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Original Article

Comparing the Analgesic Efficacy of Parecoxib and Rofecoxib for Post-operative Analgesia Following Lower Abdominal Surgery

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Abstract

Background: This study tested the hypothesis that an intravenous parecoxib 40 mg and deep intragluteal rofecoxib 40 mg will be effective for post-operative pain relief after hysterectomy and well tolerated.

Materials and Methods: In this prospective, double-blinded, placebo-controlled study, we included 90 women posted for hysterectomy under spinal anesthesia. Patients were allocated into three groups in Group A (intravenous parecoxib 40 mg), Group B (deep intragluteal rofecoxib 25 mg), and Group C (2 mL normal saline). We administered studied drug preemptively, 15 min before the surgical incision. We measured pain on visual analog scale (VAS) and recorded observations at fixed intervals to investigate the duration of post-operative analgesia. We administered 100 mg tramadol as rescue analgesic once patient complained 25% pain relief on VAS.

Results: A total of 90 patients were enrolled. All treatment groups had comparable demographics and baseline pain status. Overall, each rofecoxib dose was superior to each dose of parecoxib and parecoxib is superior to placebo for post-operative pain relief in patient who underwent hysterectomy. In our study, we observed that total duration of analgesia in Groups A-C was 3.42 ± 0.52 h, 5.23 ± 0.52 h, and 2.31 ± 0.23 h, respectively, and average duration of post-operative analgesia in Groups A-C was 1.21 ± 0.41 h, 3.04 ± 0.45 h, and 10 ± 0.18 min, respectively. All treatments were well tolerated.

Conclusions: In this study, we found that deep intragluteal rofecoxib 25 mg is more effective than intravenous parecoxib 40 mg and placebo; similarly, intravenous parecoxib 40 mg is more effective than placebo for post-operative pain relief in patients who underwent hysterectomy. Rofecoxib extends post-operative analgesia up to 5 h, parecoxib up to 3 h without any adverse effects. We did not find comparable results with previous studies.

Key words: Analgesic, Post-operative, Surgery

INTRODUCTION

"The word pain comes from the Latin word poena which means punishment (Winston CV Parris)."[1] By definition, "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[2] Therefore, many patients are more afraid and anxious about post-operative pain than surgery. Pain is very subjective and cannot be defined satisfactorily in medicine for a complete solution since long. Acute post-operative pain has specific characteristic and it is the only pain syndrome that can be predicted before its occurrence; hence, this pain is entirely different from other pain syndromes.[1] Many methods have been tried to treat post-operative pain since long back such as parenteral drugs including both narcotic and non-narcotics like anti-inflammatory and other drugs such as N-methyl-D-aspartate receptor blockers, namely ketamine and $Mgso_4$, regional techniques such as caudal epidural and peripheral nerve blocks. Nowadays, multimodal analgesic approaches are preferred over any single modality of pain management. Several years ago the concept of preemptive analgesia emerged from the experimental researches and this new approach for the

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world of pain management had been considered promising and convincing but soon became controversial because of the different results.[3] Among the different analgesics, non-selective (cyclooxygenase-1 [COX-1] and COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs) have limited use in post-operative pain relief often due to the risk of bleeding.[4] Few years, hence, some COX-2 inhibitors had been introduced as analgesics which lack the conventional side effects of non-selective NSAIDs, namely valdecoxib, celecoxib, etoricoxib, parecoxib, and rofecoxib. Many studies had been done to establish the efficacy of these COX-2 inhibitors in post-operative pain.

Parecoxib is the first injectable COX-2 selective inhibitor manufactured for the analgesia. It is a prodrug of valdecoxib and 28,000 more potent against COX-2 than COX-1,[4] rofecoxib another COX-2 selective inhibitor and is a methylsulfonyl derivative. It is found that it can selectively inhibit recombination COX-2 if compared with COX-1 selectivity in the ratio of >800.[5] Our work been done to study and compare the efficacy of recently introduced COX-2 inhibitors, parecoxib and rofecoxib for post-operative pain management after hysterectomy.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, a prospective, randomized, double-blind study was conducted in female patients which had been scheduled for hysterectomy at Netaji Subhash Chandra Bose Medical College, Jabalpur, M.P., from 2002 to 2005. 90 female patients of ASA Grades I and II of age ranging from 18 to 80 years were selected randomly who were posted for abdominal or vaginal hysterectomy under spinal anesthesia. Exclusion criteria for the present study were any contraindication for spinal anesthesia, known allergy to NSAIDs or any contraindications to NSAIDs, and history of bleeding disorder, patient was on anticoagulants, current pregnancy, breastfeeding, history of known, or suspected drug abuse. If patient was having any central nervous system, cardiovascular disorder, gastrointestinal, hepatic, renal or psychiatric disorder. After taking valid informed written consent, all the patients were examined preoperatively and vitals recorded. All the demographic data such as age, sex, weight, and height were noted. Patients were allocated into the three groups: Group A received intravenous parecoxib 40 mg, Group B patients received deep intragluteal rofecoxib 25 mg, and Group C patients received 2 mL normal saline. Group C was a control group. Under all aseptic precautions, spinal anesthesia had been administered to the study patients. Study drugs iv parecoxib, im rofecoxib, or normal saline were given as a preemptive analgesic to the patients 15 min before surgery. Injection bupivacaine 0.5% (heavy) 3 mL administered into the intrathecal space at the level of L4-L5 intervertebral space. Vitals recorded every 5 min thereafter. After confirming the adequate level of spinal block. Visual analog scale (VAS) was used to measure the post-operative pain just after surgery and then at every 30 min interval. When the patient was having only 25% pain relief on VAS, this was taken as a cessation of analgesia and rescue analgesic intravenous tramadol 100 mg was given to the patient.

RESULTS

The total duration of analgesia in Groups A-C was 3.41 ± 0.52 h, 5.23 ± 0.50 h, and 2.31 ± 0.23 h, respectively. As shown in the table, the total duration of pain relief was maximum in Group B, and the difference in means of total duration of analgesia was found to be statistically significant ($P < 0.0001$).

The total duration of post-operative analgesia was measured after the spinal anesthesia worn off completely. The duration of post-operative analgesia after the effect of spinal anesthesia was over in Groups A-C was 1.21 ± 0.41, 3.04 ± 0.45, and 0.10 ± 0.18 min, respectively. The maximum post-operative analgesia was found in Group B which was greater than Groups A and C. This difference in mean duration of post-operative analgesia was significant ($P < 0.0001$).

This table shows the distribution of the groups according to the drugs administered to the patients for post-operative analgesia. All the groups comprised 30 patients each.

Table shows comparison of pre-operative bleeding time with post-operative bleeding time at different intervals. The bleeding time was recorded before the operation, postoperatively immediately after the operation, at 12 h and 24 h. As shown by this table, this difference was found to be statistically insignificant ($P>0.05$).

The total duration of analgesia was measured by VAS. This table shows the mean post-operative pain relief at every 30 min interval in all the groups [Figures 1-7 and Tables 1-7].

DISCUSSION

Post-operative pain is a critical factor that hamper recovery from surgery, hence, relief from pain should be the first reason to provide optimum analgesia to all the patients who are suffering from pain including those who underwent surgical procedures.[6,7] Various studies suggested that parecoxib sodium and rofecoxib are effective in acute post-operative pain so we have decided to compare the efficacy of parecoxib and rofecoxib with placebo (NS)

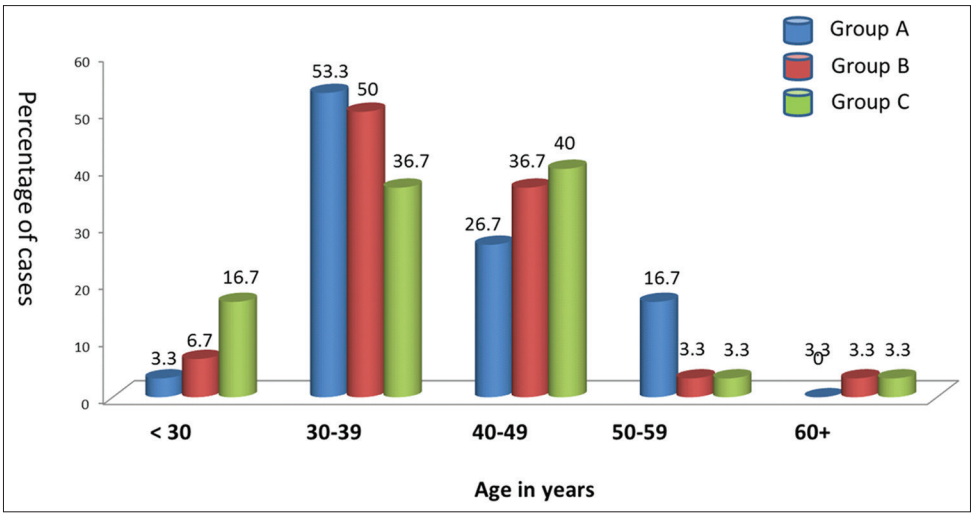

Figure 1: Distribution of the cases according to age in studied groups

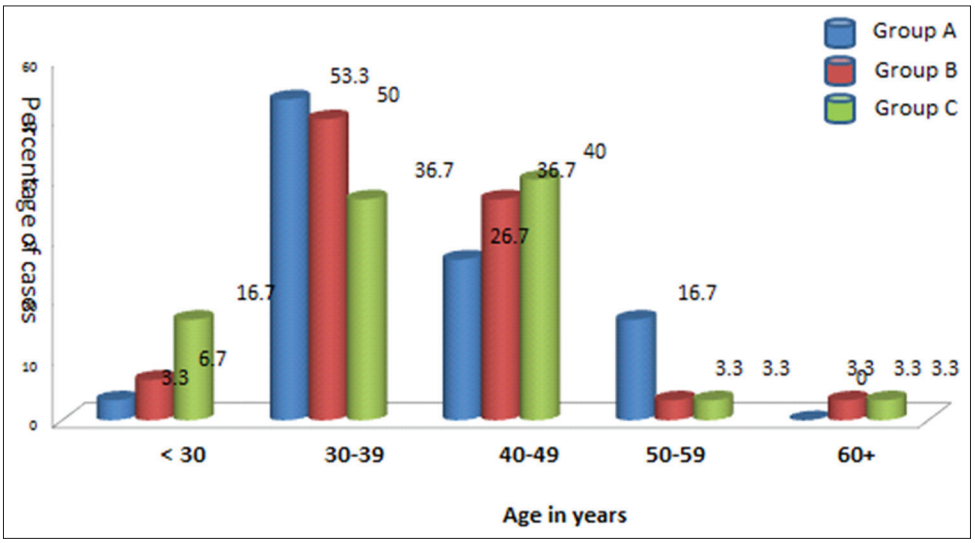

Figure 2: Distribution of the cases according to age in studied groups

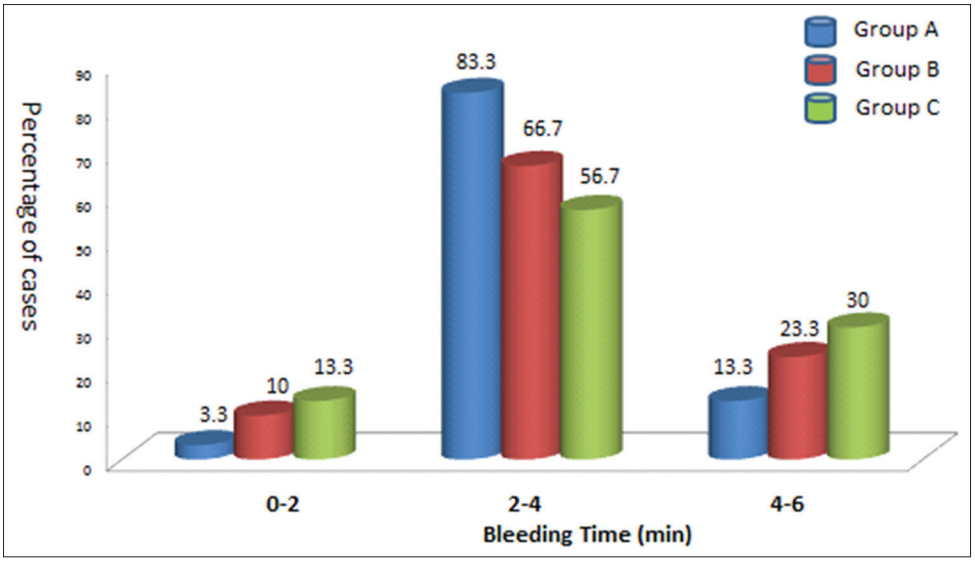

Figure 3: Study of average pre-operative bleeding time

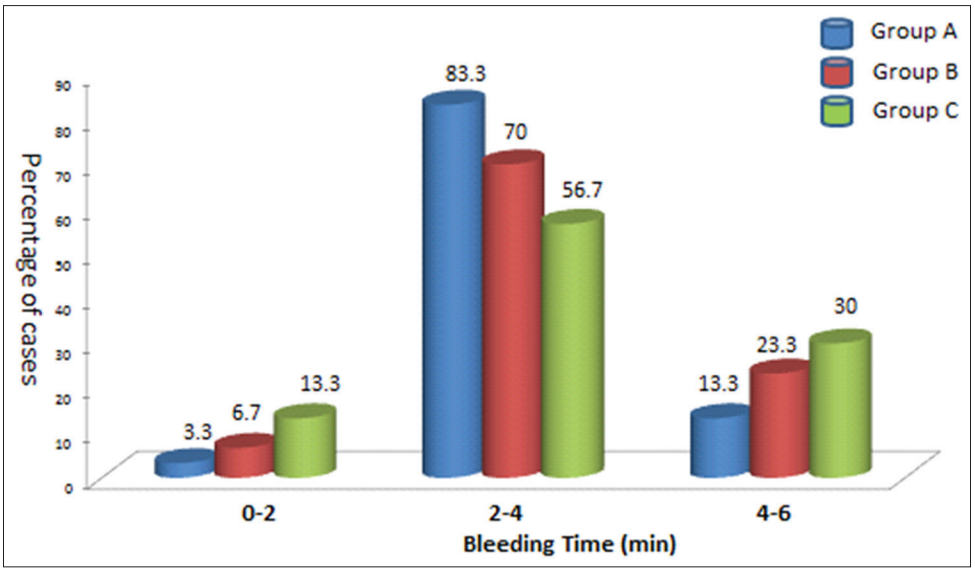

Figure 4: Study of average bleeding time immediately after operation

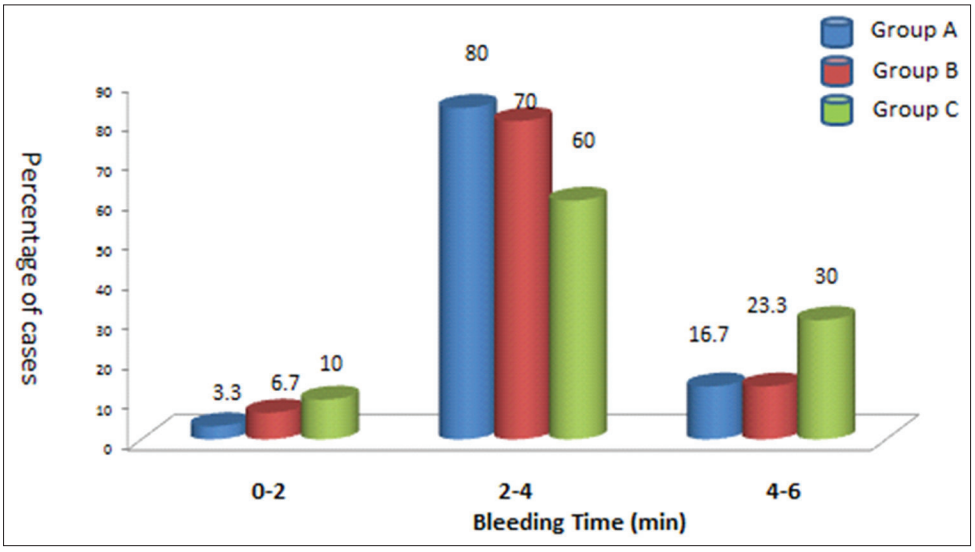

Figure 5: Study of average bleeding time 12 h

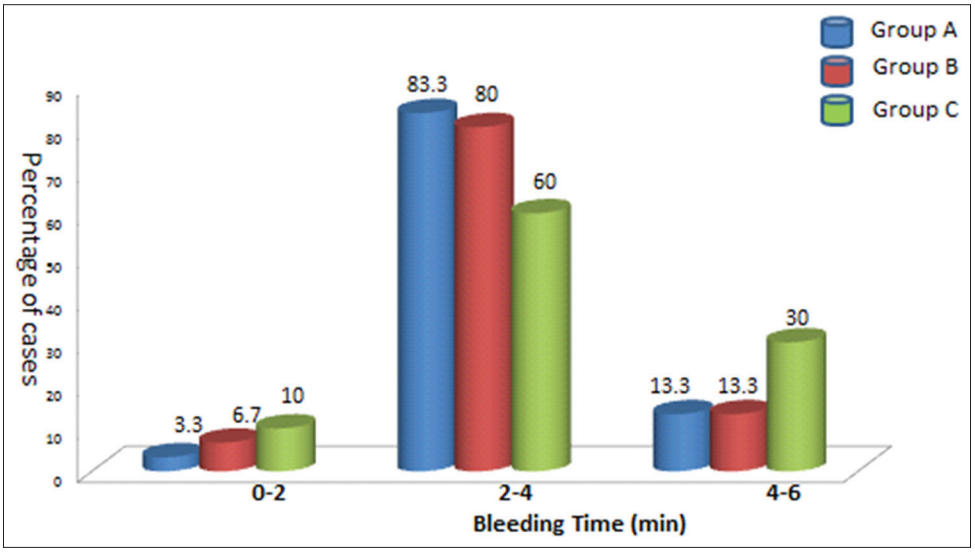

Figure 6: Study of average bleeding time 24 h

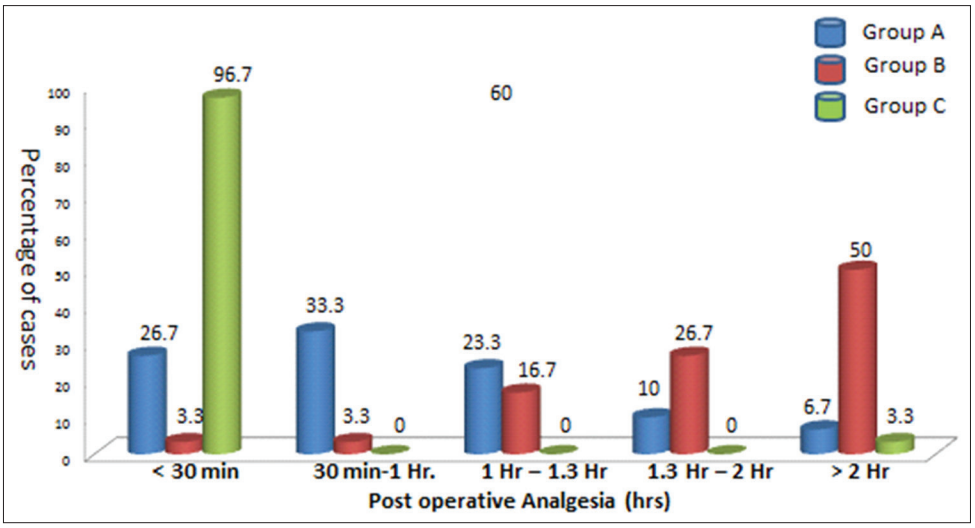

Figure 7: Comparison of post-operative analgesia in studied groups

Table 1: Distribution of the cases according to age

Age in years	Group A (%)	Group B (%)	Group C (%)
<30	1 (3.3)	2 (6.7)	5 (16.7)
30–39	16 (53.3)	15 (50.0)	11 (36.7)
40–49	8 (26.7)	11 (36.7)	12 (40.0)
50–59	5 (16.7)	1 (3.3)	1 (3.3)
60+	0 (0.0)	1 (3.3)	1 (3.3)
Total	30	30	30
Mean±SD	44.00±7.64	43.43±8.82	42.43±9.18

P>0.05. The age difference among all the groups was found insignificant

Table 2: Weight distribution of the patients in studied groups

Weight (kg)	Group A	Group B	Group C
<30	2	1	1
30–40	10	12	13
41–50	12	14	12
51–60	4	2	3
>60	2	1	1
Mean±SD	43±9.96	41.67±5.02	41.67±8.44

P>0.05. The weight difference among all the groups was found insignificant

Table 3: Comparison of total duration of analgesia in studies group (from study drug injection to VAS ≥ 25)

Total duration of analgesia in (hours)	Group A *n*=30 (%)	Group B *n*=30 (%)	Group C *n*=30 (%)
<2	1 (3.3)	0 (0.0)	4 (13.3)
2–4	19 (63.3)	1 (3.3)	26 (86.7)
4–6	10 (33.3)	24 (80.0)	0 (0.0)
>6	0 (0.0)	5 (16.7)	0 (0.0)
3.41±mean SD	3.41±0.52	5.23±0.50	2.31±0.23

P=0.0001 significant

Table 4: Comparison of post-operative analgesia at the end of spinal anesthesia (from commencement of motor recovery to VAS ≥ 25)

Duration of post-operative analgesia	Group A *n*=30 (%)	Group B *n*=30 (%)	Group C *n*=30 (%)
<0.5 h	4 (13.3)	0 (0.0)	28 (93.3)
0.5–1 h	10 (33.3)	0 (0.0)	2 (6.7)
1–1.5 h	6 (20.0)	1 (3.3)	0 (0.0)
1.5–2 h	9 (30.0)	2 (6.7)	0 (0.0)
>2 h	1 (3.3)	27 (90.0)	0 (0.0)
Mean±SD	1.21±0.41	3.04±0.45	0.10±0.18

P=0.0001 significant

Table 5: Distribution of patient's according to drugs

Group	Drug	Number of patients
A	I/V Parecoxib 40 mg+intrathecal bupivacaine heavy (0.5%) 3 mL	30
B	I/M Rofecoxib 25 mg+intrathecal bupivacaine heavy (0.5%) 3 mL	30
C	I/V normal saline (0.9%) 2 mL+intrathecal bupivaciane heavy (0.5%) 3 mL	30
	Total	90

for post-operative analgesia. Average age of the patients in Groups A-C was 44 ± 7.64 years, 43.43 ± 8.82 years, and 47.73 ± 9.18 years, respectively. Maximum number of patients was 30–39 years and the difference was statistically insignificant ($P > 0.05$). The mean weight in Groups A-C was 43 ± 9.96 kg, 41.67 ± 5.02 kg, and 41.67 ± 8.44 kg, respectively, and the difference was not significant ($P > 0.005$).

In this study, all the studied drugs were given preemptively in patients who underwent hysterectomy, and it was comparable to many previous studies as to Desjardins *et al.*, who found that preemptive injection of parecoxib is effective, safe for the management of post-operative

analgesia and well tolerated by the patients as well.[8] Karamanlioglu *et al*. investigated that pre-operative use of oral rofecoxib has remarkable analgesic efficacy and opioid-sparing effect as well in patients who underwent abdominal hysterectomies.[9] Similarly, the parecoxib dose selected for our study was 40 mg and was also comparable to the previous study which was done by Barton *et al*. for treating acute pain after gynecological laparotomy surgeries.[10] Rofecoxib 25 mg dose had been given to the patients in our study which was also comparable to the study conducted by Reicin *et al*., in their study, they investigated efficacy of single dose and multidose rofecoxib for the management of acute pain after orthopedic surgeries. They administered rofecoxib in 25 mg, 50 mg doses, and placebo and concluded that 25 mg rofecoxib is effective than placebo, but 50 mg once daily dose of rofecoxib was more superior than rofecoxib 25 g in managing post-operative pain ($P \leq 0.267$) and had more opioid-sparing effect.[11]

In our, we found that deep intragluteal rofecoxib 40 mg (Group B) has a significantly greater total duration of post-operative analgesia which was 5.23 ± 0.50 h when compared with intravenous parecoxib 40 mg (Group A) which was 3.14 ± 0.52 h and placebo (Group C) 2.23 ± 0.23 h which was comparable to previous studies.

Reicin *et al*. conducted a double-blind, randomized, placebo- and active comparator-controlled, parallel-group trial in 218 patients enrolled for orthopedic surgery. They compared two doses of rofecoxib 25mg and 50 mg in their study and they concluded that 50 mg rofecoxib is superior for once daily dose than rofecoxib 25 mg for post-operative pain management after orthopedic surgery[12] which was not comparable to previous study as we found only 5.23 ± 0.50 h post-operative pain relief after single dose of rofecoxib 40 mg.

Samra *et al*. had done a prospective study in 260 patients undergoing orthopedic, gynecological, dental, and general surgery to investigate the duration of post-operative analgesia after giving intravenous or intramuscular parecoxib 40 mg, and they found a very good pain relief in 89.6% of total cases at the end of 24 h. The mean duration of analgesia was 19.26 h in their study which was not comparable to our study as we found only 3.41 ± 0.52 h of post-operative pain relief after single preemptive dose of parecoxib iv 40 mg.[6]

In another study done by Desjardins *et al*., who investigated the analgesic efficacy of pre-operative parecoxib after bunionectomy. In this study, they found that mean duration of analgesia was 4 h 18 min in the placebo group, 7 h 5 min in the 20 mg parecoxib group, and 10 h 43 min in 40 mg parecoxib group[8] which was also not comparable to our study because we found only 3.41 ± 0.05 h of analgesia which was significantly lower than the previous studies.

Table 6: Comparison of bleeding time at different intervals

Period (minutes)	Group A	Group B	Group C
Baseline (pre-operative)	3.25±0.49	3.09±0.54	3.20±1.01
Immediately after operation	3.14±0.50	3.12±0.52	3.21±1.02
At 12 h	3.17±0.49	3.12±0.53	3.23±1.16
At 24 h	3.17±0.49	3.19±0.52	3.24±1.16
Significance	*Z*=0.86	*Z*=0.22	*Z*=0.04
	P>0.05	*P*>0.05	*P*>0.05
	Z=0.63	*Z*=0.22	*Z*=0.11
	P>0.05	*P*>0.05	*P*>0.05
	Z=0.63	*Z*=0.73	*Z*=0.14
	P>0.05	*P*>0.05	*P*>0.05

Table 7: Comparison of degree of pain relief in studied groups (VAS)

Time interval	Group A	Group B	Group C	Significance
Initial	77.50±23.99 (*n*=30)	100.00±0.00 (30)	32.50±14.90 (30)	Z A/B=5.14 *P*<0.0001 Z A/C=8.73 *P*<0.0001 Z B/C=24.81 *P*<0.0001
0.30	62.96±16.07 (*n*=27)	93.10±11.37 (29)	32.14±12.20 (7)	ZA/B=8.05 *P*<0.0001 ZA/C=3.36 *P*<0.0001 ZB/C=6.86 *P*<0.0001
1.00	42.31±15.44 (*n*=26)	82.76±16.51 (29)	25.00±0.00 (2)	Z A/B=9.39 *P*<0.0001 Z A/C=5.72 *P*<0.0001 Z B/C=18.84 *P*<0.0001
1.30	40.63±12.50 (*n*=16)	70.69±16.46 (29)	25.00±0.00	Z A/B=6.86 *P*<0.0001
2.00	27.50±7.91 (*n*=10)	58.04±18.07 (28)		Z A/B=7.21 *P*<0.0001
2.30	50.00±0.00 (*n*=1)	47.00±18.14 (25)		Z A/B=0.83 *P*<0.05
3.00	25.00±0.00 (*n*=1)	43.06±18.80 (18)		Z A/B=4.08 *P*<0.0001
3.30		35.00±12.91 (10)		NA
4.00		40.00±13.69 (5)		NA

In 2002, Reuben *et al.*[12] investigated the effect of rofecoxib as a preemptive analgesic. In this study, they divided total number of patients in three groups in which they administered single dose of 50 mg rofecoxib 1 h before the surgical incision, the post-incisional group had been given 50 mg rofecoxib after the surgery was over, and in placebo group, they administered a placebo tablet before surgery. They found that analgesia was significantly longer in pre-incisional group (803 ± 536 min) when compared to post-incisional group (461 ± 344 min) and placebo group (318 ± 180 min). If we compare their with our study results, these were not comparable as we found the mean duration of analgesia of 5.23 h which was significantly lower than that of the Ruben's study in which they found 13.38 h pain relief after administering 50 mg rofecoxib preemptively, but in our study, we had used 25 mg dose of rofecoxib so dose was also not comparable. This difference in study design also justifies the difference in results between both the studies.

There were wide variations in the mean duration of analgesia observed by different researchers. This discrepancy could be due to multiple factors such as due to different designing of research, race and ethnic variations, different types of surgeries, different doses of studied drugs, different routes of administered drugs, different types of anesthesia techniques used in different studies, and different methods used to measure pain. Some explanations may be offered on the basis of individual reaction to pain, overall psyche of the patients, and intelligence do have a definite influence.

The present study was done under spinal anesthesia in which intrathecal injection of bupivacaine 0.5% heavy 3 mL had been administered to the patients. It was observed that the mean duration of spinal analgesia in Groups A-C was 2.21 ± 0.20 h, 2.19 ± 0.18 h, and 2.21 ± 0.22 h, respectively. These values suggest that the difference between means duration of analgesia was statistically not significant ($P > 0.05$). It means parecoxib, rofecoxib, and placebo do not affect the duration of spinal analgesia.

In our study, all cases were closely observed for any incidence of complications. In this study, we did not find any. None of the patient complaint of nausea, vomiting, headache or any hypersensitivity reaction.

In the present study, bleeding time was estimated preoperatively, immediately after the operation, at 12 h and at 24 h to notice any change in bleeding time and platelet aggregation. The difference in the bleeding time at different intervals was comparable and statistically insignificant ($P > 0.05$). It was observed that parecoxib, rofecoxib, and placebo all do not affect the bleeding time and platelet aggregation. Greenberg *et al.* found that rofecoxib did not after the antiplatelet effects of low-dose aspirin. No clinical or laboratory adverse experiences were observed.

CONCLUSION

In this study, we found that deep intragluteal rofecoxib 25 mg is more effective than intravenous parecoxib 40 mg and placebo; similarly, intravenous parecoxib 40 mg is more effective than placebo for post-operative pain relief in patients who underwent hysterectomy. Rofecoxib extends post-operative analgesia up to 5 h, parecoxib up to 3 h without any adverse effects. We did not find comparable results with previous studies

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