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EFFICACY OF COMBINED ANTI-INFLAMMATORY DRUG THERAPY VERSUS SINGLE DRUG IN THE MANAGEMENT OF DENTAL PAIN AFTER SURGICAL EXTRACTION: A DOUBLE BLIND RCT

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ABSTRACT:

Introduction: In the dental procedures an event of dreadfully handled pain can create patients to defer treatment. The expansion of new pain management approaches furnish dental surgeons with further treatment alternatives that can impart more effectual pain control.

Objective: To compare the difference in the post-operative pain relief symptoms of combination therapy (anti-inflammatory agents) with single drug therapy by using visual analogue scale.

Materials and Methods:

A randomized double blinded study was conducted in oral maxilla facial surgery department of a tertiary care hospital in Karachi for a period of six month. Simple randomization was observed using deck of cards (assignment of condition was sealed in an envelope). A visual analogue scale was used to measure post-operative pain on day 1, 2 and 3 of the surgery. Two independent t-tests was used to compare the post-operative pain scores (from day 1 to day 3) between treatment group receiving combination therapy and control group receiving routine single drug therapy.

Results: A total of 64 subjects participated in the study, 32 subjects randomized to each of the test and control group. There was significant reduction in the post-operative pain scores on day three between test and control group at a p-value of <0.001 with a median score of 0.50±0.093 and 1.0±0.076, respectively. The pain scores for the respective groups did not differ significantly on the second day of follow up with a p-value of 0.351.

Conclusion: Combination therapy is relatively superior in terms of relieving post-operative dental pain following a certain time period after surgery.

Key Words: Post-operative pain management, single drug therapy, Combination anti-inflammatory drug therapy.

INTRODUCTION:

The relief of pain is crucial to patient satisfaction and prompt management in clinical dentistry. The post-operative pain following a surgical removal of an impacted tooth is experienced by the patient up to 48 hours or more (varies in some cases).[(1)] This fear of post-operative pain associated with the

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surgical procedures deters many of the patients from seeking the necessary care.[2,3] Literature has shown that psychological element of pain associated fear results in lower patient compliance towards treatment.[4,5] As a result unnecessary deferral, delayed treatment seeking and the risk of further complications is elevated.[6]

Acetaminophen has been considered as the safest first line pain management drug. Pain is ideally defined as relieved when the intensity of the pain is reduced to 50% or below 30% of maximum on any scal.[7] In this regard non-steroidal anti-inflammatory drug remains the conventional regime for managing pain of moderate intensity. This involves inhibition of cyclooxygenase pathway (COX enzyme activity) blocking the release pro-inflammatory mediators. The combination therapy including acetaminophen and NSAIDS may be more effective for their additive analgesic and anti-inflammatory component and reduced adverse events in comparison to conventional one drug therapy.[8,9] For optimum pain management, nowadays a multimodal therapy has been advocated which involves pre-operative education, combinational pharmacological and non-pharmacological therapies. [10, 11]

Non-steroidal anti-inflammatory drugs have been widely documented for the management of inflammatory conditions such as rheumatoid arthritis and Osteoarthritis; pain of cancer and dysmenorrhea.[7] However, the additive effects of NSAIDS and analgesics in the management of post-operative dental pain in patients with known anxiety are sparsely documented.[12,13] and requires further clarification. Therefore, the purpose of this research study was to find out whether combination analgesics (anti-inflammatory with Paracetamol) were superior to single drug therapy in terms of relieving post-operative pain associated with dental extractions.

OBJECTIVE:

To compare the difference in the post-operative pain relief symptoms of combination therapy (anti-inflammatory agents) with single drug therapy by using visual analogue scale.

MATERIALS AND METHODS:

Trail design: This was a double blind Randomized Control Trail conducted in a tertiary care hospital for the duration of six month.

Those patients who were advised for surgical extraction with the age group in between 15-40 years, of either gender were approached for consent. All the patients that were meeting the inclusion criteria was assessed clinically and radiographically for the presence of dense bone, hypercementosis, widely divergent, hooked or dilacerated roots, extensively carious crowns or with large restorations and retained roots in either maxillary or mandibular region.

However, medically compromised patients (as these patients mostly are on multiple medications which can interact with the given medications) , pregnancy, patients on medications such as oral contraceptives, antidepressants, steroids etc., teeth with periapical infections, recent history of antibiotics, impacted teeth, teeth which can be extracted by closed technique. Also the habitual smokers, alcohol users, consumers of betel quid/gutka and history of radiotherapy for the treatment of head and neck malignancies were excluded from the study.

Sample size: With the reference from the previous studies (8,9,17) the combination therapy was assumed to have Proportion $P_1 = 67\%$ (single therapy) $P_2 = 33\%$. With power of the study 80% and level of significance 5%.Considering 10 % drop out rate the required sample size was rounded to 60 patients i.e. 30 patients in each group.

Randomization:

i. SEQUENCE GENERATION: Selected participants (after applying inclusion and exclusion criteria, Annexure III) will be given numbers. A table of 65 random numbers was used for allocation of participants into either control or test group.

ii. ALLOCATION CONCEALMENT MECHANISM: Assignments were enclosed in sequentially numbered, Efficacy of combination and single anti-inflammatory drug was measured in terms of post-operative pain opaque, sealed envelopes (SNOSE). Investigators made certain that once the participant's information had written on the sealed envelopes, then only the envelopes were opened sequentially. No pressure sensitive or carbon papers within the envelope were used that transferred the information to the assignment card.

iii. IMPLEMENTATION: Trial statistician generated the random allocation sequence, while the single examiner enrolled and assigned the participants to interventions.

Blinding:

Neither the investigator nor the study participant had any knowledge about the assignment of the treatment group.

Intervention:

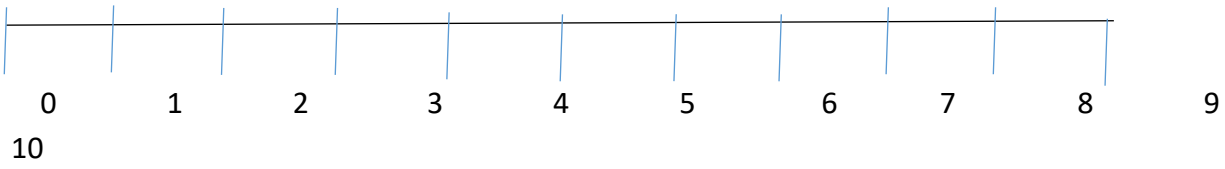
Test Group (Anti-inflammatory Combination Therapy)**:** Naproxen sodium (550mg) and Paracetamol (1g) were given immediately post-operatively and then was continued 8 hourly for three days (each dose taken 1 hour after meal) after surgical extraction.

Control Group (Single therapy) : Naproxen sodium (550mg) was given 8 hourly for three days (each dose taken 1 hour after meal) after surgical extraction.

Outcome assessment:

experienced by the patient as no pain, mild pain; moderate and severe pain on 3 post-operative days using Visual

Analogue Scale (VAS) (D. Gould et al. 2001).The recordings will be analyzed on a scale of 0-10, in two groups.



(0- no pain, 1-4 mild pain,5-7 moderate pain,8-10 severe pain)

DATA COLLECTION PROCEDURE:

Study was commenced after the approval of the Research and Ethics Committee. (Reference number insert) Subjects selected were those meeting the inclusion criteria for surgical tooth extraction. Informed consent was obtained from each subject enrolled. Every patient who filled the surgical extraction inclusion criteria was asked to pick the folded slip by his choice. Group A was given combination therapy which included Naproxen sodium (550mg) & Paracetamol (1g) immediate after extraction and then 8 hourly for three days after surgical extraction. Group B was given single drug therapy Naproxen sodium (550mg) 8 hourly for three days after surgical extraction.

Postgraduate dental surgeons who had 02 years clinical experience performed surgical tooth extraction. The basic steps of surgical extraction were followed by all the dental surgeons as: raising a mucoperiosteal (envelope) flap, removal of buccal cortical bone of tooth creating a trough to achieve a purchase point, tooth sectioning, removal of tooth with complete debridement and irrigation of the socket and primary closure with sutures. Under local anaesthesia (2% xylocaine with epinephrine 1:80,000) surgical extraction was performed. The duration of the procedure was recorded. No intraoperative or postoperative antibiotics were given along with post-operative instructions. Patient was called on 1st, 2nd and 3rd post-operative days and severity of pain was recorded as; no pain, mild, moderate or severe pain as mentioned in the operational definition on the proforma form.

Statistical Analysis:

Overall 70 subjects meeting our inclusion criteria were approached for consent. Out of which 64 subjects who volunteered to participate in the research were randomized to test and treatment groups (32 in each group) through simple randomization. Pain assessment was done post-operatively in first, second and third day of surgery. Excluding loss to follow up on the respective post-operative days, the final sample size was reduced to 30 subjects in each group.

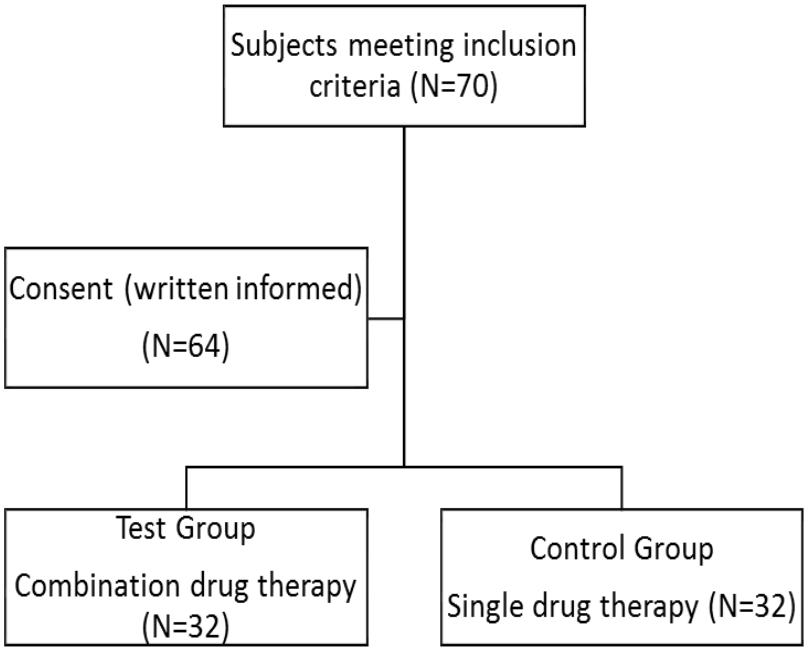


Figure 1 Final distribution of study subjects in the trial

The data was analyzed using SPSS. Descriptive analysis was reported using frequencies. Since the data was not normally distributed (indicated by p-value 0.016 in Shapiro-wilk test), therefore, Man Whitney test (for non-parametric measure) was applied to measure difference in the pain scores on first, second and third day post-operatively. The level of significance was considered at 0.05.

RESULTS:

Table 1 shows baseline characteristics of study subjects randomized to two different groups test group with combination therapy (n=32) and control group with single drug therapy (n=32). There were more females in the test group combination drug (n= 18) in comparison to control group (n=13). The subjects who received single drug therapy (control group) after extraction of molars were 75% (n=24) whereas 86% (n=26) subjects received combination therapy after the extraction of their molar tooth.

Table 1: Baseline characteristics of study participants (N=64)

Baseline characteristics of study participants (N=64)		
Characteristics	**Single Drug Control group** N=32 n(%)	**Combination Therapy Test group** N=32 n(%)
Gender		
Male	19(59.3)	14(43.7)
Female	13(40.6)	18(56.25)
Age		
15-24	04(12.5)	10(31.25)
25-34	10(31.25)	07(21.85)
35 or above	18(56.25)	15(46.25)
Marital status		
Married	27(84.37)	22(68.75)
Single	05(15.6)	10(31.25)
Tooth extracted		
Molar	24(75)	26(81.25)
Pre-molar	08(25)	06(18.75)

Table 2 Comparison of pain relief symptoms after surgical extraction

Post-operative pain relief			
	Single Drug Control group (n=30)	**Combination Drug Test group** (n=30)	**p-value**
Pain scores			
Day 1	2.0±0.89	1.5±0.138	0.019*
Day 2	1±0.082	1±0.069	0.351
Day 3	1.0±0.076	0.50±0.093	<0.001*
*level of significance <0.05, Man Whitney Test Median ± SE Standard error of mean			

Table 2 compares the pain scores of the subjects taking single drug therapy and combination drug therapy on day one two and day three of surgery. There was a difference in the pain scores between the two groups (single drug and combination therapy) on first and third day post-operatively at a p-value of about 0.019 and <0.001 respectively. However, the pain scores did not differ between the two treatment groups on second day of the surgery with p-value of about 0.351 and a median score of 1.0±0.069 for combination therapy and 1±0.082 for single drug therapy.

DISCUSSION:

Current study suggests that combination therapy relieves pain post operatively that was more prominent on day three in comparison to day two.

Paracetamol is now generally accepted drug for pain relief but it has low plasma binding (20%) as compared to other NSAIDs which has 99% plasma binding. NSAIDs are extensively metabolised in the liver to two major inactive metabolites that are rapidly and completely excreted by the kidneys whereas Paracetamol major metabolites inhibits COX-1 and COX-2 by the peroxidase function which causes inhibition of phenoxyl radical formation from tyrosine residue which is essential for the cyclooxygenase activity of COX-1 and COX-2 and prostaglandin (PG) synthesis. It shows selectivity at substantial levels of arachidonic acid and peroxides thus it does not suppress the severe inflammation. It apparently shows to have COX-2 selectivity by its poor anti-platelet activity and good gastrointestinal tolerance. Paracetamol slows the development of multiple inflammatory diseases by inhibiting myeloperoxidase which results in decreased formation of halogenating oxidants .The analgesic effects of paracetamol are reduced by inhibitors of many endogenous neurotransmitter systems including cannabinoid, serotonergic and opioid systems with devoid of anti-inflammatory actions.

In the past different large meta-analysis studies were presented among which Mehlisch DR(4) Bentley KC[14] and Cooper SA[15]showed better results with acetaminophen 500-1000milligrams in managing dental pain whereas patients with use of naproxen also showed reduction in dental pain within 30minutes and lasting for 12 hours. [4, 16, 17]

In different controlled clinical trial Naproxen sodium may be used safely in combination with other NSAIDs, gold salts whereas when it was use with corticosteroids it did not appear to cause greater improvement but with aspirin it increases the rate of excretion. In the two clinical trials it was analyzed that after oral administration of naproxen sodium the time to achieve the peak plasma concentration was within 1–2 hours with half-life of 12–17 hours. Naproxen sodium proves to be better comparator choice in different clinical trials having high effective analgesic property with its consistent levels in blood.[18] Keeping in mind the patient's compliance and convenience a standard-dose combination regime gives desirable

result, although it may potentially limits the scope for dosage adjustment. [21]

Various analgesic combinations have been studied in systematic review and meta-analysis by Au AHY in 2015 and he reported the objective analgesic efficacy and the adverse effects of various combination of drugs literature. The objective efficacy measurements of SPID6 and TOTPAR6 of Ibuprofen 400mg + oxycodone HCL 5mg was considered to be more effective analgesic in relieving acute dental pain and was considered as the pivotal finding. Literature also suggest that ibuprofen 400mg have a higher analgesic efficacy than acetaminophen 1g.Furthermore, when different opioids were compared to each other as oxycodone HCL, codeine phosphate and hydrocodone bitartrate the stronger opioid among them was oxycodone HCL.The analgesic potency of oxycodone HCL is around 1.5–2.0 times stronger than hydrocodone bitartrate and 15–20 times stronger than codeine phosphate. When compared to other analgesic combinations these were found to be more superior. Centrally acting analgesic common side effects include drowsiness, dizziness, headache and nausea and vomiting but some effects have low prevalence rate as itching, dry mouth, flashes, sweating and chills[19]

The clinicians are reluctant to prescribe narcotic analgesics because of the adverse event profile.

In 2008 Shah conducted study in Pakistan to compare the analgesic efficacy of Tramadol Hydrochloride with Diclofenac Sodium in dentoalveolar surgery, clinical experience of tramadol in dental practice is either less or not documented[20]. After dentoalveolar surgery patients feel moderate to severe pain for which dental surgeons usually prescribe NSAIDs to attain its ceiling effect and for minimizing opioid dose and its side effects NSAIDs are significantly effective(21).Furthermore, studies have suggested that combination drug therapy results in lower frequency of unpleasant events than appeared for either product alone with different modes of action and related therapeutic effects. [4, 17]

The strength of the study is to focus more on the logical connection between the drug prescribed and the clinical diagnosis. The limitation of the study is that sample size is less and in future studies it can be increased to attain more distinct results, different combination of anti-inflammatory medications can be used in more than two groups so its efficacy can be assess. For the future recommendation multicenter studies high quality randomized controlled trials should be conducted in those instances in which the patient's pain cannot be managed with non-opioids and alternative regime which may include COX-2 selective inhibitors and its combination should be explored to reach firm conclusions with regard to its therapeutic dosage.

CONCLUSION:

Following conclusion has been drawn from the study.

Combination therapy is relatively superior in terms of relieving post-operative dental

pain following a certain time period after surgery.

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