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To Evaluate and Compare the Efficacy of Non-Steroidal Anti- Inflammatory Drug with and without Serratiopeptidase, and Curcumin with Piperine in Reducing Post Endodontic Pain: A Clinical Study

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Abstract

Objectives: To evaluate and compare the efficacy of non-steroidal anti-inflammatory drug with and without serratiopeptidase and curcumin in reducing post endodontic pain through Visual analogue scale (VAS).

Material and Methods: In this prospective clinical study 90 patients were included with carious or traumatic tooth with acute irreversible pulpitis requiring endodontic treatment. All the patients were randomly divided into three groups and pre and post endodontic pain relief was recorded using Visual Analogue Scale (VAS) at 48 and 96 hours.

Results: At days 2 and 4, patients receiving curcumin with piperine showed similar improvement in severity of pain when compared with aceclofenac with and without serratiopeptidase. The pre and post VAS scores was analyzed using Friedman test and Wilcoxon signed rank test and the difference was statistically highly significant ($p<0.000$).

Conclusion: This study shows curcumin with piperine has similar efficacy to aceclofenac with and without serratopeptidase with fewer side effects hence, curcumin with piperine can be an alternative treatment option in the patients with Post endodontic pain.

Keywords: Serratiopeptidase, curcumin, piperine, aceclofenac, endodontic pain

Introduction

Oral cavity is a heterogenous ecosystem with different microorganisms habituated within distinct niches. Unlike the oral cavity, the root canal system in healthy and intact state is free of infection. Any microorganism found within the root canal system are considered as a potential pathogen. Commensal microbiota of the oral cavity lives in equilibrium with the host. Under certain conditions i.e.by a diet rich in carbohydrates there are changes in this ecosystem where, few microorganisms can dominate and initiate disease.[1]

Dental caries and periodontitis are one of the most prevalent diseases known to mankind. Progression of caries can lead to consequences that may vary from a simple reversible pulpitis to the necrosis of the pulpal tissue and eventually formation of a periapical lesion.[2]

Robbins has defined inflammation as "a protective response intended to eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult". Pulpitis is typically caused by an opportunistic infection of the pulp space by commensal oral microorganisms.[3,4] Pulpitis can occur due to various mechanical, chemical and thermal irritants. Reversible pulpitis is characterized by the absence of bacteria, localized area of coagulation and liquefaction necrosis immediately surrounding the irritant, whereas irreversible pulpitis is characterized by the presence of the bacteria or their by-products in the dental pulp and predominant infiltration of acute inflammatory cells in the pulp.[5,6] Acute irreversible pulpitis can be an extremely painful condition and is believed to be one of the main causes for patients to seek emergency dental treatment.[7]

One of the most common sequalae following root canal therapy is post endodontic pain with prevalence rate of around 25 to 40%.[8] Pulpal inflammation causes excruciating pain due to release of inflammatory mediators such as prostaglandins that activate sensitive nociceptor in periapical tissues.[9] Thus, the rationale for the pharmacological management of post endodontic pain is focused on the reduction of chemical inflammatory mediators that activate or sensitize peripheral nociceptors.[10]

Commonly used drugs for management of acute dental pain belong to two major groups: the non-narcotic analgesics (e.g. non-steroidal anti-inflammatory drugs and paracetamol) and the opioids (or narcotics).[11] Other drug that can be used for managing inflammation is corticosteroid, but their use is very limited due to various side effects i.e. susceptibility to infection, delayed healing of wounds, peptic ulcers, osteoporosis and suppression of hypothalamic-pituitary-adrenal axis.[12]

Non-steroidal anti-inflammatory drugs (NSAIDS) are most commonly used drug for post-operative endodontic pain management. It has combined anti-inflammatory and analgesic action, thus provide good to excellent pain relief.[11] NSAIDs are cyclooxygenase (COX) inhibitors that inhibit prostaglandin and thromboxane synthesis, selectively inhibit COX-2 and are usually specific to inflamed tissue and decreases the risk of peptic ulcer. Aceclofenac is a preferential COX-2 inhibitor which also inhibits cytokines like interleukin-1 (IL-1), tumor necrosis factor (TNF), and prostaglandin E2 (PGE2) production.[13]

Paracetamol is COX-3 inhibitor with analgesic and anti-pyretic effects, which acts primarily in the central nervous system.[14] It is a weak inhibitor of COX-1 and COX-2 thus at therapeutic dose it does not inhibit prostaglandins present in peripheral tissues, hence has milder anti-inflammatory action.[15,16]

Opioids are powerful analgesics but its use in acute dental pain is a matter of concern due to its side effects which

includes nausea, emesis and respiratory depression and opioid abuse.[17,18] Opioids should be used as an adjunct to nonnarcotic drugs considering their relative ratio of therapeutic benefits versus risks.[11]

Serratiopeptidase is a protein obtained from bacteria, Serratia species, belonging to enterobactericeae family.[19] Serratiopeptidase has analgesic effect by inhibiting the release of pain-inducing amines, such as bradykinin, from inflamed tissue.[20] When combined with NSAIDs it acts as an anti-inflammatory agent.[21] Due to peptide nature, there is lack of evidence regarding the oral absorption of serratiopeptidase.[22]

Various studies have shown effectiveness of NSAIDS with and without serratiopeptidase as a potent analgesic and anti-inflammatory agent.[23,24] However, their long-term use cannot be sustained due to inadequate pain relief, immune disturbances, and serious gastrointestinal and cardiovascular adverse events.[25] NSAIDS alone or in combination with serratiopeptidase is costly hence, their judicious use is mandatory. Therefore, herbal therapies with anti-inflammatory properties and minimum side effects are needed especially after the withdrawal of many Food and Drug Administration-approved anti-inflammatory drugs.[26]

Curcumin is a medicinal herb with anti-inflammatory, antioxidant, antimicrobial, antimutagenic properties. Curcumin has been shown to downregulate NF-κB activation increased by various inflammatory stimuli and have potential efficacy against several of these diseases.[27] Clinical evidence confirmed that curcumin is safe for human use and inhibits increased acid secretion to prevent gastric ulcer aggravation.[28,29] The major drawback is its poor bioavailability due to poor absorption, rapid metabolism, and rapid systemic elimination.[30] Piperine is an alkaloid derived from fruits and roots of nigrum and Piper longum species of Piperaceae family. It has anti-inflammatory, analgesic, antipyretic and immunomodulatory properties.[31] Piperine when combined with curcumin increases its bioavailability by reducing the activity of glucuronidase enzymes both at the site of intestinal brush border and liver, resulting in improved absorption of curcuminoids.[32]

Hence the present study was undertaken to evaluate and compare the effectiveness of herbal anti-inflammatory medication with no known side effects to NSAIDs with and without serratiopeptidase.

Aim

To evaluate and compare the efficacy of non-steroidal anti-inflammatory drug with and without serratiopeptidase and curcumin with piperine in reducing post endodontic pain.

Objectives

1. To evaluate the role of NSAIDS without serratiopeptidase in relieving endodontic pain
2. To evaluate the role of NSAIDS with serratiopeptidase in relieving pain post endodontic pain
3. To evaluate the role of curcumin in post endodontic pain.
4. To compare the relief in pain between the three groups through Visual Analogue Scale

Material And Methods

Ninety patients having carious/traumatic tooth presenting with acute irreversible pulpitis were included in the study. Written and informed consent was taken from selected patients and were randomly divided into three groups. Group A was given aceclofenac with serratiopeptidase, Group B was given aceclofenac without Serratiopeptidase and Group C was given curcumin with piperine.

Inclusion criteria

1. Patients with carious/traumatic tooth involving pulp

Exclusion criteria

1. Patients already on analgesics for last 24 hours
2. Immunocompromised patients
3. Patients with systemic disorders
4. Pregnant and lactating mothers

The interventions used in this clinical study was analgesic (100mg aceclofenac with 15 mg serratopeptidase [Zerodol S; IPCA, Mumbai, India]) two times daily for 3 days in group A. Patients in group B was given analgesic (100mg aceclofenac [Zerodol; IPCA, Mumbai, India]) two times daily for 3 days and group C herbal tablet (300mg curcumin with 5mg piperine [Turmix; SANAT PRODUCTS LTD., Delhi, India]) thrice daily for 3 days. Improvement in pain intensity was recorded on the Visual Analogue Scale at baseline and on subsequent visits after 48 and 96 hours and pre and post scores were compared by using Friedman test and Wilcoxon signed rank test.

Results

Clinical assessment of pain on VAS at baseline was similar between the treatment groups, and was further assessed after 48 and 96 hours. All the data were analyzed statistically using non parametric test i.e. Friedman test and Wilcoxon signed rank test.

All the three groups showed relief in pain after day 2 and 4 when compared to baseline VAS scores (Table 1).

There was a statistically significant difference in severity of pain after day 2 and 4 in all the three groups with $\chi 2$ =129.572, p=0.000(Table 2).

There was a statistically highly significant reduction in severity of pain as measured by VAS score (Table.3) at baseline and at day 2 and 4 in group 1 (z=-4.811, p=0.000), group 2 (z=-4.837, p=0.000) and group 3 (z=-4.815, p=0.000).

Thus, in our study curcumin with piperine has shown similar improvement in severity of pain after day 2 and 4 when compared with aceclofenac with and without serratiopeptidase.

Table 1. Mean Vas Score of Group 1,2 & 3

Drugs	N	Intervals	Minimum	Maximum	Mean Score	Standard Deviation
Aceclofenac with Serratopetidase	30	Pre	7	10	8.1000	.92289
		Post (48,96 hours)	2	5	3.50	1.106
Aceclofenac Without Serratopetidase	30	Pre	7	10	7.8000	.88668
		Post (48,96 hours)	2	4	2.67	.606
Curcumin with Piperine	30	Pre	7	10	7.9000	.95953
		Post (48,96 hours)	2	5	2.93	.868

Table 2. Chi-Square Test Value, Degree Of Freedom (Df) And Significance Level

N	30
Chi-square ($\chi 2$)	129.572
Df	5
Asymp. Sig.	.000

Friedman test

Table 3: Comparison of Pre And Post Vas Score of Group 1,2 &3

Group	Pre	Post	Z Score	Asymptomatic Significance (2- Tailed)
Group 1	Aceclofenac with serratopeptidase	Aceclofenac with serratopeptidase	-4.811	.000
Group 2	Aceclofenac without serratopeptidase	Aceclofenac without serratopeptidase	-4.837	.000
Group 3	Curcumin with piperine	Curcumin with piperine	-4.815	.000

Wilcoxon Signed Ranks Test

Discussion

Non-steroidal anti-inflammatory drugs are one of the most important drugs used in endodontic practice considering the clinical efficacy, cost-effectiveness and safety profile. Other commonly used non-narcotic analgesics in dentistry are aspirin, ibuprofen and paracetamol, all of which are available as 'over the counter' medications. Historically, acetaminophen has not been classified as an NSAID, and the mechanism for its analgesic action has been unknown.[33] Aspirin is acetyl salicylic acid is not the drug of choice for treatment of endodontic pain due to its dose related hepatotoxicity which generally occurs when aspirin is used in full anti-inflammatory doses (i.e., not 75-300 mg, as used in antiplatelet indications).[34]

The rationale behind use of NSAIDS for management of post endodontic pain are as follows: First, due to inflammation of tissues chemical mediators like prostaglandin are produced that activate or sensitize peripheral nociceptors that induces pain. NSAIDS inhibits production of these of chemical mediators and further events involved in pain perception.[35] Second, NSAID are widely available without prescription and studies have suggested its effectiveness in managing post endodontic pain.[36]

In our study aceclofenac with serratiopeptidase was used in first group. Serratiopeptidase is a proteolytic enzyme which when used alone or in combination with NSAIDS has superior anti-inflammatory and analgesic action. In first group there was reduction in mean VAS pain score from 8.10 being pre-operative to 3.50 post-operative after day 2 and 4 and the results were highly significant (($p<0.0001$). Similar results have been seen in a systemic review conducted by Holstein et al.2002 and stating that NSAIDs are effective for treating post endodontic pain.[37] Smithe et al.2017 in a systematic review and metanalysis has stated effectiveness of NSAIDS in post endodontic pain patients.[36] Bhagat et al.2013 in his systematic review has stated the effectiveness of serratiopeptidase in dental practise.[38] However, serratiopeptidase alone or in combination with NSAIDs is costly and the exact mechanism by which this enzyme reaches the site of inflammation when administered orally is not clear.[39]

In second group patients were given only aceclofenac to get relief from post endodontic pain. Aceclofenac is a phenylacetic acid derivative oral NSAID that has both analgesic and anti-inflammatory property. It acts by inhibition of both COX-1 and COX-2 enzyme. A meta-analysis of 13 double-blind, randomised, controlled studies indicated that aceclofenac had the lowest incidence of upper GI bleeding than other NSAIDS included in the analysis.[40] In our study this group has also shown reduction in mean VAS pain score from 7.80 being pre-operative to 2.67 post-operative after day 2 and 4 and the results were highly significant (($p<0.0001$). Similar results have been shown in study conducted by Menke et al.2000 where NSAIDS has shown reduction in post endodontic

pain after day 2 and 3 by VAS score.[41] However in a recent review article Nagi et al.2015 has stated various side effects of NSAIDS i.e. gastrointestinal haemorrhage or perforation; cardiovascular adverse effects; hepatotoxicity; renal effects and hypertension; dermatological adverse effects and others.[35]

In third group patients were given curcumin with piperine to reduce post endodontic pain. Curcumin is an active component of dietary spice turmeric. It has immense potential as an anti-inflammatory agent as it inhibits transcription factor NF-κB, scavengers free radicals, decreases the expression of pro-inflammatory cytokines i.e. IL-1β, IL-6 and TNF-α and acute phase proteins i.e. C-reactive protein, and upregulates antioxidant enzymes. Piperine also has anti-inflammatory, analgesic and immunomodulatory properties. Concomitant administration of curcumin and piperine was shown to increase the half-life and bioavailability of curcumin by 2000% and reduce its clearance with no adverse effects.[42] A crossover study was conducted on six healthy adult males who took 2 g of curcumin with or without 5mg of piperine, after one-week blood samples were taken and evaluated which has shown 3-fold increase in bioavailability of curcumin in group where curcumin + piperine combination was given.[43] In our study patients in third group has also shown reduction in mean VAS pain score from 7.90 being pre-operative to 2.93 post-operative after day 2 and 4 and the results were highly significant ((p<0.0001).

In all the three groups the results were highly significant ((p<0.0001) when comparing VAS score at baseline and two different time intervals of 48 and 96 hrs. Similar results were found in study conducted by Shep et al.2019 with the objective to compare the efficacy and safety of curcumin with those of NSAIDs in patients with knee Osteoarthritis.[44]

The results of this present study states that an herbal transition from NSAIDS which has many deleterious effects in comparison to curcumin with piperine can be advocated in alleviating post endodontic pain with no side effects.

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