ORIGINAL RESEARCH PAPER

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PAIN CONTROL EFFICACY OF IBUPROFEN IN THERAPEUTIC PREMOLAR EXTRACTION: PRE-TREATMENT VS POST TREATMENT ADMINISTRATION-A RANDOMISED COMPARATIVE STUDY.

KEY WORDS: Preemptive analgesia; Ibuprofen; pre-extraction; post-extraction; therapeutic extraction; pain

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ABSTRACT

Background: - The concept of pre-emptive analgesia is often underused for the management of postoperative pain following dental extraction and often, post-operative analgesics is what is put into routine use.

Aim: - The purpose of this study is to compare the analgesic and anti-inflammatory effects of preoperative (1 h before surgery) and postoperative (1 hour after completing the surgical procedure) administration of ibuprofen in the therapeutic extraction of premolars.

Objectives: - Assessment of pain using the VAS in "pre-extraction ibuprofen" & "post-extraction ibuprofen" study groups at the 2 hour and 6 hour postoperative period.

Materials and methods: - Of the samples selected (n=101) , all samples were allotted to both the study groups one side at a time.

Results: The group which received pre-treatment ibuprofen reported lower VAS scores during the first 2- hour post-operative period.

The comparison at 6 hours across the groups revealed that the pain scores were on the lesser side in the pre-emptive analgesic group than in the post op group

The results of the present study have shown that pre-treatment with ibuprofen significantly decreased post-operative pain ($P<0.005$)

Conclusion: The pre-emptive analgesic efficacy of ibuprofen at 2 hours post extraction showed less VAS scores compared to those at 2 hours and 6 hours post extraction administered ibuprofen

INTRODUCTION

According to International Association of the Study of Pain (IASP)[1],Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Management of pain, in dentistry, is a real challenge and an unmet need, specially as pre-emptive analgesia. The key role of analgesics in pain management relies on the knowledge and the potential of the drug being administered to control pain of the host. Many a times, clinicians feel that they fail to appropriately manage complex pain conditions or are inadequately trained in judicious use of opioid analgesics. In dental extraction procedures, pain and its severity experienced by the patient may vary individually[2].

Pre or post-operative pain reduces on administration of oral medication and thus improves the clinical outcome, making it an integral part of surgical practice. Pre-operative preparation of patient should include adjustments of preoperative medications to avoid withdrawals effect, treatment to reduce preoperative pain/anxiety, and preoperative initiation of treatment as part of a multimodal pain management plan.[3]

The idea of pre-emptive analgesia to reduce the duration and severity of post-operative pain was first introduced by Woolf[4]. PRE-EMPTIVE analgesia is an anti-nociceptive treatment that prevents establishment of altered processing of afferent input, which amplifies postoperative pain[5]. Inflammation triggers body's protective mechanisms in response to injury. In tissue injury, the release of cyclooxygenase-2 in turn induces the activity of prostaglandin which sensitizes peripheral nociceptors. It has been proposed that the administration of non-steroidal anti- inflammatory drugs (NSAIDs) before to surgery may be more effective when compared with postoperative administration.

OBJECTIVE:

The impetus of this study is to compare the analgesic and anti-inflammatory effects of preoperative (1 hour before surgery) and postoperative (1 hour after completing the surgical procedure) administration of ibuprofen in therapeutic extraction of premolars.

MATERIALS & METHOD

This Randomised Case-Control study was conducted on 101 patients of both gender ranging between 12-30 years selected from the outpatient clinic of the Department of Oral & Maxillofacial Surgery, PMS College of Dental Science & Research indicated for bilateral premolar orthodontic extraction.The PMS Dental College Ethical Committee reviewed the study and the IRB number granted was PMS/IEC/2017/10[ER]. Teeth with any carious or periapical lesion, cases that need mucoperiosteal flap elevation requiring open technique, medically compromised patients, smokers and patients with any history of allergy to ibuprofen or other NSAIDs, lactose intolerance, gastrointestinal pathology were excluded from the study. A randomized controlled study in which the same patients were categorized into two groups. The group of patients undergoing orthodontic extraction on one side of the arch were put on pre-operative oral ibuprofen 10 mg per kg dose 1 hour before

procedure and the same group of patients while undergoing orthodontic extraction on the other side of the arch were put on post-operative oral ibuprofen 10 mg per kg dose 1 hour after procedure.

A written informed consent was obtained from each patient before the surgical procedure. During their first appointment ibuprofen 10mg/kg body weight was given one hour before the procedure. Then local anesthesia (2% lignocaine hydrochloride plus adrenaline, 1:200,000)- buccal and palatal infiltration and inferior alveolar nerve block was used to anesthetize the extraction site for maxillary and mandibular premolars respectively. After achieving aesthesia forceps extraction was carried out without flap elevation. The post extraction instructions were given. The postoperative pain evaluation done after 2 hours and 6 hours was recorded using visual analogue scale.(Figure 2,3)

During the next appointment for the extraction on the other side, the same intra-alveolar extraction procedures described above was done except that ibuprofen10mg/kg body weight was given 1 hour after the procedure. Postoperative pain evaluation was done 2 hours and 6 hours postoperatively using visual analogue scale.In Visual Analogue Scale (Figure 1) calibrated from 0-10, patient marked a line depending upon the severity of pain.

STATISTICAL ANALYSIS:

Same patient for bilateral premolar extraction indicated for orthodontic tooth movement,where selected and divided into two groups in extracting from each side respectively.Thus the bias and matching was addressed and handled.

Statistical analysis was performed by using Medcalc Software for Windows version 13.1. Intergroup and intragroup comparison of VAS scores were done by ANOVA(Table 5). Level of significance was assessed by using Tukey - Kramer test(Table 6) with $p < 0.5$.

RESULTS:

Among the 101 samples, none of them reported any side effects after taking the medicine. There were no drop-out in the cases,all reported for follow up and scoring.Overall,60 females and 41 males participated in this study. The VAS scores for the premedicated and post medicated groups are depicted in Figure 2 and Figure 3 respectively.

Table 1 shows the values amongst the 1hour PRE-OPERATIVLEY Ibuprofen administered extraction event assessed at 2 hours. As depicted in graph No1 (Figure 2), out of the 101 samples, 69 had a VAS score of 0, 10 had a VAS score of 1, 17 had a VAS score of 2 and 5 had a VAS score of 4. For the 101 samples belonging to the study Population (M =41 ; F=60) the Values Ranged from 0 to 4 the mean was 0.633±1.70SD with the confidence interval for mean set 95%, median value was observed as 0 with the confidence interval for median set as 95%. The Relative Standard deviation of 1.7103 denotes a scattering of the observed values to either extremes of the mean value & the variance of 1.1745 observed in this data set denotes the average variation of each of the values from the mean. The standard error of mean in this data set was computed to be 0.1078 and the magnitude indicates a less chance of error when the sample is compared to the true population. The coefficient of kurtosis 2.3939 indicates that the curve is platykurtic (Flat curve) when a chart showing the dispersion is made

Table 2 shows the values amongst the PRE-OPERATIVLEY Ibuprofen administered extraction event assessed at 6 hours. As depicted in graph No1 (Figure 2), out of the 101 samples, 26 had a VAS score of 0, 63 had a VAS score of 2, 9 had a VAS score of 4 and 3 had a VAS score of 6. For the 101 samples belonging to the study Population (M =41 ; F=60) the Values Ranged from 0 to 6 the mean was 1.7822±1.35SD with the confidence interval for mean set 95%, median value was observed as 2 with the confidence interval for median set as 95%. The Relative Standard deviation of 0.7595 denotes a 75.95% scattering of the observed values to either extremes of the mean value & the variance of 1.8321 observed in this data set denotes the average variation of each of the values from the mean. The standard error of mean in this data set was computed to be 0.1347 and the magnitude indicates a less chance of error when the sample is compared to the true population. The coefficient of kurtosis 1.4305 indicates that the curve is platykurtic (Flat curve) when a chart showing the dispersion is made

Table 3 shows the values amongst the POST-OPERATIVLEY Ibuprofen administered extraction event assessed at 2 hours.As depicted in graph No2(Figure 3), out of the 101 samples,5 had a VAS score of 0, 13 had a VAS score of 2, 67 had a VAS score of 4, 9 had a VAS score of 6 and 7 had a VAS score of 8. For the 101 samples belonging to the study Population (M =41 ; F=60) the Values Ranged from 0 to 8 the mean was 4.000±1.67SD with the confidence interval for mean set 95%, median value was observed as 4 with the confidence interval for median set as 95%. The Relative Standard deviation of 0.4183 denotes a 41.83% scattering of the observed values to either extremes of the mean value & the variance of 2.8000 observed in this data set denotes the average variation of each of the values from the mean. The standard error of mean in this data set was computed to be 0.1665 and the magnitude indicates a less chance of error when the sample is compared to the true population. The coefficient of kurtosis 1.5453 indicates that the curve is platykurtic (Flat curve) when a chart showing the dispersion is made5

Table 4 shows the values amongst the POST-OPERATIVLEY Ibuprofen administered extraction event assessed at 6 hours. As depicted in graph No2(Figure 3), out of the 101 samples,6 had a VAS score of 0, 66 had a VAS score of 2, 4 had a VAS score of 3, 25 had a VAS score of 4.For the 101 samples belonging to the study Population (M =41 ; F=60) the Values Ranged from 0 to 4 the mean was 2.4158±1.0514SD with the confidence interval for mean set 95%, median value was observed as 2 with the confidence interval for median set as 95%. The Relative Standard deviation of 0.4352 denotes a 43.52% scattering of the observed values to either extremes of the mean value & the variance of 1.1503 observed in this data set denotes the average variation of each of the values from the mean. The standard error of mean in this data set was computed to be 0.1046 and the magnitude indicates a less chance of error when the sample is compared to the true population. The coefficient of kurtosis 0.07359 indicates that the curve is platykurtic (Flat curve) when a chart showing the dispersion is made

Table (1) shows comparatively less pain response (Mean and S.D = 0.6337±1.70) among pre- operatively Ibuprofen administered extraction event than the pain response (Mean and S.D = 4.00±1.67) among the post-operatively Ibuprofen administered extraction event at 2 hours. Similarly, pain response(Mean and S.D = 1.78±1.35) among pre-operatively Ibuprofen administered extraction event(Table 2) was found to be less than the pain response(Mean and S.D = 2.4158± 1.05) among post-operatively Ibuprofen administered extraction event at 6hours.

The study interventions had a significant effect on pain sensation compared between the groups (Table 5) as shown by the ANOVA analysis ($F = 115.231$; $P < 0.001$; between-group Factor).The VAS scores for the premedicated and post-medicated groups are depicted in Figure 2 and Figure 3 respectively.

DISCUSSION

The postoperative pain is a complication or rather a response to the tissue insult whether it is minor oral surgery or

otherwise. After an extraction procedure, prolonged pain stimuli cause suffering and may have a negative effect on patient recovery. It is necessary to assess the characteristics and intensity of pain so as to decide the type of analgesic intervention. A randomised control study focuses on the effect of pre or post extraction analgesic, Ibuprofen. The results of this study have shown that pre-treatment with ibuprofen significantly decreased post- operative pain. Of the 101 samples,69 patients recorded VAS scores as low as 0 or NIL 2 hours after extraction, on being administered Ibuprofen 1 hr before procedure. Similarly, 63 patients reported VAS scores as low as 2, 6 hours after procedure (Figure 2).

Many pharmacological strategies have been developed to prevent peripheral and central sensitization pathways, thereby attenuating or even preventing the amplification of pain sensations postoperatively. Activation of the arachidonic acid pathway leads to the production of prostanoids and leukotrienes. Immune cells further release mediators including cytokines and growth factors and lead to spontaneous pain.[6,7] Non– steroidal anti– inflammatory drugs (NSAIDs) inhibit COX enzymes and thereby reduce the formation of prostaglandins. Ibuprofen is a non-selective inhibitor of an enzyme called cyclooxygenase (COX), which is required for the synthesis of prostaglandins via the arachidonic acid pathway. This PGH2 is then converted to prostaglandins[6].The inhibition of COX by ibuprofen pre-operatively, lowers the level of prostaglandins made by the body and thus pain in such patients can be less compared to those given ibuprofen post operatively. Preventing the initial neural cascade could lead to long-term benefits by eliminating the hypersensitivity produced by noxious stimuli.[8]A release of prostaglandins on stimulus during any procedure and the related fall of events can be avoided in pre-emptive analgesia. In treatment of moderate pain, Ibuprofen and paracetamol are among the most commonly used analgesic compounds .According to Shafie L et al, the results of a multicenter and double blind study in patients with postoperative dental pain showed that 400 mg ibuprofen provided superior analgesia over 1000 mg paracetamol both clinically and statistically significant.[9] Therefore, in this study ibuprofen was used as the premedication analgesic.

The results of our study demonstrates a dominant suppression of the sensory and affective pain, as well as of the final pain with the pre-emptive administration of Ibuprofen. This was particularly pronounced during the first 2 hours of the early postoperative period (Figure 2). In the first group given pre-emptive analgesic and assessed 2 hours later,69 had a VAS score of 0, whereas in the post op group only 5 samples had 0 score and 67 were score 4 .. In the post-operative group, when observed at 2 hours, the values are higher than the values of the pre-operative group at 2hours. The comparison at the end of 6hours across the groups revealed that out of the 101 samples in the pre group 26 had score 0 and 63 score 2, whereas in the post group only 6 had score 0 ,and 25 had a VAS score of 4. This shows that the pain scores were on the lesser side in the pre-emptive analgesic 6hour group than the group given drug post op and evaluated at 6hours. In the pre-operative analgesic group, there was an increase in the VAS scores to score 6 in 3 patients, when observed at 6 hours. However, all 3 patients had a acceptable score of 2 after 2hours, post extraction. This could be attributed to the fact that, by the end of 6 hours post operatively, the Peak Plasma Concentration (attained in 1 to 2 hours) of the drug had already worn off(elimination half-life being 1.8 to 2 hours)[10]and the time elapsed after drug administration has been 7 hours. A dose repeated at a 6 hour interval after the log dose of the drug could possibly solve this issue. Pre-emptive analgesia starts before incision and covers both the period of the operation and the initial postoperative period [5]. Pre-emptive analgesia aims to result in lower analgesic consumption by preventing or minimizing any "memory" of pain in the central nervous system.

A randomized, triple-blind, placebo-controlled clinical trial by L. Aznar-Arasa et al[11] showed that peak pain occurred at 6 h post-operativley, with a higher value for the control group ($p > 0.05$). Three of our cases in this study, showed pain above the average value after 6hours of extraction in group 1, which may be attributed to the onset of analgesia prior to procedure. Administration of Ibuprofen 1 hour before procedure and prolonged duration of successful[7] atraumatic extraction may lead to the action of analgesia to be further reduced when noted at 6 hours post extraction.

These outcomes are similar to observations on NSAID pre-emptive analgesia in other surgical procedures in the oral cavity. VOGEL et al. compared the efficacy of medicating with ibuprofen immediately prior to procedure to medicating immediately after procedure on postoperative pain associated with periodontal surgery.[12] They found that administration of ibuprofen immediately before or immediately after periodontal surgery to a significant extent delays the onset of pain compared to those given placebo, with postsurgical dosing demonstrating a significantly greater delay onset of pain compared to presurgical dosing of the drug . As our study were on extraction of teeth which involved more trauma to the bone and hence more inflammatory reaction to the body than a soft tissue procedure, the pre surgical medication demonstrated better pain control than post-operative dosing of the drug. Dermot Kelly et al[13] stated that the most important conditions for establishment of effective pre-emptive analgesia were the establishment of an adequately effective level of antinociception prior to the tissue insult, and the continuation of this effective analgesic level well into the post-traumatic period to prevent central sensitization during the inflammatory phase.

Multi modal therapy is more effective than single agent therapy which may attenuate central nocioceptive processing and the former may be associated with fewer side effects than a single agent high-dose therapy[13].

Although single-agent therapy may attenuate the central nociceptive processing, multi- modal therapy is more effective, and may be associated with fewer side effects compared with the high- dose, single-agent therapy[13].

Another meta analysis conclusively proved that the effects of pre-emptive NSAID administration on the intensity of postoperative pain did not attain levels of adequate statistical significance to yield a positive conclusion A more recent meta-analysis claimed that the effects of pre-emptive NSAIDs administration on postoperative pain intensity did not reach levels of statistical significance sufficient to draw a positive conclusion.Nevertheless, a trend towards lower postoperative pain scores and reduced need of supplemental analgesic consumption was noted [8]

CONCLUSION

Pre-emptive analgesia although not a new concept, but dates back to the early twentieth century. It involves delivery of analgesic therapy that precedes, adequately blocks, and out lasts the nociceptive stimuli that accompanies the tissue injury. This is aimed to prevent the peripheral and central sensitization that occurs in response to a painful stimuli while leaving physiological pain responses unchanged. Such an effect reduces primary and secondary hyperalgesia, allodynia and the receptive field changes of dorsal horn cells.

In conclusion, this study has shown that pre-medication with ibuprofen significantly reduced the VAS score during the first 2hrs and 6 hours following extraction of premolars for orthodontic purposes.

CONFLICT OF INTEREST:

There are no conflicts of interests.

ETHICAL APPROVAL :
The study was approved by the Ethics Committee (EIC) of the PMS college of Dental Science and Research

SOURCE OF FUNDING:
No funding

Table 1: Statistics of VAS scores at 2hours in ibuprofen administered pre-operatiely

Sample size	101
Lowest value	0.0000
Highest value	4.0000
Arithmetic mean	0.6337
95% CI for the mean	0.4197 to 0.8476
Median	0.0000
95% CI for the median	0.0000 to 0.0000
Variance	1.1745
Standard deviation	1.0837
Relative standard deviation	1.7103 (171.03%)
Standard error of the mean	0.1078
Coefficient of Kurtosis	2.3939 (P=0.0026)

Table 2: Statistics of VAS scores at 6hours in ibuprofen administered pre-operatiely

Sample size	101
Lowest value	0.0000
Highest value	6.0000
Arithmetic mean	1.7822
95% CI for the mean	1.5150 to 2.0494
Median	2.0000
95% CI for the median	2.0000 to 2.0000
Variance	1.8321
Standard deviation	1.3535
Relative standard deviation	0.7595 (75.95%)
Standard error of the mean	0.1347
Coefficient of Kurtosis	1.4305 (P=0.0251)

Table 3: Statistics of VAS scores at 2hours in ibuprofen administered post-operatiely

Sample size	101
Lowest value	0.0000
Highest value	8.0000
Arithmetic mean	4.0000
95% CI for the mean	3.6697 to 4.3303
Median	4.0000
95% CI for the median	4.0000 to 4.0000
Variance	2.8000
Standard deviation	1.6733
Relative standard deviation	0.4183 (41.83%)
Standard error of the mean	0.1665
Coefficient of Kurtosis	1.5453 (P=0.0189)

Table 4: Statistics of VAS scores at 6hours in ibuprofen administered post-operatiely

Sample size	101
Lowest value	0.0000
Highest value	4.0000
Arithmetic mean	2.4158
95% CI for the mean	2.2083 to 2.6234
Median	2.0000
95% CI for the median	2.0000 to 2.0000
Variance	1.1053
Standard deviation	1.0514
Relative standard deviation	0.4352 (43.52%)
Standard error of the mean	0.1046
Coefficient of Kurtosis	0.07359 (P=0.7304)

Table 5:ANOVA

Source of variation	Sum of Squares	DF	Mean Square
Between groups (influence factor)	597.3465	3	199.1155
Within groups (other fluctuations)	691.1881	400	1.7280
Total	1288.5347	403	
F-ratio	115.231		
Significance level	P < 0.001		

Table 6:Tukey-Kramer test for all pairwise comparisons

Factor	n	Mean	SD	Different (P<0.001[a]) from factor nr
(1) POST_VAS_2_HRS	101	4.0000	1.6733	(2)(3)(4)
(2) POST_VAS_6_HRS	101	2.4158	1.0514	(1)(3)
(3) PRE_EMP_VAS_2_HRS	101	0.6337	1.0837	(1)(2)(4)
(4) PRE_EMP_VAS_6_HRS	101	1.7822	1.3535	(1)(3)

Figure 1:Visual Analog Scale (vas)score

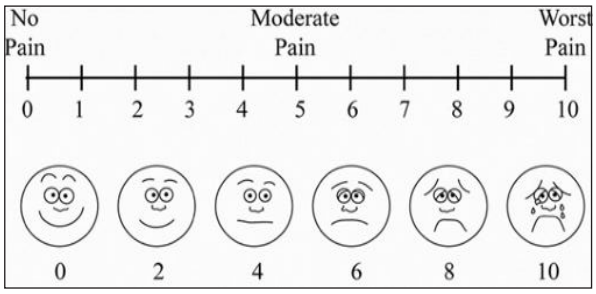


Figure2: Distribution of VAS scores in the Group given Ibuprofen 1 hr prior to procedure at 2hours and 6 hours post extraction

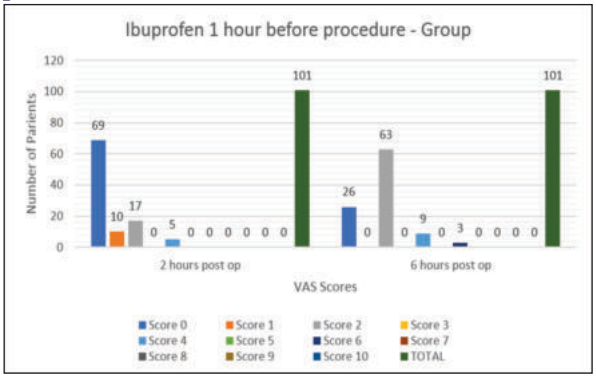
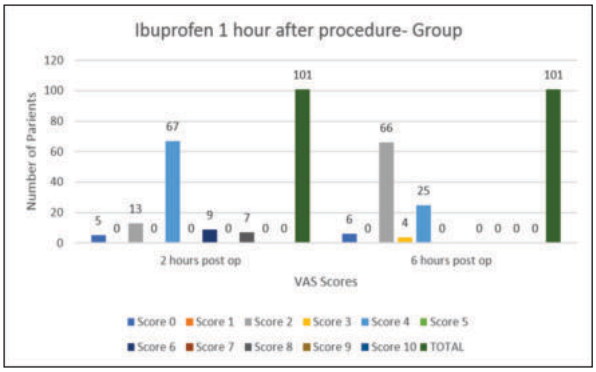


Figure 3: Distribution of VAS scores in group given Ibuprofen one after procedure,at 2 hours and 6 hours post extraction



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