Intracanal Analgesic Solutions to Control Interappointment Pain during Root Canal Treatment in Patients with Symptomatic Irreversible Pulpitis - A Pilot Study

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Authors’ contributions

This work was carried out in collaboration between both authors. Author SP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MSN managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Mefenamic acid is a Non Steroidal Anti Inflammatory Drug belonging to anthranilic acid group while Aceclofenac is an acetic acid derivative. Aceclofenac is a non selective cyclooxygenase inhibitor while Mefenamic acid is a potent cyclooxygenase inhibitor with both central and peripheral actions. The use of Mefenamic acid and Aceclofenac has reduced due to their side effect of gastrointestinal irritation. The idea of this study is to use Mefenamic acid and Aceclofenac as intracanal agents to achieve localized action without having systemic side effects.

Patients with symptomatic irreversible pulpitis with symptomatic apical periodontitis were identified and divided into three groups of 10 each. After cleaning and shaping of the root canals, 0.1ml of the analgesic solution was injected within the root canals. The pain was evaluated at the end of 6 hours. There was significant reduction in pain in patients who received intracanal Mefenamic acid followed by the group that received Aceclofenac.

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This proves that intracanal administration of analgesics controls inter appointment pain during endodontic treatment and also prevents systemic side effects that are likely to occur due to oral use of the drugs.

Keywords: Mefenamic acid; Aceclofenac; intracanal analgesia; inter appointment pain; root canal treatment; analgesics; symptomatic irreversible pulpitis; symptomatic apical periodontitis.

1. INTRODUCTION

Mefenamic acid, a non steroidal anti-inflammatory drug belonging to the anthranilic acid group is a potent analgesic that is used to relieve mild to moderate pain [1]. It is well known for controlling pain and reducing blood flow in cases of dysmenorrhea and menorrhagia. Mefenamic acid is usually taken as an oral formulation. It is also used to diminish pain of post operative period, musculoskeletal injuries, osteoarthritis, headache and endodontic treatment [2]. It is a highly plasma bound drug and is metabolized in the liver. The use of Mefenamic acid has greatly been reduced these days due to the adverse gastrointestinal side effects that include diarrhea, steatorrhea and inflammation of the bowel [2,3].

Aceclofenac is a non steroidal anti-inflammatory drug belonging to the acetic acid group and is believed to be a prodrug of diclofenac [4]. It is being used as an analgesic, antipyretic, anti inflammatory and anti rheumatic drug [5-7]. It is a highly plasma bound drug and acts by preferentially inhibiting COX-2 pathway [8]. Aceclofenac is known to cause gastrointestinal side effects and hepatic toxicity [9,10].

The idea of this study is to use Mefenamic acid and Aceclofenac solutions as intracanal analgesic solutions to reduce pain of endodontic therapy. Since these drugs are highly protein bound, the concentration of the drugs used to achieve intracanal analgesia would be much less than the documented effective serum concentration of the drugs which is about 20µg/ml for Mefenamic acid after oral administration of 250mg and 9µg/ml for Aceclofenac after oral administration of 100mg [11]. Administering such a low dose for local analgesia would not result in systemic side effects too. There are no studies done where standardized doses of the drugs are used for intracanal analgesia.

We have numerous highly cited publications on well designed clinical trials and lab studies [12–27]. This has provided the right platforms for us to pursue the current study. Hence the aim of this study is to assess intracanal analgesia achieved by setting the concentration of the drug to its LD50 concentration.

2. MATERIALS AND METHODS

2.1 Preparation of Mefenamic Acid and Aceclofenac Solutions

Mefenamic acid and Aceclofenac were procured in a powder form for this study. Since Mefenamic acid is soluble in basic hydroxides, Sodium hydroxide was used as a solvent for dissolving the drug [28]. 0.1g of Sodium hydroxide pellet was dissolved in 10 ml of distilled water. To this solution, 0.1g of Mefenamic acid powder was added. Mefenamic acid dissolved in this solvent giving a clear solution. Aceclofenac is known to be soluble in phosphate buffer saline of a pH 6.8 [29]. Phosphate buffer saline was prepared by mixing 1.38 grams of potassium dihydrogen sulfate and 3.5 grams of disodium hydrate in 100ml of distilled water. 0.1g of Aceclofenac was dissolved in 10ml of phosphate buffer saline to get a clear solution.

2.2 Methodology

Patients with symptomatic irreversible pulpitis with symptomatic apical periodontitis in mandibular and maxillary molars with mild to moderate pain ranging from 4-10 on VAS scale were included in this study. Patients with periapical lesions or those undergoing single visit endodontic treatment were excluded from the study. 30 patients were taken for the study and they were divided into 3 groups of 10 each by simple random sampling. Group A received intracanal Mefenamic acid solution, Group B received intracanal Aceclofenac solution and Group C was taken as control which received intracanal saline.

Root canal treatment was initiated in the first appointment following which the root canals were cleaned and shaped. 0.1 ml of analgesic solutions were loaded in 2ml syringes up to the first gradation on the syringe and introduced within the canal with a 30 gauge needle. The
solution was pumped using gutta percha cones to allow the analgesic solution to seep into the periapical area. The access cavity was closed and pain was evaluated at the end of 6 hours using a 10 point VAS scale.

2.3 Statistical Analysis

All the data entered was entered in Microsoft Excel 2010. Means of all the three groups were calculated and ANOVA test was carried out to compare between the groups. Pairwise comparison was done using Tukey’s post hoc analysis.

For all the above tests, p-value was considered statistically significant when it was <0.05. The software used was SPSS (Statistical Package for Social Sciences) version 17.

3. RESULTS AND DISCUSSION

There was a marked difference in the mean VAS scores after the administration of intracanal analgesics (Table 1). This study showed no statistically significant difference between the groups before administration of intracanal analgesics while a statistically significant difference was seen after delivering the analgesics (Table 2, Graphs 1 and 2). Also statistically significant reduction in pain was achieved after the administration of intracanal analgesics (Table 2, Graph 3).

Tukey’s post hoc analysis was performed which showed statistically significant difference in VAS scores and percentage reduction in pain after intervention (Table 3).

Table 1. Represents the mean VAS scores of every group before and after the administration of intracanal analgesics along with percentage reduction in pain with different analgesic agents

| Groups      | N | VAS score before the use of analgesic | VAS score after the use of analgesic | Percentage pain reduction |
|-------------|---|--------------------------------------|-------------------------------------|---------------------------|
| Mefenamic acid | 10 | 7.10 ± 0.994                        | 3.30 ± 0.949                       | 53.7860                   |
| Aceclofenac   | 10 | 6.90 ± 0.738                        | 5.20 ± 0.789                       | 24.7590                   |
| Control      | 10 | 7.60 ± 0.843                        | 6.80 ± 0.789                       | 10.3950                   |

Graph 1. Depicts the mean VAS scores of each group before the use of analgesics. Here, X axis represents the groups receiving different analgesic solutions while the Y axis represents the mean VAS scores before the use of analgesics. ANOVA test shows no statistically significant difference between the groups before the intervention (p value - 0.195)
Table 2. Depicts the ANOVA test where comparisons have been made between and within the groups before and after the use of intracanal analgesics. Also percentage pain reduction between the groups has been assessed. The table shows no statistically significant difference between the groups before the administration of intracanal analgesics (p value - 0.195) while a statistically significant difference in pain scores and percentage reduction in pain exists between the groups after intervention.

|                         | Sum of squares | df | Mean square | F      | Sig. |
|-------------------------|----------------|----|-------------|--------|------|
| **VAS score before the use of analgesic** |                |    |             |        |      |
| Between groups          | 2.600          | 2  | 1.300       | 1.738  | .195 |
| Within groups           | 20.200         | 27 | .748        |        |      |
| Total                   | 22.800         | 29 |             |        |      |
| **VAS score after the use of analgesic** |                |    |             |        |      |
| Between groups          | 61.400         | 2  | 30.700      | 42.948 | .000 |
| Within groups           | 19.300         | 27 | .715        |        |      |
| Total                   | 80.700         | 29 |             |        |      |
| **Percentage pain reduction** |                |    |             |        |      |
| Between groups          | 9772.235       | 2  | 4886.117    | 78.114 | .000 |
| Within groups           | 1688.873       | 27 | 62.551      |        |      |
| Total                   | 11461.107      | 29 |             |        |      |

Table 3. Represents the Tukey’s post hoc analysis carried out for pairwise comparison of groups. The test shows no statistically significant difference between the groups before intervention and statistically significant difference in the pain scores and percentage reduction in pain after intervention.

|                         | Group 1 vs Group 2,3 | Group 2 vs Group 1,3 | Group 3 vs Group 1,2 | Group 1 vs Group 2,3 | Group 2 vs Group 1,3 | Group 3 vs Group 1,2 |
|-------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| **VAS score before the use of analgesic** | p>0.05               | p>0.05               | p>0.05               | p>0.05               | p>0.05               | p>0.05               |
| **VAS score after the use of analgesic** | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              |
| **Percentage pain reduction** | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              | p<0.05*              |

**Indicates statistically significant difference (p<0.05)**

Graph 2. Depicts the mean VAS scores after the use of analgesics. Here X axis represents the groups receiving different analgesic solutions and Y axis represents the mean VAS scores after the use of analgesics. ANOVA test shows statistically significant difference after the use of intracanal analgesics (p value- 0.000)
Mefenamic acid and Aceclofenac are usually taken as oral formulations. Since they are potent prostaglandin inhibitors and show superior analgesic activity, they have been used to treat mild to moderate pain [1]. The extensive use of these drugs was later discontinued due to severe gastrointestinal side effects which included diarrhoea, steatorrhoea, and inflammation of the bowel and hepatic toxicity [1,30]. This led to the idea of using Mefenamic acid and Aceclofenac locally to minimize systemic side effects.

This study deals with the use of Mefenamic acid and Aceclofenac solutions for intracanal analgesia to relieve post endodontic pain. In the root canal, the pain site is very specific and the surface area is also small which makes it possible for target oriented drug delivery. The concentration of the drug for intracanal analgesia is also less when compared to the concentration used for systemic administration.

The documented therapeutic effective serum concentration of Mefenamic acid is 20 µg/ml after oral administration of 250 mg of the drug [31–33] and Aceclofenac is 6-8 µg/ml after oral administration of 100 mg. Since Mefenamic acid and Aceclofenac are highly protein bound, the amount of drug reaching the periapical area for analgesia would be much less than the documented effective therapeutic concentration [30,34]. The median lethal dose of Mefenamic acid and Aceclofenac is found to be much higher than the therapeutic serum concentration of the drug. The LD50 of Mefenamic acid and Aceclofenac is found to be much higher than the concentrations proposed for clinical trials, which ends at 20 µg/ml and 8 µg/ml. This gives us a wide safety margin for intracanal use of this drug.

There have been studies done earlier to control pain of endodontic treatment by use of various solutions within the root canal. The earliest study dates back to 1954 where hydrocortisone solution was proved to be effective in relieving endodontic pain [35]. Later in 1984, Moskow et al used the dexamethasone solution as an endodontic anodyne [36]. Negm et al in 1994 showed that analgesics like Diclofenac and Ketoprofen when used as solutions to irrigate root canals showed significant reduction in post treatment pain. These findings were similar to those observed in this study. Also, Rogers et al in 1999 compared the effect of intracanal use of Dexamethasone and Ketorolac over oral ibuprofen and stated that intracanal analgesics

Graph 3. Represents the bar graph where percentage pain reduction between the three groups are studied after intervention. Here, X axis represents the groups receiving different analgesic solutions while Y axis represents the mean percentage pain reduction. This graph shows maximum pain reduction in the group receiving Mefenamic acid where about 53.79% of pain reduction is observed.

Error Bars: +/- 1 SD
were more effective in managing post operative pain of root canal treatment in comparison to oral formulations [37,38]. The main drawback in all these studies was that, in none of these studies the concentrations of the drugs were standardized. Hence this study was designed after evaluating the cytotoxic effect of the drug for clinical trials so as to standardize the concentration of drug for intracanal analgesia.

4. CONCLUSION

Mefenamic acid and Aceclofenac can be used as safe and effective drugs for intracanal analgesia. This study showed that Mefenamic acid was more effective than Aceclofenac in controlling inter appointment pain. This could mainly be due to the additional action of inhibiting preformed prostaglandins apart from inhibiting the cyclooxygenase pathway. Further studies are necessary with larger sample sizes to generalize the results.

DISCLAIMER

The products used for this research are the ones used commonly in areas of dental practice as analgesics. There are no competing interests between the author and the producer of these products, these products are used in this study only for advancement of knowledge. This study was not funded by producer of these products or any other agencies but was funded by the authors alone.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mavrikakis ME, Madkour MM, Buchanan WW. The place of mefenamic acid in the treatment of rheumatoid arthritis. Scottish Medical Journal. 1978;23:189–190.
2. Rowe NH, Shekter MA, Turner JL, et al. Control of pain resulting from endodontic therapy: A double-blind, placebo-controlled study. Oral Surgery, Oral Medicine, Oral Pathology. 1980;50:257–263.
3. Stockman A, Varigos GA, Muirden KD. Comparison of effectiveness of mefenamic acid and ibuprofen in treatment of rheumatoid arthritis. Medical Journal of Australia. 1976;2:819–820.
4. Moore RA, Derry S, McQuay HJ. Single dose oral aceclofenac for postoperative pain in adults. Cochrane Database Syst Rev. 2009;CD007588.
5. González-Alvaro I, Carmona L, Díaz-González F, et al. Aceclofenac, a new nonsteroidal antiinflammatory drug, decreases the expression and function of some adhesion molecules on human neutrophils. J Rheumatol. 1996;23:723–729.
6. Legrand E. Aceclofenac in the management of inflammatory pain. Expert Opin Pharmacother. 2004;5:1347–1357.
7. Lemmel E-M, Leeb B, De Bast J, et al. Patient and physician satisfaction with aceclofenac: Results of the european observational cohort study (experience with aceclofenac for inflammatory pain in daily practice). Aceclofenac is the treatment of choice for patients and physicians in the management of inflammatory pain. Curr Med Res Opin. 2002;18:146–153.
8. Cho JY. Immunomodulatory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) at the clinically available doses. Archives of Pharmacal Research. 2007;30:64–74.
9. Pareek A, Chandanwale AS, Oak J, et al. Efficacy and safety of aceclofenac in the treatment of osteoarthritis: A randomized double-blind comparative clinical trial versus diclofenac - An Indian experience. Curr Med Res Opin. 2006;22:977–988.
10. Lapeyre-Mestre M, de Castro AMR, Bareille MP, et al. Non-steroidal anti-inflammatory drug-related hepatic damage in France and Spain: Analysis from national spontaneous reporting systems. Fundam Clin Pharmacol. 2006;20:391–395.
11. Medhi B, Joshi R, Prakash A, et al. Effect of aceclofenac on pharmacokinetic of phenytoin. Pak J Pharm Sci. 2012;25:295–299.
12. Ramaraoo S, Sathyanarayanan U. CRA Grid - A preliminary development and calibration of a paper-based objectivization of caries risk assessment in undergraduate dental education. J Conserv Dent. 2019;22:185–190.

13. Poorni S, Srinivasan MR, Nivedhitha MS. Probiotic strains in caries prevention: A systematic review. J Conserv Dent. 2019;22:123–128.

14. Manohar MP, Sharma S. A survey of the knowledge, attitude, and awareness about the principal choice of intracanal medicaments among the general dental practitioners and nonendodontic specialists. Indian J Dent Res. 2018;29:716–720.

15. Azeem RA, Sureshbabu NM. Clinical performance of direct versus indirect composite restorations in posterior teeth: A systematic review. J Conserv Dent. 2018;21:2–9.

16. Jenarthanan S, Subbarao C. Comparative evaluation of the efficacy of diclofenac sodium administered using different delivery routes in the management of endodontic pain: A randomized controlled clinical trial. J Conserv Dent. 2018;21:297–301.

17. Nandakumar M, Nasim I. Comparative evaluation of grape seed and cranberry extracts in preventing enamel erosion: An optical emission spectrometric analysis. J Conserv Dent. 2018;21:516–520.

18. Malli Sureshbabu N, Selvarasu K, V JK, et al. Concentrated growth factors as an ingenious biomaterial in regeneration of bony defects after periapical surgery: A report of two cases. Case Rep Dent. 2019;2019:7046203.

19. Siddique R, Nivedhitha MS, Jacob B. Quantitative analysis for detection of toxic elements in various irrigants, their combination (precipitate), and para-chloroaniline: An inductively coupled plasma mass spectrometry study. J Conserv Dent. 2019;22:344–350.

20. Teja KV, Ramesh S, Priya V. Regulation of matrix metalloproteinase-3 gene expression in inflammation: A molecular study. J Conserv Dent. 2018;21:592–596.

21. Rajakeerthi R, Ms N. Natural Product as the Storage medium for an avulsed tooth – A systematic review. Cumhuriyet Dental Journal. 2019;22:249–256.

22. Siddique R, Nivedhitha MS. Effectiveness of rotary and reciprocating systems on microbial reduction: A systematic review. J Conserv Dent. 2019;22:114–122.

23. Janani K, Sandhya R. A survey on skills for cone beam computed tomography interpretation among endodontists for endodontic treatment procedure. Indian J Dent Res. 2019;30:834–838.

24. Siddique R, Sureshbabu NM, Somasundaram J, et al. Qualitative and quantitative analysis of precipitate formation following interaction of chlorhexidine with sodium hypochlorite, neem, and tulsi. J Conserv Dent. 2019;22:40–47.

25. Rajendran R, Kunjusankaran RN, Sandhya R, et al. Comparative evaluation of remineralizing potential of a paste containing bioactive glass and a topical cream containing casein phosphopeptide-Amorphous calcium phosphate: An in Vitro study. Pesqui Bras Odontopediatria Clin Integr. 2019;19:1–10.

26. Govindaraju L, Neelakantan P, Gutmann JL. Effect of root canal irrigating solutions on the compressive strength of tricalcium silicate cements. Clin Oral Investig. 2017;21:567–571.

27. Khandelwal A, Palanivelu A. Correlation between dental caries and salivary albumin in adult population in Chennai: An in vivo study. BDS. 2019;22:228–233.

28. Bani-Jaber A, Hamdan I, Al-Khalidi B. Sodium mefenamate as a solution for the formulation and dissolution problems of mefenamic acid. Chemical & Pharmaceutical Bulletin. 2007;55:1136–1140.

29. Islam SMA, Islam S, Shahriar M, et al. Comparative in vitro dissolution study of aceclofenac marketed tablets in two different dissolution media by validated analytical method. J Basic Appl Pharm Sci. 2011;1:87.

30. Stockman A, Varigos GA, Muiroen KD. Comparison of effectiveness of mefenamic acid and ibuprofen in treatment of rheumatoid arthritis. Medical Journal of Australia. 1976;2:819–820.

31. Moll R, Derry S, Moore RA, et al. Single dose oral mefenamic acid for acute postoperative pain in adults. Cochrane Database Syst Rev. 2011;CD007553.

32. Moore RA, Andrew Moore R, Derry S, et al. Single dose oral mefenamic acid for acute postoperative pain in adults.
33. Cimolai N. The potential and promise of mefenamic acid. Expert Rev Clin Pharmacol. 2013;6:289–305.

34. Roy S. A double-blind comparison of a propionic acid derivative (ibuprofen) and a fenamate (mefenamic acid) in the treatment of dysmenorrhea. Obstet Gynecol. 1983;61:628–632.

35. Rogers MJ, Johnson BR, Remeikis NA, et al. Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. J Endod. 1999;25:381–384.

36. Wolfsohn BL. The role of hydrocortisone in the control of apical periodontitis. Oral Surg Oral Med Oral Pathol. 1954;7:314–321.

37. Moskow A, Morse DR, Krasner P, et al. Intracanal use of a corticosteroid solution as an endodontic anodyne. Oral Surg Oral Med Oral Pathol. 1984;58:600–604.

38. Negm MM. Effect of intracanal use of nonsteroidal anti-inflammatory agents on posttreatment endodontic pain. Oral Surgery, Oral Medicine, Oral Pathology. 1994;77:507–513.