

Comparative study of analgesia of ketorolac, tramadol, and flupirtine in the management of third molar surgery

ABSTRACT

Introduction: The most commonly performed surgical procedure in most oral and maxillofacial surgery practices is the removal of third molars. Postoperative pain is considered a form of acute pain due to surgical trauma with an inflammatory reaction.

Materials and Methods: One hundred and fifty patients were included in the study which were divided into GROUP-A, B, and C-50 patients each; those who underwent third molar removal under local anesthesia. Local anesthesia was obtained by inferior alveolar, lingual, long buccal, posterior superior alveolar, and greater palatal nerve block injections after first complain of pain, all patients were prescribed analgesics (Ketorolac-10 mg), (Tramadol-50 mg), (Flupirtine-100 mg), and antibiotics co-amoxiclav-625 mg) T. D. S in all the three groups A, B, C, respectively, for 5 days and the timing noted in the patients assessment sheet. The statistical analysis was done using SPSS Version 15.0 statistical analysis software.

Results: The flupirtine group has early onset and also had minimum side effects. All the groups showed similar trend in change in pain score from 3 h. P. O to different time intervals. It was observed the pain score increased significantly till 6 h. Post operative a decreased trend was found at 24 h, 48 h, 78 h, after 6 h. and this change was found to be statistically significant for all three groups.

Conclusion: Flupirtine had faster onset and comparable pain management profile as compared to tramadol, it also had minimum side effects, hence the use of flupirtine might be recommended for postoperative pain management in cases undergoing third molar surgery.

Keywords: Analgesia, flupirtine, ketorolac, third molar surgery, tramadol

INTRODUCTION

The most commonly performed surgical procedure in most oral surgery practices is the removal of third molars.

The pain of tooth extraction varies among individuals, and each extraction of an individual may be quite different.^[1,2]

Pain associated with removal of third molars usually occurs in between moderate to severe in the first 24 h after surgery, with pain peaking between 6 and 8 h.^[3] The problem of dental pain can be tackled using peripherally acting or centrally acting drugs. Here, the effect of ketorolac, tramadol, and flupirtine in the management of pain after third molar extraction is considered.

Aim and objective

Comparing analgesic efficacy of orally administered ketorolac,

tramadol, and flupirtine in management of third molar surgery as per the following parameter:

1. Onset of analgesia
2. To compare the efficacy of analgesia postoperatively
3. Duration of analgesia after 1st dose of drug given
4. To compare adverse effect.

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Received: 29 November 2020, **Revised:** 24 December 2020, **Accepted:** 06 May 2021, **Published:** 15 June 2022

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How to cite this article: Gupta AK, Kohli M, Pandey PK, Dwivedi PD, Singh VP. Comparative study of analgesia of ketorolac, tramadol, and flupirtine in the management of third molar surgery. Natl J Maxillofac Surg 2022;13:262-8.

Access this article online

Website:
www.njms.in

DOI:
10.4103/njms.NJMS_261_20

Quick Response Code



MATERIALS AND METHODS

A prospective study was conducted in the Department of Oral and Maxillofacial Surgery, Chandra Dental College and Hospital, Barabanki. Ethical clearance obtained from Ethical Committee of Chandra Dental College and Hospital, Safedabad, Barabanki, Uttar Pradesh, India, reference no: Cdch/os/12-15/01, dated: 10/02/14. In this study, 150 patients, divided into groups A, B, and C— fifty patients each those who underwent third molar removal under local anesthesia were included in the study. Sample size was calculated by characteristic visual analog scale (VAS) of superior group and inferior group. Randomization was done by systematic sampling technique as shown in Table 1.

Patient inclusion criteria

All cases included were ASA Grade-I healthy patients in the 20–50 years age group with unilateral or bilateral third molar irrespective of their angulations and were free from any inflammatory symptoms including hyperemia, pericoronitis, swelling, and trismus at the time of the procedure.

Patient exclusion criteria

Cases with a known history of systemic disorder, immunocompromised patient, and patient suffering from mental illness were excluded from the study. Patients with a history of sensitivity to ketorolac, tramadol, and flupirtine was excluded from the study, and patients requiring incision and bone cutting for tooth removal were also excluded from the study.

Material used

Basic instruments required for extraction:

- Tablet Ketorolac 10 mg
- Tablet Tramadol 50 mg
- Cap. flupirtine 100 mg
- Visual analog scale
- Postoperative pain.

Operative technique

A standardized surgical approach to the removal of the third molars was followed, Local anesthesia was obtained by inferior alveolar, lingual, long buccal, posterior superior alveolar, and greater palatal nerve block injections using 2% lignocaine with 1:80,000 adrenaline.

RESULTS

The mean \pm standard deviation (SD) age of Group-I was 38.75 ± 9.25 ranged (20–50). The mean \pm SD age of Group-II was 38.50 ± 8.25 ranged (20–50). The mean \pm SD age Group-III was 38.48 ± 8.77 ranged (21–50). We found there was no statistically significant difference in age of the three

Table 1: Distribution of study population

Group	Analgesic	Number of case (%)
Group-1	Tablet ketorolac 10 mg	50 (33.33)
Group-2	Tablet tramadol 50 mg	50 (33.33)
Group-3	Capsule flupirtine 100 mg	50 (33.30)

groups ($F = 0.987$, $P = 0.315$, NS). Age-wise groups were similar as shown in Table 2.

Male population was higher than the female population. Male was 62% in Group-I and III and 58% in Group-II and female was 38% in Group-I and Group-III and 42% in Group-II. On comparison, there was no significant difference in gender of the three groups ($P = 0.894$, NS) Three groups were similar sex wise as shown in Table 3.

Out of 150 patients enrolled in the study, site of tooth involved in maxillary jaw was one third of total patients ($n = 50, 33.33\%$), and in mandibular jaw was two third of total patients ($n = 100, 66.67\%$). There was a significant difference in the site of the tooth in the three groups ($P = 0.81$, NS) as shown in Table 4.

- Mean \pm SD of onset of Group-I was 40.50 ± 6.94
- Mean \pm SD of onset of Group-II was 44.00 ± 5.05
- Mean \pm SD of onset of Group-III was 41.50 ± 6.00
- On comparison by ANOVA $P = 0.013$ (Sig).

There is significant difference in the time of onset of analgesia in the respective three groups. On patients of HOC test (Tukey) Group-I versus Group-II $P = 0.12$ (Sig) onset. There was less in Group-I than Group-II and significant.

Group-I versus Group-III $P = 0.68$ (NS). Time of onset is less in Group-I than Group-III but non significant. Group-II versus Group-III $P = 0.10$ (NS). Time of onset is more in Group-II than Group-III. Time of onset is least in Group-I and maximum in Group-II.

- Mean \pm SD of duration of analgesia in Group-I was 6.40 ± 0.49 h
- Mean \pm SD of duration of analgesia in Group-II was 6.70 ± 0.46 h
- Mean \pm SD of duration of analgesia in Group-III was 6.80 ± 0.61 h
- On comparison by ANOVA the $P = 0.001$ which is statistically significant as shown in Table 5.

Intergroup pair wise comparison between duration of analgesia, after first dose by tukey test method as shown in Table 6.

I versus II duration of analgesia is significantly more in Group-II than Group-I $P = 0.013$.

I versus III duration of analgesia is significantly more in Group-III than Group-I $P = 0.001$.

Table 2: Intergroup comparison of age of study population

Group	Number of cases	Minimum	Maximum	Median	Mean \pm SD	ANOVA
Group-1	50	20	50	40.0	38.76 \pm 9.25	F=0.987
Group-2	50	20	50	38.5	38.50 \pm 8.25	P=0.315
Group-3	50	21	50	36.00	38.48 \pm 8.77	NS

SD: Standard deviation, NS: Not significant

Table 3: Intergroup comparison of gender of study population

Gender	Group-I, n (%)	Group-II, n (%)	Group-III, n (%)	χ^2 , df	P
Female (n=59)	19 (38.0)	21 (42.0)	19 (36)	0.224, 2	0.894
Male (n=91)	31 (62.0)	39 (58.0)	31 (62.0)		

Table 4: Intergroup comparison of site of tooth involved

Site of tooth	Group-I, n (%)	Group-II, n (%)	Group-III, n (%)	χ^2 , df	P
Maxillary (n=50)	18 (36.0)	15 (30)	17 (34)	0.420, 2	0.81 (NS)
Mandibular (n=100)	32 (64.00)	35 (70)	33 (66.0)		

NS: Not significant

Table 5: Intergroup comparison of time of onset of analgesia (min) of study population

Group	Number of cases	Minimum	Maximum	Median	Mean \pm SD	ANOVA	Group-wise comparison
Group-1	50	30	45	45.0	40.50 \pm 6.94	F=0.44	I versus II P=0.012
Group-2	50	40	55	40.0	44.00 \pm 5.05	P=0.013	I versus III P=0.687
Group-3	50	30	50	45.0	41.50 \pm 6.00	Significant	II versus III P=0.100

SD: Standard deviation

Table 6: Intergroup comparison of duration of analgesia (h) after first dose of study population

Group	Number of cases	Minimum	Maximum	Median	Mean \pm SD	ANOVA	Group-wise comparison (by Tukey test)
Group-1	50	6	7	6	6.40 \pm 0.49	F=7.86	I versus II P=0.013
Group-2	50	6	7	7	6.70 \pm 0.46	P=0.001	I versus III P=0.001
Group-3	50	6	8	7	0.61 \pm 0.61		II versus III P=0.608

SD: Standard deviation

II versus III duration of analgesia is more in the Group-III than Group II P = 0.608 (NS)

Duration of analgesia is maximum in Group III than in Group-II and least in Group-I.

AT 3 h:

- Group-I versus Group-II: No. significant difference in pain score P = 0.25
- Group-I versus Group-II: Pain significantly more in Group-I than Group-III P = 0.013
- Group-II versus Group-III: No significant difference in pain score P = 0.16.

AT 6 h:

- Group-I versus Group-II: Pain is significantly more in Group-I than Group-II P = 0.025
- Group-I versus Group-III: Pain is significantly more in Group-I than Group -III P = 0.002
- Group-II V. Group-III No significantly difference in pain score in Group-II and Group-III P = 0.25.

AT 24 h.

- Group-I versus Group-II: No significant difference in pain score among in groups
- Group-I versus Group-III: No significant difference in pain score among groups
- Group-II versus Group-III: No significant difference in pain score among groups.

AT 48 h:

- Group-I versus Group-II: Pain is significantly more in Group-I than Group-II, P = 0.042
- Group-I versus Group-III: No significantly difference in Group-I and Group-III, P = 1
- Group-II versus Group-III: Pain is significantly more in Group-III than Group-II, P = 0.042.

AT 72 h.

- Group-I versus Group-II: No significant difference in pain score among groups
- Group-I versus Group-III: No significant difference in pain score among groups

- Group-II versus Group-III: No significant difference in pain score among groups as shown in Table 7a and b.

All the groups showed a similar trend in change of pain score from 3 h postoperative to different time intervals. It was found that a statistically significant increase in pain score was observed at 6 h postoperative and thereafter at 24 h p. o., 48 h p. o., and 72 h p. o. a subsequent decrease with time from that at 3 h was observed and this change was found to be statistically significant in all the three groups as shown in Table 8.

Proportion of patients with side effects after first dose was found to be lower in Group I and Group III (8.00%) as compared to Group II (14.00%), but this difference was not found to be statistically significant.

Proportion of patients with side effects after the second dose was found to be higher in Group II (26.00%) followed by Group I (20.0%) and lowest in Group III (12.0%).

Proportion of patients with side effects after the third dose was found to be higher in Group II (30.00%) followed by Group I (20.0%) and lowest in Group III (16.0%) as shown in Table 9.

DISCUSSION

The present study is the first study comparing the efficacy of flupirtine (100 mg) administered postoperatively through oral route with tramadol (50 mg) and ketorolac (10 mg) administered through similar route following same dosage schedule, the results showed its comparability on pain intensity and a better control on the side effects. In the present study, the proportion of males was higher as compared to females (1.5:1 however, as the three groups were matched for gender, hence these confounding effects, if any were evenly distributed among the groups.

In the present study, the onset time for analgesia ranged from 30 to 55 min. Mean onset time was comparable for ketorolac (40.50 ± 6.94 min) and flupirtine (41.50 ± 6.00 min) groups and was significantly higher for the tramadol group

(44.00 ± 5.05 min). Delayed onset of tramadol (50 mg) as compared to ketorolac (10 mg) at same dosages has also been reported by Shaik *et al.*^[4] There is no study available evaluating the use of flupirtine (100 mg) as compared to oral tramadol (50 mg) or ketorolac (10 mg) for postoperative pain among patients undergoing third molar surgery and hence, it is difficult to comment on the pharmacological differences resulting in the early onset of flupirtine as compared to tramadol.

The faster action of flupirtine as compared to tramadol could be attributed to its dual therapeutic effect with both analgesic and muscle relaxant properties that has utility in the treatment of pain, including that associated with muscle tension.^[5]

In the present study, tramadol and flupirtine groups had a relatively longer analgesic effect as compared to ketorolac for the first dose of the drug. This might be attributed to a shorter half-life and smaller dose of ketorolac (10 mg) as compared to the other two drugs.

In the present study, 3 h postoperative pain scores were found to be significantly lower in the flupirtine group as compared to ketorolac whereas no significant difference between tramadol and ketorolac and tramadol and flupirtine was observed at this time interval. For evaluation up to 72 h, throughout no significant difference between tramadol and flupirtine group was observed except at 48 h when pain scores in tramadol group were significantly lower as compared to both flupirtine and ketorolac groups. Ketorolac showed significantly higher pain scores as compared to both flupirtine and tramadol at 6 h postoperative interval too. Thus, tramadol and flupirtine outperformed ketorolac at several occasions, whereas tramadol and flupirtine showed comparable results for most of the postoperative periods.

In all the three groups, between 3 and 6 h postoperative intervals an increase in mean pain scores was observed, however, in subsequent intervals with the passage of time a significant reduction in pain scores was observed in all the three groups.

Although statistically significant differences in pain scores of three groups were observed, however, clinically, pain

Table 7a: Intergroup comparison of postadministration of drug (after first reporting of pain) visual analog scale score at different time intervals (KruskalWallis H-test)

Duration/VAS	3 h	6 h	24 h	48 h	72 h
Group-1 (mean±SD)	3.30±0.46	4.50±0.68	2.10±0.30	2.0±00	1.58±1.11
Group-2 (mean±SD)	3.2±0.40	4.30±0.46	2.06±0.24	1.92±0.27	1.48±1.22
Group-3 (mean±SD)	3.10±0.30	4.20±0.40	2.10±0.30	2.0±0.0	1.42±1.18

VAS: Visual analog scale, SD: Standard deviation

scores were of mild-to-moderate category during first 6 h (scores 3-5) and thereafter in mild category (scores <3) at 24 and 48 h intervals. At 72 h, though some patients had pain scores as high as 5 and 6 yet in general most of the

patients had pain scores of mild order only. Mean pain scores were <2 at this time interval.

In general, all the three groups showed almost equivalent analgesic activity and control of pain clinically notwithstanding the statistically significant differences in pain scores.

However, as far as statistically significant differences in pain scores are concerned, in the present study, tramadol showed a better control as compared to ketorolac. In a study comparing the preemptive use of intravenous (IV) tramadol with IV ketorolac, Ong and Tan^[6] reported a better postoperative pain control in third molar surgery cases for cases receiving ketorolac.

Mishra *et al.* in their study comparing preoperative and postoperative use of oral dose of ketorolac (20 mg) with

Table 7b: Comparison between groups for postadministration of drug (after first reporting of pain) visual analog scale score at different time intervals (MannWhitney U-test)

	Group-I versus Group-II		Group-I versus Group-III		Group-II versus Group-III	
	Z	P	Z	P	Z	P
3 h postoperative	1.149	0.25	2.48	0.013	1.39	0.16
6 h postoperative	2.23	0.025	3.14	0.002	1.149	0.25
24 h postoperative	0.74	0.46	0.0	1.0	0.73	0.46
48 h postoperative	2.03	0.042	0.0	1.0	2.03	0.542
72 h postoperative	1.57	0.11	1.86	0.062	0.25	0.79

Table 8: Intragroup change in pain score from 3 h of postadministration of drug (after first reporting of pain) (Wilcoxon signed-rank test)

	Group I			Group II			Group III		
	Mean±SD	Z	P	Mean±SD	Z	P	Mean±SD	Z	P
6 h	1.200±0.990	5.421	<0.001	1.10±0.30	6.784	<0.001	1.10±0.30	6.784	<0.001
24 h	-1.200±0.404	6.583	<0.001	-1.14±0.50	6.364	<0.001	-1.00±0.14	7.071	<0.001
48 h	-1.300±0.463	6.450	<0.001	-1.28±0.45	6.472	<0.001	-1.10±0.30	6.784	<0.001
72 h	-1.720±1.126	5.730	<0.001	-1.72±1.29	5.476	<0.001	-1.69±1.25	5.329	<0.001

SD: Standard deviation

Table 9: Intergroup comparison of side effects at different doses

Side effects	Group I (n=50), n (%)	Group II (n=50), n (%)	Group III (n=50), n (%)	Statistical significance	
				χ^2	P
At 1 st dose					
No complication	46 (92.0)	43 (86.0)	46 (92.0)	12.433	0.257
Diarrhea	1 (2.0)	0	0		
Hypotension	0	1 (2.0)	0		
Nausea	2 (4.0)	0	2 (4.0)		
Sedation	0	3 (6.0)	2 (4.0)		
Sweating	1 (2.0)	3 (6.0)	0		
At 2 nd dose					
No complication	40 (80.0)	37 (74.0)	44 (88.0)	15.862	0.322
Diarrhea	2 (4.0)	0	1 (2.0)		
Hypotension	2 (4.0)	2 (4.0)	0		
Nausea	3 (6.0)	3 (6.0)	2 (4.0)		
Sedation	0	3 (6.0)	3 (6.0)		
Sedation+hypotension	0	1 (2.0)	0		
Sweating	2 (4.0)	4 (8.0)	0		
Sweating+nausea	1 (2.0)	0	0		
At 3 rd dose					
No complication	40 (80.0)	35 (70.0)	42 (84.0)	31.017	0.006
Constipation	0	1 (2.0)	0		
Diarrhea+hypotension	3 (6.0)	0	0		
Hypotension	0	4 (8.0)	0		
Nausea	4 (8.0)	1 (2.0)	4 (8.0)		
Sedation	0	5 (10.0)	3 (6.0)		
Sweating	3 (6.0)	1 (2.0)	1 (2.0)		
Sweating+nausea	0	3 (6.0)	0		

tramadol (50 mg) showed statistically no significant difference between two drugs for both preoperative and postoperative administration for control of postoperative pain up to 6 h postoperative interval. However, in the present study ketorolac (10 mg) at 6 h had significantly higher pain score as compared to tramadol (50 mg) at 6 h interval, thus indicating that the dosage of ketorolac (10 mg) used in the present study was not optimized and needs an increment in order to achieve a comparable pain control as for tramadol.

Similar to our study, where tramadol (50 mg) and flupirtine (100 mg) were found to be comparable for postoperative pain management at a similar regimen (postoperative, 5 days \times tds), Naser *et al.*^[7] a similar efficacy of two drugs throughout the period of evaluation. In another study, Moore *et al.*^[8] while comparing flutirpine (100 mg) against another opioid (dihydrocodeine 60 mg) through oral route found similar efficacy of two in postoperative pain attenuation.

The findings in the present study thus underline that the three drugs used for comparison of postoperative pain management had a similar profile, however, indicating the need of upgradation and optimization of ketorolac dosage to obtain a comparable performance. These findings are in accordance with the findings in the literature, as shown above, however, the onset of action and long-term efficacy of the drugs was dependent on the pharmacokinetics and pharmacodynamics using different pathways for pain control.

In the present study, for first and second doses, the side effect profile of the three drugs was similar and did not show a significant difference among groups, however, at third dose, rate of side effects was higher (30%) in the tramadol group as compared to ketorolac (20%) and flupirtine (16%) groups.

Tramadol is an opioid. Opioids are known to have a poor side effect profile and toxic effects on the central nervous system.^[9,10] Flutirpine and ketorolac reportedly have lower side effects owing to difference in mechanism and mode of action.^[5,7,11,12]

The findings in the present study, thus suggested that 100 mg flupirtine capsule has a similar analgesic profile as for tramadol (50 mg) but with fewer side effects it was the most suitable drug for postoperative pain control in cases undergoing third molar surgery. Although, ketorolac (10 mg) also showed fewer side effects as

compared to tramadol at the given dosage (10 mg), it was less effective in pain management as compared to the other two regimens.

Both flupirtine and ketorolac had a faster onset and better side effect profile as compared to tramadol. A few studies have reported depression to be a side effect of flupirtine,^[8,13] however, in the present study no such side effect was noted. Given the limited number of clinical trials evaluating and comparing the efficacy of three analgesic regimens as used in the present study, we would recommend more studies on the issue before making any recommendations for clinical practice.

CONCLUSION

The findings in the present study showed that flupirtine had a faster onset and comparable pain management profile as compared to tramadol and ketorolac, it also had minimum side effects, hence the use of flupirtine might be recommended for postoperative pain management in cases undergoing third molar surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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