeding tendencies and coagulopathy, severe cerebrovascular disease etc. were excluded from the study. Also those having hypersensitivity to NSAIDs and use of analgesics for chronic pain were not included.

The eligible patients were thoroughly examining in pre-anesthetic clinic a day before surgery and were explained the Four point Pain scale for pain intensity and Five point scale for pain relief to record pain and subjective sensations, shows in **Table 1**. On the day of surgery patients were randomly divided into two groups of 50 each. Appearance of the reconstituted drug and normal saline was similar; therefore, the observer and performer were not aware about the formulation given to the patients:

Group I: Cases in this group were given *40 mg* of Parecoxib I.V. *one hour* prior to induction of anesthesia and 2 cc normal saline I.V. at the end of surgery.

Group II: Cases in this group were given 2 cc normal saline I.V. *one hour* prior to induction of anesthesia and 2 cc Parecoxib I.V. at the end of surgery.

Patients were pre-medicated with alprazolam *0.5 mg* orally night before. In pre-operative room I.V. line was secured with 18 G I.V. cannula and Normal saline drip started. The formulation was given according to above Groups *1 hour* prior to induction of anesthesia. Injection Ondansetron *4 mg* I.V. was given at time of induction as prophylaxis against nausea and vomiting. Anesthesia was induced with propofol *2 mg/kg* I.V. and endotracheal intubation was facilitated with vecuronium *0.1 mg/kg*. Anesthesia was maintained with 66% nitrous oxide in oxygen, 0.5% halothane and adequate doses of vecuronium along with intermittent positive pressure ventilation to maintain normocarbia. Intra-operative analgesia was provided by inj Fentanyl *0.1 µg/kg* I.V. At the end of surgery patient received either *2 ml* saline or *40 mg* parecoxib, according to group allocation already described.

The primary objective was to determine the duration of analgesia post-operatively in two groups, the efficacy of analgesia and hemodynamic effects. Secondary objective was to determine the side effects. We compared the following parameters *i.e.*, Systolic Blood Pressure (BP), diastolic BP, mean BP, pulse rate, intensity of pain and number of patients requiring rescue analgesia in two Groups at baseline and immediately post-operatively at the end of surgery and henceforth at *30 minutes* and *1, 2, 4, 6, 8, 12 hours*. We also recorded any adverse effects noted by the patients like nausea, vomiting, headache, itching, fever etc.

Results

The baseline demographic features were comparable in two Groups with mean age of 37.38 ± 6.63 in Group I and *38.12 ± 6.84 years* in Group II (t:0.549, p:0.584) and weight was also comparable in both Groups (I : 51.70 ± 10.05 *kg*; II: 54.46 ± 5.77 *kg*; p: 0.096). Group I comprised of 13 male and 37 female patients, whereas in Group II there were 18 males and 32 females.

The hemodynamic parameters were comparable at baseline in two Groups. Post-operatively the mean systolic, diastolic and mean BP was slightly higher in Group II as compared to Group I which was statistically in-significant. Similarly pulse rate was marginally higher in Group II but that was also not significant, shows in **Table 2**.

The mean time weighted score of pain intensity was significantly higher in Group II cases as compared to Group I. Similarly time weighted pain relief score was significantly lower in Group II, shows in **Table 3**. Thus, patients in Group II demanded rescue analgesia at a relatively early time 125.40 ± 111.87 min as compared to Group I patients *357.24 ± 231.37 min* (t:6.379, p:0.000). The two Groups were also compared on the number of patients requiring rescue analgesia at varied intervals post-operatively, shows in **Table 4**. As shown only 24% of the patients in Group I required rescue analgesia in first *two hours* in comparison to 72% of the patients in Group II.

Side effects observed with Parecoxib were nausea, vomiting, headache, itching and fever. The incidence was comparable in both groups *i.e.*, nausea (I:5, II:4); vomiting (i:5, II:6); headache (I:4, II:5); itching (I:2, II:3); fever (I:1, II:4).

Table 1: Pain intensity scale and pain relief scale

Four Point scale for pain intensity		Five point scale for pain relief	
Pain Intensity	**Scale**	**Pain relief**	**Scale**
No pain	0	No relief	0
Mild pain	1	Little relief	1
Moderate pain	2	Some relief	2
Severe pain	3	A lot of relief	3
		Complete relief	4

Table 2: Comparison of hemodynamic parameters in two groups at baseline and at varied intervals post-operatively (Mean ± SD)

Time (*Hours*)	Systolic BP			Diastolic BP			Mean BP			Pulse Rate/Minute		
	Group I	Group II	(t-, p- value)	Group I	Group II	(t-, p- value)	Group I	Group II	(t-, p- value)	Group I	Group II	(t-, p- value)
Baseline	114.4 ± 6.0	113.96 ± 6.4	0.38,0.70	75.2 ± 7.2	74.9 ± 9.3	0.13,0.89	86.9 ± 5.8	87.7 ± 6.6	0.61,0.54	71.6 ± 7.2	73.2 ± 8.1	1.15,0.25
0	115.1 ± 6.8	117.0 ± 5.4	1.52,0.131	75.4 ± 9.2	75..6 ± 7.3	0.13,0.895	85.5 ± 6.7	85.8 ± 7.5	0.21,0.832	71.7 ± 4.4	74.0 ± 7.5	1.84,0.069
0.5	118.3 ± 5.3	119.9 ± 5.5	1.45,0.149	76.9 ± 6.3	79.0 ± 6.6	1.57,0.118	87.3 ± 5.0	89.2 ± 5.4	1.82,0.071	72.6 ± 9.5	75.2 ± 9.2	1.38,0.170
1	116.8 ± 7.4	118.8 ± 6.1	1.51,0.134	77.3 ± 5.6	79.7 ± 7.4	1.88,0.063	87.14 ± 5.1	89.5 ± 6.6	1.99,0.059	73.0 ± 8.1	76.0 ± 8.3	1.80,0.075
2	117.6 ± 8.1	118.1 ± 9.0	0.29,0.772	78.6 ± 3.7	79.6 ± 7.2	0.92,0.358	88.3 ± 4.2	89.3 ± 7.2	0.77,0.442	75.8 ± 8.9	76.8 ± 11.2	0.51,0.608
4	116.8 ± 7.6	118.7 ± 10.6	1.02,0.309	77.7 ± 5.5	80.1 ± 8.5	1.70,0.092	87.4 ± 4.9	89.8 ± 8.5	1.64,0.103	76.8 ± 11.1	79.1 ± 9.5	1.08,0.281
6	116.3 ± 6.7	118.6 ± 7.3	1.68,0.095	78.1 ± 4.9	78.1 ± 6.7	0.03,0.937	87.6 ± 4.4	88.2 ± 5.7	0.61,0.543	75.2 ± 8.6	77.8 ± 7.1	1.59,0.114
8	116.8 ± 5.6	118.7 ± 6.0	1.58,0.116	76.4 ± 7.8	78.9 ± 5.4	1.93,0.056	86.9 ± 6.5	88.4 ± 4.8	1.28,0.203	74.8 ± 8.5	75.9 ± 4.6	0.84,0.399
12	115.0 ± 6.7	116.6 ± 5.3	1.33,0.186	75.1 ± 7.3	76 ± 4.6	1.40,0.165	85.1 ± 6.7	86.8 ± 4.1	1.51,0.134	72.6 ± 7.3	74.3 ± 5.9	1.32,0.189

Table 3: Time weight pain intensity and pain relief score (Mean ± SD)

	Group I	Group II	*t*-value, *p*-value
Time weighted pain intensity	1.61 ± 0.34	1.92 ± 0.10	6.058, 0.000***
Time weighted pain relief	1.72 ± 0.56	1.13 ± 0.18	6.941, 0.000***

Table 4: Number of patients receiving rescue analgesia at various time intervals post-operatively

Time (*hours*)	Group I	Group II
0	2	4
0.5	3	7
1	3	15
2	4	10
4	8	10
6	8	3
8	12	1
12	10	0

Discussion

The concept that pain should be anticipated and pre-empted with analgesic techniques targeted at the peripheral sensory inflow in nerves and cells in the central nervous system is in existence for a long-time. This concept of pre-emptive analgesia has received renewed interest in the recent past.

We used parecoxib sodium *40 mg* pre-operatively and post-operatively in our patients to see whether on time pre-operative intervention of parecoxib will lead to pre-emptive effect on analgesia or not. Desjardin PJ *et al.* (2001),[21] used parecoxib sodium *20 mg*, *40 mg*, *80 mg* and found no significant difference between *40 mg* and *80 mg*, suggesting that the analgesic effect of pre-operatively administered parecoxib sodium reaches a plateau at *40 mg*. Cheer SM and Goa KL (2001)[11] have reported the t1/2 of I.V. *50 mg* valdecoxib to be *0.69 hrs* in 12 healthy volunteers. Hence, we used parecoxib in a dose of *40 mg* pre-operatively *one hour* prior to induction to have maximum pre-emptive effect.

Tan *et al.* (2016)[22] while demonstrating the pharmacokinetics and analgesic effectiveness of intravenous parecoxib for tonsillectomy and adenoidectomy used parecoxib *0.9 mg/kg* in a *2 years-old*, *0.75 mg/kg* in a *7 years-old*, and *0.65 mg/kg* in a *12 years-old* child that achieves dose equivalence of *40 mg* in a standard *70 kg* person. They showed that doses above 1 *mg/kg* provide no additional analgesia and the time to peak valdecoxib concentration was approximately *0.5 hour*.

In our study, the mean time weighed score of pain intensity was 1.61 ± 0.34 in Group I while it

was 1.92 ± 0.10 in Group II ($p < 0.01$) whereas the mean time weighed score of pain relief was 1.72 ± 0.56 in Group I while it was 1.13 ± 0.18 in Group II ($p < 0.01$). These findings correlate well with the results of study carried out by Fricke J *et al.* (2002)[23] who observed that the patients receiving a single dose of *40 mg* valdecoxib experienced significantly greater reduction in pain intensity score and significantly improved pain relief compared with those receiving a single dose of *50 mg* rofecoxib or placebo ($p < 0.01$). The mean pain intensity difference and pain relief scores for the *40 mg* valdecoxib Groups were significantly superior to those of the *50 mg* Rofecoxib Groups *45 min* after study drug administration until the end of *24 hrs* assessment period. Patient in the *40 mg* Valdecoxib Group experienced a significantly greater overall magnitude of pain relief compared with those patients who received *50 mg* of rofecoxib ($p < 0.05$).

Gan TJ *et al.* (2004)[24] in their study used pre-operative parenteral parecoxib to see the quality of patient recovery and length of stay in 263 patients undergoing laproscopic cholecystectomy surgery. They reported a statistically significant reduction in pain intensity and shorter length of stay in post-anesthesia care unit compared with those taking placebo.

Desjardin *et al.* (2001),[21] in their study evaluated pre-emptive analgesic efficacy of parecoxib in different doses in comparison to placebo in 224 patients. An increase in mean pain intensity (VAS) scores was observed in all groups over the first *four hours* after surgery, largely reflecting the waning effect of the local anesthetic. However, from the *2 hours* assessment (*i.e.*, *2 hours* after the completion of surgery) onward all parecoxib sodium groups exhibited mean time specific pain intensity scores that were statistically lower than those for placebo. The mean scores for the parecoxib sodium *40 mg* group were significantly lower than those for the parecoxib sodium *20 mg* group at the *4 hours* assessment upto the *24 hours* assessment. There was no statistically significant difference s between the parecoxib sodium *40* and *80 mg* groups.

Bajaj *et al.* (2004),[17] in their study reported 100% pain relief at *12 hours* in pre-operative parecoxib group. They have reported very high incidence of analgesia which could be because they had used spinal anesthesia in 57% of cases. Thus, the difference in analgesia could be because of difference in type of anesthesia.

Bunyavejchevin and others (2012)[19] used pre-emptive parecoxib in patients undergoing outpatient diagnostic laparoscopy. In their study, pre-operative administration of *40 mg* parecoxib provided significantly superior post-operative relief of both shoulder and wound pain at *2, 6, 12,* and *24 hours* after diagnostic laparoscopy as was the case in our study. However, in our study most patients who were given pre-operative parecoxib reported increased pain beyond *6 hours* post-operatively. This may be due to greater extent of tissue damage in elective surgical cases as compared to diagnostic laproscopic procedure.

Siri bumrungwong and co-workers (2015)[25] compared parecoxib and ketorolac as pre-emptive analgesia in patients undergoing posterior lumbar spinal fusion. They found that both partecoxib and ketorolac were effective in reducing post-operative pain compared to placebo. The wound pain scores of the patients as assessed by the VNRS after surgery showed that there was a statistically significantly average lower pain score reported at both *0* and *1 hours* after surgery in the Ketorolac Group over the control group, and a statistically significantly average lower pain score at *0 hours* after surgery in the group receiving parecoxib compared to the control group. In our study, we found that pain intensity scores were significantly better upto *4 hours* post-operatively in patients who had received parecoxib pre-operatively. This could be because we used parecoxib in general surgical patients with surgical times approximately *1 hour* while they had patients undergoing long, major orthopedic operations.

In our study, the mean time to demand rescue analgesic was *357.24 ± 231.37 mins* in Group I while it was *125 ± 111.87 min* in Group II ($p < 0.01$). Our findings correlate well with the results of study carried out by Barton SF *et al.* (2002)[26] in his study on patients undergoing total abdominal hysterectomy or myomectomy. He demonstrated the mean time to rescue analgesic in I.V. parecoxib *20 mg* to *40 mg* group and I.V. ketorolac *30 mg* group to be *6–6.5 hrs*. which was significantly longer than median time to rescue analgesic for placebo (*1 hr 50 min*).

Desjardin PJ *et al.* (2001)[21] used single doses of parecoxib sodium (*20, 40, 80 mg*) before oral surgery. In their study they had administered *7.2 ml* of 2% lidocaine with 1:100000 epinephrine in soft tissue surrounding the oral molar in which it is observed that 48% of the parecoxib sodium *40 mg* group required rescue medication in the *24 hour* study period compared with the 93% of patients in the placebo group in 224 patients. The median time to rescue medication was *2 hrs 51 min* for patients receiving placebo compared with *6 hours 17 min* in patients receiving *20 mg* parecoxib and *24 hrs*

for patients receiving parecoxib sodium *40 mg* ($p < 0.03$). An increase in mean pain intensity score was observed in all groups over the first *four hours* after surgery reflecting the waning of effect of the local anesthetic .There mean time for demand to rescue analgesia was higher in I.V. parecoxib *40 mg* group than in our study because they had taken only patients of molar extraction and haad used preoperative local anesthetic also.

Akaraviputh T *et al.* (2009)[18] while determining the efficacy of peri-operative parecoxib injection on post-operative pain relief after laparoscopic cholecystectomy found that maximum intensity of pain that required rescue analgesia occurred approximately *6 hrs* post operatively. This was similar to our study, also they found that the need of opiod infusion to control pain post-operatively was significantly lower than in patients who has received pre-emptive parecoxib.

More recently Bian *et al.* (2018)[27] while evaluating the role of Parecoxib Sodium in the Multimodal Analgesia after Total Knee Arthroplasty used *40 mg* parecoxib pre-operatively and *12 hrs* post-operatively. They used PCA pump with morphine bolus whenever patient complained of pain. The VAS scores for pain post-operatively were maximum at *6–12 hrs* post-operatively, peaking around *12 hrs*. This was later than that recorded in our study. The difference may be attributed to the fact that we gave parecoxib *1 hr* prior to surgery and they used it *30 mins* before surgery. However, the PCA consumption was significantly lower in parecoxib group as compared to placebo group demonstrating the efficacy of pre-emptive parecoxib in early post-operative period (*24 hrs*).

Desjardin PJ *et al.* (2001)[21] and Fricke J *et al.* (2002)[23] reported incidence of headache as 11% and 12.5% respectively in there studies, which was comparable to our study, where it was 8% in Group I and 10% in Group II. Also, Desjardin PJ *et al.* noticed nausea in 9% patients receiving *40 mg* parecoxib. In our study, incidence of nausea was 10% and 8% in Group I & II respectively. In contrast Bian *et al.* (2018)[27] reported nausea and vomiting in 8 out of 46 patients (17.4%) who received parecoxib pre-operatively. The higher incidence of nausea could be because of use of PCA morphine bolus in their study. Siribumrungwong and co-workers (2015)[25] also found that there was no significant difference in adverse events in parecoxib and ketorolac group as compared to control group.

This study demonstrated that pre-operative administration of parecoxib sodium was effective in reducing or eliminating post-operative pain in elective general surgery. As measured by time to rescue medication was less in patients getting parecoxib sodium pre-operatively as compared to the patients who were given parecoxib post-operatively. Parecoxib pretreated patients had less side effects compared to the patients who were given parecoxib post-operatively.

This study suggests that the pre-operative dose of parecoxib was more effective than the post-operative dose in providing pain relief in post-operative period in patients undergoing elective general surgery. Both the regimens were well tolerated. It appears that post-operative dose of parecoxib *40 mg* I.V. is a useful option for pre-emptive analgesia in general surgical procedures for management of post-operative pain.

A limitation in our study was that there was no control group in our study. Also we used only single dose of parecoxib post operatively. So, further studies are needed to demonstrate its efficacy using multiple doses and different types of surgical procedures.

Conclusion

Pre-operative parecoxib has an effective pre-emptive analgesic effect by decreasing the post-operative pain and delaying the the time to demand of rescue analgesia as compared to its use post-operatively.

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