

ORIGINAL ARTICLE

COMBINATION OF DICLOFENAC WITH PARACETAMOL OFFER BETTER PAIN RELIEF THAN IBUPROFEN ALONE IN IMPACTED THIRD MOLAR EXTRACTION: A RANDOMIZED CONTROLLED TRIAL

Hemant L Dhusia¹, Prasad D Bhang², Mahesh D Sonar³, Sanjaykumar H Maroo^{4*}, Ketan R Patel⁵, Rakesh U Ojha⁴

¹Department of Dental Surgery, Lokmanya Tilak Municipal Medical College Sion, Mumbai, Maharashtra

²Department of Dentistry, Seth G.S. Medical College & KEM Hospital, Parel, Mumbai, Maharashtra

³Department of Oral and Maxillofacial Surgery, M.G.M Dental College and Hospital, Kamothe, Navi Mumbai, Maharashtra

⁴Medical Services Department, Troikaa Pharmaceuticals Ltd., Ahmedabad, Gujarat

⁵Chairman and Managing director, Troikaa Pharmaceuticals Limited, Ahmedabad, Gujarat

ABSTRACT

BACKGROUND: Combination of non-steroidal anti-inflammatory drugs (NSAIDs) with paracetamol for management of acute postoperative pain is widely used in clinical practice, but therapeutic superiority of such combination over NSAID alone remains controversial. The aim of this study was to evaluate whether the combination of diclofenac 50mg and paracetamol 500mg (Dynapar tablet) twice daily regime offer superior analgesia than thrice daily regime of Ibuprofen 400mg tablet in management of dental pain following impacted third molar extraction. **MATERIALS AND METHODS:** 150 postoperative patients were randomized to receive either treatment for four days. Primary efficacy endpoints were time to onset of analgesia, time to maximum pain relief and pain relief at 8 hrs while secondary efficacy endpoints included improvement in pain intensity at 8 hours, pain relief scores at 24, 48 hours and on day 4, global assessment by patients and investigator; rescue analgesia requirement. **RESULTS AND DISCUSSION:** Dynapar tablet offers significantly better improvement in postoperative pain intensity (3.00 ± 2.29 versus 2.067 ± 2.12 , $P=0.0025$) and pain relief (2.58 ± 0.92 versus 2.06 ± 0.92 , $P < 0.0001$) than Ibuprofen at 8 hour. Pain relief at 24 ($P < 0.0001$), 48 hours ($P < 0.0001$) and on day 4 ($P = 0.0001$) in Dynapar group was significantly higher than Ibuprofen. Also, global assessment of investigators and patients were significantly more favourable towards Dynapar tablet. No statistically significant differences were found in other efficacy endpoints. **CONCLUSION:** Dynapar tablet offers superior analgesia compared to ibuprofen in management of acute postoperative pain following impacted third molar extraction

Keywords: Diclofenac, Paracetamol, Ibuprofen, acute postoperative pain, impacted third molar extraction

INTRODUCTION

Pain is a common complaint after tooth extraction.¹ Third molar tooth extraction is very efficient analgesic model allowing good discrimination between weak and strong analgesics² with very few confounding factor since participants are do not ordinarily suffer from complicating medical conditions and they have moderate to severe pain of relatively short duration (hours to days) and requiring analgesic therapy postoperatively.^{3,4}

An ideal analgesic should alleviate pain with no undesirable side effects.⁵ NSAIDs are widely available to relieve intense postoperative pain caused by third molar surgeries and effective in managing endodontic pain.^{6,7} Ibuprofen is one of the most frequently used NSAIDs for control of post operative pain associated with root canal treatment⁶ and also used extensively in the management of postoperative pain after dental surgical procedures,⁷ and has good efficacy and safety profile.⁶ It has also been reported that ibuprofen 400 mg significantly reduce pain intensity and offer better pain relief after third molar extraction.³ Diclofenac is also among the most extensively used NSAIDs⁶ and offer better pain relief in postoperative third molar surgery pain model.⁸ Cochrane review has found that paracetamol is also a safe, effective drug for the treatment of postoperative pain following the surgical removal of lower wisdom teeth⁹ and has rapid onset of analgesic action.² As the NSAIDs

*Corresponding Author

Dr. Sanjaykumar .H Maroo
Medical Services Department,
Troikaa Pharmaceuticals Ltd.,
Ahmedabad, Gujarat.
E-mail: medicalservices@troikaapharma.com

have effect mainly on peripheral tissues while paracetamol acts on peripheral tissues as well as on central nervous system.⁶ Combination of non-steroidal anti-inflammatory drugs (NSAIDs) with paracetamol for management of acute postoperative pain is widely used in clinical practice, but therapeutic superiority of such combination over NSAID alone remains controversial.¹⁰ The rationale underlying the practice of combining drugs in pain management is based on two considerations. First, combining drugs with different mechanisms may enhance the pain relief. Second, single drug that provide satisfactory pain relief may cause at the same time, unacceptable side effects. Drug combination allows reduction in the dose of single component to achieve the same analgesic effect with reduced incidences of side-effects.¹¹ Despite the above consideration, therapeutic superiority of a combination of paracetamol and NSAID combination over either drug alone remains controversial. Menhinick et al have shown that the combination of NSAIDs with paracetamol may be more effective than NSAID alone for the management of postoperative endodontic pain.¹² In addition, Meta analysis suggested that combination of paracetamol and NSAID may offer superior analgesia compared with either drug alone in various acute pain models.¹³ In contrast to the results of above studies, Raisian et al have reported that combination of NSAID with paracetamol and caffeine does not offer any clinical advantages compared with NSAID alone for alleviating acute postoperative pain after third molar surgeries.⁷ Further, Wells et al reported that there were no significant differences in analgesic efficacy between combinations of NSAID with paracetamol and NSAID alone in management of post operative endodontic pain.¹⁴ The efficacy and safety of diclofenac with paracetamol in comparison of Ibuprofen alone in management of dental pain following impacted third molar extraction has not been studied. Dynapar tablet is the fixed dose combination 50 mg and paracetamol 500 mg developed by Troikaa pharmaceutical ltd based synergistic effect associated with the combination of dual analgesics. As Dynapar tablet is formulated using a decompaction technology which facilitates faster disintegration of the tablet into microfine particles. We therefore proposed that the Dynapar tablet offer faster and assured good pain relief. The purpose of this study was to compare the safety and efficacy of Dynapar tablet with ibuprofen 400 mg in the management of dental pain following impacted third molar extraction. Ibuprofen was selected as a comparator because, it is considered as one of the most preferred NSAIDs in the management of dental pain.

MATERIALS AND METHODS

Patients of either sex aged 18-45 years, undergoing impacted third molar extraction under local anesthesia during April 2011 to February, 2012 were enrolled from three different hospitals in Mumbai, India. The study was registered at clinical trial registry-India (CTRI) before first patient enrollment (CTRI/2011/091/000169). The study was conducted according to the protocol approved by ethics committees of each participating study centre. The study was conducted in compliance with the ethical standards laid down in the Declaration of Helsinki, 1964 and its later amendments; Good Clinical Practice (GCP) guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India; Ethical guidelines for biomedical research on human participants, Indian Council of Medical Research (2006), New Delhi. All patients were explained the procedure clearly and written informed consent was obtained from each participant before their participation in the study. At the time of screening, medical history was obtained; physical examination and laboratory investigations were performed. Patients with known hypersensitivity or contraindications to diclofenac, ibuprofen, paracetamol or other NSAIDs and having the history of severe kidney or liver disease or peptic ulcers or gastrointestinal bleeding were excluded. The patients taking medicines like ACE inhibitors, diuretics and anticoagulant or anti-platelet drugs on daily basis were also excluded from the study. The women of child bearing age underwent the urine pregnancy test; the pregnant and lactating women were excluded in the present study. Total 150 patients were recruited in the study as per eligibility criteria. Enrolled subjects were equally divided into two groups as per computer generated simple randomization sheet. One group received fixed dose combination of Diclofenac 50mg and Paracetamol 500mg (Dynapar Tablet, manufactured by Troikaa Pharmaceuticals Ltd, Ahmedabad, India) orally twice daily and another group received Ibuprofen 400mg tablet (Brufen manufactured by Abott laboratories, Goa, India) orally three times daily for four days. Tooth extraction was carried out using routine procedure under local anesthesia. Both the study drugs were administered post-operatively when patient felt moderate to severe pain (Visual analogue scale 5 to 8) after recovery from the anesthesia. This was considered as baseline intensity of post operative pain. Following administration of first dose of both the study drugs, the time to onset of analgesia (in minutes) was assessed by the patients. The intensity of pain was assessed using a 10 point visual analogue scale (VAS; where 0 indicates no pain and 10 indicates

worst possible pain) at 30 minutes, 60 minutes, 2 hours, 4 hours, 6 hours, 8 hours; at 24 hrs (1st post extraction day), 48 hours (2nd post extraction day) and 96 hours (4th post extraction day). At the same time points, degree of pain relief was also assessed using a five- point categorical scale of 0- 4 (none-0; little-1; moderate-2; a lot-3; complete-4).¹⁵Patients stayed at the hospital for 4 hours after receiving the first dose, in order to complete the 4-hour assessment. Study medications along with rescue analgesics (paracetamol 500 mg orally to a maximum of 4 doses per day) and daily diary were dispensed to each patient as per the randomization sheet. Assessments of pain intensity and degree of pain relief at the time points from 6 hours to 48 hours were made by patients and were recorded in the daily diary. Patients were instructed to visit the investigator on the 4th post-extraction day for rest of the assessments. Details of rescue medication taken during the study period were recorded in the daily diary and CRF of respective patient. All the patients were encouraged to wait at least 1 hour before taking rescue medication after study drug administration. Each patient was observed for adverse events during study period and the same was also recorded in case record form (CRF). At the end of study period, global assessment of treatments based on efficacy and safety was assessed by investigators and patients. Primary efficacy endpoints were time to onset of analgesia, time to maximum pain relief and pain relief at 8 hrs while secondary efficacy endpoints included improvement in pain intensity at 8 hours, pain relief scores at 24, 48 hours and on day 4, global assessment by patients and investigator; rescue analgesia requirement. Sample size calculation was performed using software, PS Power and Sample Size Calculations Program, version no.3. Based on the study comparing efficacy and safety of diclofenac and aceclofenac in controlling post extraction dental pain^[16] a standard deviation (SD) of 1.64 was taken for post operative pain score as determined by visual analogue scale (VAS). To detect clinically significant difference of 1 on VAS score between two groups, the sample size was calculated at 95 % power and at 5% level of significance using two sided test. The desired number of patients in each group was 71. Considering a drop out rate of 5 %, 75 patients were required in each treatment group. Quantitative data are presented as mean \pm SD, whereas categorical data are expressed as absolute number/proportion of patients. Quantitative data of both the treatments groups were analyzed by unpaired "t" test or Mann Whitney test based on the distribution of data. Chi-square test or fisher exact test was used to compare the categorical data of

both the treatment groups. P value of less than 0.05 was considered as statistically significant difference between both the treatment groups. All statistical analyses were performed using software, GraphPad prism, version no.5.

RESULTS

Total 160 post operative patients were screened at three study centres. Among them 10 patient did not fulfill the eligibility criteria, hence 150 postoperative patients were enrolled. Out of 150, one patient was lost to follow up in Dynapar tablet group. The data obtained from 149 postoperative patients were subjected to statistical analysis. Demography and baseline characteristics (age, gender, height, weight and baseline intensity of postoperative pain) were comparable between both the treatment groups (Table 1). The mean time to onset of analgesia was less in Dynapar group (42.68 + 22.82 minutes) as compared to ibuprofen group (54.00 + 44.83 minutes). However, difference was not statistically significant between the treatment groups (P=0.0872, Mann Whitney test).

The mean time to maximum pain relief in the Dynapar group was 34.71hrs \pm 34.39 while in ibuprofen group it was 27.67 hrs \pm 33.63. There was no statistically significant difference in the mean time to maximum pain relief between the both the treatment groups (P = 0.0639, Mann Whitney test). However, the degree of pain relief was significantly higher in Dynapar group as compared to ibuprofen group at 1 hour, 2hour, 4 hour, 8 hour, 24 hour , 48 hour and on day 4 (Table 2). There was gradual reduction in intensity of post operative pain over a period of four days in both the treatment groups as observed from the reduction in the VAS scores from baseline. However, improvement in intensity of post operative pain from baseline was significantly higher in Dynapar group as compared to ibuprofen group at all the time points throughout the study period (Table 3). More number of patients in Ibuprofen group (18.66%) required rescue medication as compared to Dynapar group (8.1 %). However, there was no statistical significant difference between both the treatment groups (P = 0.0587, Fisher's exact test). Global assessment of treatment by patients and investigator significantly favored the Dynapar group as compared to ibuprofen group (Table 4). In ibuprofen group, one patient experienced gastritis whereas in Dynapar group, no case of any adverse event was reported. No cases of any unexpected and serious adverse events were observed and reported during study period in either of the treatment groups.

Table 1: Demography and baseline characteristics of the patients

Characteristic	Dynapar Group (N = 74)	Ibuprofen Group (N = 75)	P value
Age (Year)	30.81±06.75	30.87±06.20	0.955*
Gender (Male/Female)	32/42	37/38	0.0908**
Weight (Kg)	62.96±09.54	62.17 ± 10.85	0.638*
Height (cm)	157.53±09.10	156.04±11.94	0.394*
Intensity of post operative pain	05.31±01.70	05.67±01.78	0.211*

Values are expressed in Mean ± SD for age, weight and height; absolute number for gender; N = number of patients in treatment group. *Data were analyzed by unpaired 't' test; **Data were analyzed by Fisher's exact test.

Table 2: Degree of pain relief

Time points (hours)	Mean Score of Pain Relief		P value
	Dynapar Group (N = 74)	Ibuprofen group (N = 75)	
0.5	1.284 ± 0.9725	1.027± 0.9149	0.0743
1	1.527 ± 0.8476	1.280± 0.8473	0.0472
2	1.757 ± 0.8571	1.467± 0.9492	0.0169
4	1.946 ± 0.9347	1.560 ± 0.9040	0.0082
6	2.095 ± 1.049	1.81 ± 0.9543	0.0652
8	2.581 ± 0.9217	2.067+ 0.9202	< 0.0001
24	2.986 ± 0.8192	2.347± 1.072	< 0.0001
48	3.189 ± 0.7706	2.493± 1.095	< 0.0001
96	3.365 ± 0.8205	2.60 ± 1.315	0.0001

Values are expressed in Mean ± SD; N = Number of subject in treatment group. Data were analyzed by Mann Whitney test..

Table 3: Improvement in intensity of post operative pain

Time points (hours)	Difference in mean VAS score from baseline		P value
	Dynapar Group (N = 74)	Ibuprofen group (N = 75)	
0.5	0.0872 ± 1.52	0.2533 ± 1.637	0.0448

1	1.162 ± 1.672	0.5467 ± 1.727	0.0220
2	1.797 ± 1.930	0.7067 ± 2.032	0.0016
4	2.095 ± 2.075	0.8400 ± 2.314	0.0003
6	2.243 ± 2.42	1.213 ± 2.361	0.0059
8	03.00 ± 02.29	2.067 ± 2.120	0.0025
24	03.932 ± 02.056	2.733 ± 2.101	< 0.0001
48	4.459 ± 1.988	3.680 ± 2.138	0.0014
96	4.811 ± 1.826	4.360 ± 1.936	0.0133

Values are expressed in Mean ± SD; N = Number of subject in treatment group. Data were analyzed by Mann Whitney test..

Table 4: Global Assessment by patients and investigators

Global Assessment	Patient's global assessment		Investigator's global assessment	
	Dynapar Group (N = 74)	Ibuprofen group (N = 75)	Dynapar Group (N = 74)	Ibuprofen group (N = 75)
Excellent	41	07	44	09
Good	23	23	19	24
Fair	10	36	11	31
Poor	0	09	0	11
P value	< 0.0001		< 0.0001	

N = Number of subjects in treatment group. Numerical represent number of subjects for particular assessment. Data were analyzed by Chi square test

DISCUSSION

In our study, both the study drugs were effective in management of dental pain following impacted third molar tooth extraction. However, fixed dose combination of diclofenac and paracetamol was more effective in relieving the postoperative dental pain as compared to Ibuprofen monotherapy. Dynapar tablet showed faster onset of analgesia compared to ibuprofen, although the difference was not statistically significant, mostly due to larger variation in each group. Faster onset of analgesia with Dynapar tablet may be attributed to its faster disintegration into microfine granules. On the contrary to the time to onset of analgesia; time for maximum pain relief was less with ibuprofen compared to Dynapar tablet. The difference was not

statistically different due to larger variance in each group. However, degree of pain relief obtained was significantly higher with Dynapar tablet throughout the study period after 1 hour. The improvement in post operative pain intensity was also significantly better with Dynapar tablet. This observation shows that maximum pain relief with ibuprofen is faster but significantly lower compared to Dynapar tablet. It is known that combination of two drugs with differing modes of action results in an additive or synergistic analgesic effect.¹⁷ The analgesic effect of NSAIDs is primarily due to the inhibition of prostaglandin biosynthesis through inhibition of cyclooxygenase enzymes: COX-1 and COX-2. On the other hand, the mechanism of action of paracetamol includes inhibition of COX-3 in central nervous system, interaction with spinal 5-HT₃ receptors and peripheral β -endorphin receptors.^{18, 19} Differences in the mechanism of action of paracetamol and NSAIDs make them a viable option for an effective combination. Animal studies have shown possibility of synergism between paracetamol and NSAIDs.^{20,21} These observations support the higher analgesia and better pain relief observed in our as well as several other published studies.^{22,23,24,25} However, studies showing contrary results have also been published.^{26,27} The difference in the results can be due to difference in study design, patient population and baseline pain intensity.^[28] Moderately severe baseline pain is required to show to achieve adequate sensitivity because it may not be possible to detect any difference if there is little or no pain.²⁹ Global assessment of the treatment by investigator and patients was more favorable towards Dynapar tablet.

CONCLUSION

Fixed dose combination of diclofenac and paracetamol (Dynapar tablet) offer superior analgesia compared to ibuprofen in the management of acute postoperative pain following impacted third molar extraction.

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