Comparison of Pre-Emptive Analgesic Effect of Paracetamol, Ibuprofen, and Placebo in Reducing Post-Operative Pain in Intra-Alveolar Tooth Extraction at the University of Benin Teaching Hospital, Benin City. A randomized Trial

*Okoh M, **Owolabi JO, ***Egbor PE
Correspondence: Okoh M,
Email: mercy.okoh@uniben.edu

*Department of Oral and Maxillofacial Pathology and Medicine, University of Benin, Benin City
**Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City
***Department of Oral and maxillofacial Surgery, University of Benin, Benin City

Key words: Intra-alveolar extraction, Pain, Paracetamol, Ibuprofen, Placebo

ABSTRACT

Objective: Pain is one of the most common postoperative complications of extraction. Thus, this study is aimed at determining the effectiveness of pre-emptive paracetamol and ibuprofen in the management of post extraction pain.

Materials and Methods: A randomized, placebo-controlled, single-blinded comparative study of patients who needed intra-alveolar extraction of posterior teeth. Sixty-nine patients aged 18 years and above were randomly assigned to one of three groups: (A) paracetamol 1g; (B) ibuprofen 400mg; and (C) (calcium lactate) 300mg. Each of the three tablets was given 30 minutes before administration of the local anesthetic agent. The pain level was assessed using the visual analogue scale®. Chi-square (X^2) test, one-way analysis of variance (ANOVA) with an appropriate post-hoc test was used. Level of significance was set at 95% (p-value < 0.05).

Results: Ibuprofen and paracetamol groups showed lower pain scores compared to placebo. Although, there was no significant difference between the VAS scores at the post-operative period (P= 0.080). There was a significant difference in time taken for use of rescue medication among the three groups (p = 0.022), with those in placebo group 8 times more likely to use rescue medication relative to the analgesics.

Conclusion: The use of preemptive analgesics showed lower pain scores compared to placebo, and significantly increased the time for use of rescue medication postoperatively.

INTRODUCTION

Pain is one of the most common postoperative complications of extraction and can be caused by the release of pain mediators, mainly prostaglandins and others such as bradykinin, adenosine triphosphate[1], from the injured tissues, which could discourage patients from seeking dental treatment.[2-6] In particular, postoperative pain increases the patient's suffering and anxiety, and can disrupt the homeostatis of the circulatory and endocrine systems. Since it has been reported that postoperative pain can have a negative influence on wound healing, reliable and fast-onset analgesia is needed.[7,8]

Pre-emptive analgesic intervention is aimed at attenuating or entirely blocking both peripheral and central pain sensitization, leading to reduced pain in the postoperative period.[9,10]Post extraction pain could be a

problem for the patients during the first few hours after tooth extraction because of both soft and hard tissue trauma during the operation, despite the use of local anesthesia.[9,11] Thus, some studies[1,5] have shown that pre-emptive analgesia, due to the analgesic drug before nociception, would be more effective than the same intervention if commenced afterwards. This advantageous effect would outlast the pharmacological duration of action of the analgesic concerned.

Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are common analgesics used post-operatively as pain relief for tooth extraction.[1,12-14] Although, a few studies[1,15-17]have evaluated the postoperative action of ibuprofen and paracetamol alone or in comparison with other types of drugs when used pre-emptively, these studies were done on primary tooth extraction. Thus, this study is designed to determine the pre-emptive effectiveness of paracetamol and ibuprofen in the management of post extraction pain. It is also intended to be used to establish a protocol in the study location for the use of these drugs pre-emptively in a bid to appropriately manage post extraction pain in permanent tooth extraction.

MATERIALS AND METHODS

Study Design: This study conforms to guidelines from the Consolidated Standards of Reporting Trials (CONSORT Statement).[18] This was a single blinded, parallel, placebo-controlled, randomized clinical trial. The allocation ratio used was 1:1. Informed consent was obtained from the study participants, and approval was obtained from the Research and Ethics Committee of the University of Benin Teaching Hospital (UBTH)with protocol number (ADM/E 22/A/VOL.VII/14831023). This study was conducted in compliance with international statutes and national legislation on ethics in research involving human subjects. The present trial was retrospectively registered in February 2023, under the Pan African Clinical Trial Registry, with the registration number PACTR202302774048699.

The study was conducted at the Department of Oral and Maxillofacial Surgery, UBTH, Benin City, Edo state, from August 2021 to July 2022, on patients undergoing intra-alveolar extraction, who met the inclusion criteria of minimum age of 18 years, with indications for tooth extraction of non-mobile posterior teeth notably the molars, and could read and understand the pain score sheet. Patients allergic to NASIDs, paracetamol, or local anaesthetic agents with history of gastrointestinal disorders, active asthma, hemorrhagic disorder, kidney stones and pregnant/nursing mothers were excluded.Out of the 75-sample size estimated based on the formula for a comparison study of equal sample sizes with a continuous measurement endpoint,[19] only 69took part, with23 subjects per group, namely paracetamol group (A), Ibuprofen group (B) and placebo group (C).

Assessments: The patients' demographic details were recorded, and each diagnosis made after careful history with relevant investigations. Pain assessment was done using the visual analogue scale (VAS). The VAS consists of an interval scale ranging from 0, representing no pain to 10cm, representing maximum possible pain experienced by the concerned individual. Clinical assessments were done using the VAS at one hour, two hours, and six hours after extraction. The drugs administered (1000mg paracetamol, 400mg ibuprofen, and 300mg calcium lactate tablet as placebo) were enclosed in white dispensing sachet with the codes (A, B, and C). Consecutive patientswho fulfilled the inclusion criteria were, through simple randomization according to the CONSORT flow-diagram (fig 1),selected into the three groups: (i) Group A: Paracetamol 1000mg (Panadol®, Glaxo Smith Kline (GSK) Pharmaceutical Company); (ii) Group B: Ibuprofen 400 mg (Brustan-N®, Ranbaxy Pharmacy); and (iii) Group C: Calcium lactate: 300mg (Meyer Organics Pvt limited). The VAS form was explained, pre-emptive drug administered 30 minutes before the extraction, and local anaesthesia(LA) injection given 10 minutes before extraction.

The intra-alveolar technique or forceps' extraction method was used in tooth extraction 10 minutes after the administration of 1.8ml of 2% lignocaine hydrochloride with 1:80,000 adrenaline as reported in previous studies[7,20]. Thereafter, the patient was given a form that contained the VAS to evaluate the post-extraction pain

afterone, two, and six hours. All the participants in this study were observed for the 1st hour in the hospital and the VAS recorded, and then given the VAS form to evaluate the post-extraction pain experienced aftertwo and six hours while at home. Patients were monitored via phone calls to remind them to fill the forms and ensure adherence to instructions given to them. The patients were given 1000mg of paracetamol as an 'escape analgesic' which they were instructed to take should the pain become unbearable, and the time noted on the form (this represents the duration of analgesia of the administered drugs). Also, each patient was instructed to note down on the form any side effects from the medication taken. Chi-square (X^2) test, a one-way analysis of variance (ANOVA) with an appropriate post-hoc test was used. Level of significance was set at 95% (p-value < 0.05).

RESULTS

Overall, 75 participants were enrolled for this study and evaluated for eligibility criteria, and 69 were recruited and included in the analyses (Figure 1) with 23 in each group.

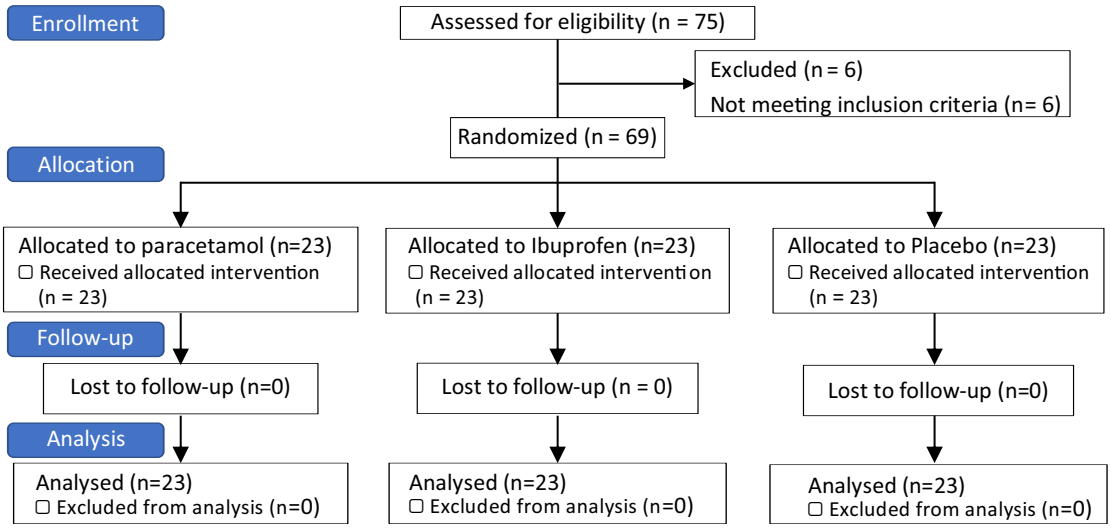

Figure 1: Flowchart adapted from CONSORT

Table 1 showed the demographic characteristics of the participants characterized by groups A, B, and C. The average age of the participants in groups A (Paracetamol), B (Ibuprofen), and C (Placebo) was 40.3 ± 17.8 years, 37.6 ± 16.9, and 40.7 ± 15.8 years respectively.

Characteristic	Paracetamol (A)(n= 23)	Ibuprofen (B)(n= 23)	Placebo (C)(n=23)	p-value
Age (years)				0.794
Mean (**S.D**)	40.3 (17.8)	37.6 (16.9)	40.7 (15.8)	
Range	18.0, 78.0	19.0, 75.0	18.0, 69.0	
Gender				0.840
Male	11 (47.83%)	12 (52.17%)	13 (56.52%)	
Female	12 (52.17%)	11 (47.83%)	10 (43.48%)	
Occupation				0.681
Business	1 (4.35%)	3 (13.04%)	6 (26.08%)	
Civil servant	7 (30.43%)	5 (21.74%)	5 (21.74%)	
Student	7 (30.43%)	9 (39.13%)	5 (21.74%)	
Trader	2 (8.70%)	1 (4.35%)	2 (8.70%)	
Others	6 (26.09%)	5 (21.74%)	5 (21.74%)	
Education Level				0.976
Primary	2 (8.70%)	1 (4.35%)	2 (8.70%)	
Secondary	6 (26.08%)	7 (30.43%)	5 (21.74%)	
Tertiary	15 (65.22%)	15 (65.22%)	16 (69.56%)	

A side-by-side comparison of the average VAS of the groups at different time periods indicates that at one and two hours after surgery, the highest VAS scores were recorded in placebo group C (1.8, 2.6) while the least was recorded in paracetamol group A (0.9, 1.2). However, there were no statistically significant differences between the groups one and two-hour post-surgery (F = 1.499, p = 0.231) (F = 2.311, p = 0.107). Six hours post-surgery, group A (paracetamol) had the highest VAS score while group B (Ibuprofen) had the least VAS score. However, there was also no significant difference between the VAS scores during this period (F = 2.630, p = 0.08). (Table 2)

Table 2: Comparing the average VAS score of the groups at the different post-surgery periods.

	VAS Score			
Post-surgery period	**Paracetamol (S.D)**	**Ibuprofen (S.D)**	**Placebo (S.D)**	**P-value**
1 Hour	0.9 ± 1.7	1.0 ± 1.9	1.8 ± 2.3	0.231
2 Hours	1.2 ± 1.7	1.4 ± 2.3	2.6 ± 2.8	0.107
6 Hours	3.0 ± 2.4	1.5 ± 1.8	1.9 ± 2.4	0.080

In paracetamol group (A), the average VAS score one hour post-operation was 0.9 ± 1.7. This increased to 1.2 ± 1.7 after two (2) hours. After six (6) hours post-operation, the highest average VAS score, 3.0 ± 2.4 was observed. A one-way repeated measures ANOVA showed that there was a significant difference among the VAS scores (p = 0.002). BonferroniPost hoc testshowed that the VAS score at six hours post-surgery was responsible for the significant difference observed. This implies significant reduction in pain control for the paracetamol group at 6 hours postoperatively. In groups B (Ibuprofen) and C (Placebo), the average VAS score at one, two, and six hours were not significantly different from one another(Table 3).

Table 3: Effect of time on the analgesic effect of the drugs

Code	Time	n	MeanVAS	S. D	SEM	F	p-value [1]
Paracetamol	1h	23	0.9	1.7	0.4	10.385	**0.002***
	2h	23	1.2	1.7	0.4		
	6h	23	3.0	2.4	0.5		
Ibuprofen	1h	23	1.0	1.9	0.4	0.678	0.453
	2h	23	1.4	2.3	0.5		
	6h	23	1.5	1.8	0.4		
Placebo	1h	23	1.8	2.3	0.5	0.704	0.500
	2h	23	2.6	2.8	0.6		
	6h	23	1.9	2.4	0.5		

[1]One-way repeated measures ANOVA

*There was significant reduction in pain control for the paracetamol group at 6 hours post-operation.However, one significant observation was that at six hours post-operation, the mean VAS values for the paracetamol group was 3.0, while that of the placebo group was 1.9 (Table 3).The only plausible deduction is that at six hours post-surgery, over half of the population (60.9%) in the placebo group had used as much as twice as many rescue analgesics as the paracetamol group (Table 4).

Table 4: Descriptive statistics of use and time of rescue medication characterized by the group

Characteristic	Paracetamol N = 9	Ibuprofen N = 8	Placebo N = 14	p-value1
Use of rescue Medication (%)	39.1	34.8	60.9	0.163
Maximum time (minutes)				0.022*
Mean (S.D)	341.7 (85.5)	346.2 (135.8)	222.3 (116.0)	
Range	180 – 420	154 – 600	60 – 480	

1One-way ANOVA*Significant difference in time taken for rescue medication use among the 3 groups (p = 0.022). Placebo differed significantly from analgesic groups.

Concerning the proportion of participants who took rescue medication, majority (60.9%) of group C (Placebo), 39.1% and 34.8% in groups A (paracetamol) and B (ibuprofen) respectively used rescue medication (Table 4).An investigation into the maximum time taken to use rescue medication showed that in the paracetamol group (n = 9), the time ranged from 180 – 420 minutes, with the average time being 341.7 ± 85.5 minutes. In ibuprofen group (n = 8), the average time was 346.2 ± 135.8 minutes. Placebo (group C)had the lowest average time of 222.3 ± 116 minutes. Therefore, there was a significant difference in the time taken before use of rescue medication among the three groups (p = 0.022). The post hoc test revealed that group C differed significantly from group A (p = 0.0205) and group B (p = 0.0204). (Table 4)

Table 5 is an outcome of a binary logistic regression that investigated the association between demographic factors and the use of rescue medication. Concerning gender, females were 7 times more likely to use a rescue medication relative to the males (OR = 7.04, 95% CI = 0.95 - 1.10, P = 0.033), and those in group C (placebo) were 8 times more likely to use a rescue medication relative to group A (paracetamol) (OR = 8.22, 95% CI = 1.29 - 92.6, P = 0.047). (Table 5)

Table 5: Factors associated with the use of rescue medication

Characteristic	OR[1]	95% CI[1]	p-value
Age (years)	1.02	0.95, 1.10	0.5
Gender			
Male	—	—	
Female	7.04	1.33, 52.4	**0.033**
Occupation			
Business	—	—	
Civil servant	14.3	0.93, 428	0.080
Student	10.6	0.67, 300	0.12
Trader	0.09	0.00, 3.19	0.2
Others	5.28	0.48, 85.8	0.2
Education level			
Primary	—	—	
Secondary	0.06	0.00, 1.36	0.10
Tertiary	0.17	0.00, 4.26	0.3
Group			
Paracetamol (A)	—	—	
Ibuprofen (B)	1.49	0.30, 7.60	0.6
Placebo (C)	8.22	1.29, 92.6	**0.047**

[1]OR = Odds Ratio, CI = Confidence Interval

DISCUSSION

Adequate pain management is of utmost importance when treating dental patients.[5, 7, 20-22] It encourages patients' attendance at the dental clinic for future dental care. Clinically, the findings of this study revealed that the pre-emptive analgesics (at a dosage of 1000mg paracetamol and 400mg ibuprofen tablets) reduced the post intra-alveolar extraction pain intensity and the need for rescue analgesic as compared with the placebo (300mg calcium lactate tablet). This alignswith a recent study,[1] whereby the use of pre-emptive ibuprofen or paracetamol showed lower pain scores compared to placebo in a randomized clinical trial.

In the present study, there were only 34.8% of patients in ibuprofen group and 39.1% in the paracetamol group who requested rescue medication postoperatively as against 60.9% of patients in the placebo group. This finding is relatively similar to a previous study,[12] where 35% of patients each in paracetamol and ibuprofen groups required supplementary rescue analgesia respectively. Interestingly, pre-emptive analgesics resulted in increased time to first rescue analgesic. There was also a significant difference in time taken for the use of rescue medication among the three groups ($p = 0.022$). The placebo group differed significantly from the analgesics'. Rescue medication was used at the earliest at I hour postoperatively in the placebo group, 3 hours in the paracetamol group, and 2:34 hours in the ibuprofen group. This replicates a previous study[23] in which rescue medication for those in the paracetamol group was first used at 3 hours postoperatively and earliest in the placebo. This reflects poor pain control in the placebo group as **compared** to the analgesics'.

Although, the ibuprofen group had better pain control 6 hours postoperatively in comparison with the paracetamol and placebo groups using the VAS, there was no significant difference in pain control among the three groups. Our findings are inconsistent with previous studies[1,12,15,23,24] which reported that pre-emptive administration of ibuprofen and paracetamol significantly decreased pain scores compared to a placebo. However, the present study is consistent with another report,[16] which did not show significant differences in pain scores among the three groups, though there was better pain control with the analgesics with ibuprofen having the best pain control with the least VAS score at 6 hours post-operatively.

Tooth extraction is a dental procedure that produces inflammation and pain. Ibuprofen and paracetamol are the most regularly prescribed analgesics in post-extraction pain control.[14, 15] In this study, pre-treatment with ibuprofen and paracetamol exhibited differences in pain scores although, this was not statistically significant. This finding alignswith that of an earlier study[17] in which both analgesics seemed to have a positive effect in reducing post-operative pain when applied pre-emptively, although the reduction was not statistically significant. However, this is in contrast to the findings in another study,[25] where 400mg ibuprofen was significantly more effective than 1000mg paracetamol in all three ratings.

The analgesic effect of paracetamol in this studyseemed to reduce over time with significant reduction in pain control ($p=0.002$) at 6 hours post extraction. The VAS score was higher in the paracetamol group compared to the ibuprofen group at 6 hours postoperatively. This may be because paracetamol is an analgesic with efficacy for mild to moderate pain, and completely devoid of anti-inflammatory activity,[26,27] whereas, ibuprofen has excellent analgesic and anti-inflammatory properties, which are especially important following dental extractions.[1,28,29] This notwithstanding, paracetamol remains a viable alternative to the NSAIDs and should be preferred in patients prone to side effects from the NSAIDs.

Among the factors investigated for use of rescue medication, gender and the drug groups were significant. This may be due to the fact that females,more than males, tend to self-medicate for pain due to their lower tolerance for pain as exemplified by previousstudies.[30-32] This finding is in contrast to another study[17] that reported no

statistically significant difference in gender perception of pain. The reason for this contrasting view may be due to the fact that the previous study was carried out on a much younger group with higher tolerance to pain[33] in comparison to this present study.

This study recorded no adverse effects in the patients studied. This is a pointer to the degree of safety of the drugs administered with careful application of the exclusion and inclusion criteria for the study.

CONCLUSION

The use of pre-emptive analgesics showed lower pain scores compared to the placebo, and significantly increased the time for use of rescue medication postoperatively. Additionally, the reduction in post intra-alveolar extraction pain intensity in the paracetamol and ibuprofen groups were comparable using the VAS, although there was a significant increase in pain intensity among the paracetamol group 6-hours postoperatively.

Conflict of Interest:

The authors declare no conflict of interest.

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