



Analgesic Efficacy of Corticosteroids Used as Intracanal Solutions to Control Inter Appointment Pain during Root Canal Treatment – A Systematic Review

Sneha Pai¹ and M. S. Nivedhitha^{1*}

¹Department of Conservative Dentistry and Endodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India.

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 NMS managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Patients often associate endodontic treatment with pain. Inter appointment pain is common during endodontic treatment and is due to acute inflammation of the apical periodontal ligament space. Till date, several agents have been employed to manage inter appointment pain by administering them through different routes. All the agents for pain control were administered orally in the past. In order to bypass the unwanted side effects and achieve immediate and effective pain control, local administration was followed by intracanal administration. This systematic review analyzes the effect of intracanal delivery of various steroid solutions and their effectiveness in pain management. A search was performed in electronic database (i.e. Pubmed Central, Google and Hand Search) till August 2019. All in vivo studies that used intracanal corticosteroids for controlling inter appointment pain during endodontic treatment were selected. The outcome measure was to evaluate the reduction of pain in the inter appointment period after intracanal drug delivery.

*Corresponding author: E-mail: nivedhitha@saveetha.com;

Since all the studies included for this review showed high risk of bias, no conclusion could be drawn on intracanal use of corticosteroid solutions for analgesia. Further studies have to be conducted with a proper design, standardization of the drug and appropriate statistical analysis to obtain accurate results.

Keywords: NSAIDs; corticosteroids; intracanal delivery; analgesia; endodontic treatment.

1. INTRODUCTION

The incidence of inter appointment pain during endodontic treatment is of main concern to both the patient and the dentist. Many of them associate endodontic treatment with pain. Therefore effective methods of anesthesia and analgesia are being commonly practiced to make endodontic treatment pain free.

Endodontic pain can occur prior, during or after the treatment. Post endodontic pain comprises of inter appointment pain and post obturation pain and is reported to occur in 25% - 40% of the patients undergoing endodontic treatment [1–4]. Endodontic pain is due to acute inflammatory reaction of the apical periodontal ligament which could be due to injury to vital nerve or pulp tissue, over instrumentation, forcing of debris or medicament beyond the apex or due to occlusal trauma [5–8]. Several drugs have been used to control this pain by interfering with the periapical inflammation. The commonly used drugs are non-steroidal anti-inflammatory drugs and steroids [9].

Various stimuli result in release of arachidonic acid from the phospholipid membrane of the cell [10]. The arachidonic acid forms the precursor and travels through two pathways. The first pathway requires the enzyme cyclo-oxygenase and gives rise to potent inflammatory mediators prostaglandins and thromboxanes. The other pathway utilizes the enzyme lipo-oxygenase and produces even more potent mediators of inflammation namely leukotrienes. Non steroidal anti inflammatory drugs inhibit the cyclo-oxygenase pathway and block the release of prostaglandins and thromboxanes while steroids inhibit the precursor arachidonic acid and blocks both cyclo-oxygenase and lipo-oxygenase pathways, thereby controlling inflammation effectively [10,11].

Use of corticosteroids topically for control of inflammation in a wide range of cases from pulp hyperemia to partial suppurative pulpitis was proposed by Schroeder in 1965 [12]. Mosteller in 1962 conducted a study where prednisolone was

compared with control over 726 teeth undergoing operative procedure and found that the study group treated with prednisolone showed decrease in thermal sensitivity [13]. Corticosteroids have been in use as pulp capping agents and have also been suggested for control of pain in endodontics [12,14–16]. Corticosteroids are believed to stabilize cell membrane thereby blocking nerve impulse transmission [17].

Smith in 1976 has proved the topical application of steroid preparation to pulp or periapical tissues to symptomatically relieve endodontic pain [16]. A study conducted by Wolfson in 1954 proved the use of hydrocortisone in acute serous and suppurative pulpitis to reduce inflammation [17]. Gurney in 1974 was the first one to suggest that corticosteroids be gently forced into the periapical area for pain relief [18].

When corticosteroids are delivered locally, the dosage required would be much less than the oral formulation that is conventionally used as the local delivery would surpass first pass metabolism thereby reducing the magnitude of adverse effects as well as achieve target oriented drug delivery and effective pain control [19,20].

2. MATERIALS AND METHODS

For identification of studies included or considered for this review, detailed search strategies were carried out on PUBMED database and Google search. Articles were also hand searched in 'International Endodontic Journal', 'Journal of Endodontics', 'Oral Surgery Oral Medicine Oral Pathology' and 'Oral Surgery'. No limits and language restrictions were applied during the electronic search. No time restrictions were applied. Reference list of reviews and of the identified in vitro studies were also checked for possible additional studies.

The inclusion criteria for this systematic review included:

- *In vivo* studies on patients having irreversible pulpitis

- Patients undergoing multiple visit endodontic treatment
- Studies where corticosteroid solution is used to control pain
- Studies where corticosteroid solution is compared either with NSAID or Placebo.

Case reports, case series, studies where corticosteroids were used as a paste or medicament and studies where only intracanal NSAIDs and calcium hydroxide were used for inter appointment pain control were excluded from this review.

3. RESULTS AND DISCUSSION

The search identified 73 publications out of which 61 were excluded after reviewing the title and the abstract and 8 were excluded after reading the full article (Table 1). A total of 4 publications fulfilled all criteria and were included in this review as shown in the PRISMA flow chart. (Table 2, Fig. 1).

3.1 Risk of Bias of Included Studies

The assessment for the four main methodological quality items is shown in the table. The study was assessed to have a 'high risk' of bias if it did not record a 'Yes' in three or more of the main four categories, 'Moderate' if two out of four categories did not record a 'Yes' and 'Low' if randomization assessor blinding and

completeness to follow up were considered adequate (Tables 3 and 4).

3.2 Quality Assessment

The quality assessment of included trials was undertaken independently as a part of the data extraction process. Four main criteria that were examined were method of randomization, allocation concealment, blinding and completeness of follow up. Other methodological criteria examined included presence or absence of sample size calculation, comparability of the groups at the start and clear inclusion and exclusion criteria (Figs 2 and 3).

The purpose of this review was to evaluate the use of intracanal corticosteroid solutions in the management of inter appointment pain during endodontic treatment. Four *in vivo* studies fulfilled the criteria for being included in this review. (Moskow et al 1984; K Chance et al 1987; L R G Fava 1992; Rogers et al 1999)

3.3 Meta – Analysis

Mostly, systematic reviews perform meta-analysis, which involves the statistical pooling of data from individual studies when the studies are similar. A meta-analysis can yield a more precise overall estimate of the treatment effect. However, meta-analysis may not be appropriate in many situations. Owing to the heterogeneity among the

Table 1. Characteristics of excluded studies

No	Author	Year	Reason for exclusion
1.	Wolfson	1954	The control group had electrosterilized hydrocortisone like the study group along with camphorated parachlorophenol and polyantibiotic paste.
2.	Edward Keefe	1976	Comparison was made with formocresol which did not follow the inclusion criteria of this review.
3.	Glassman et al	1989	Dexamethasone was given orally.
4.	Liesinger et al	1993	Dexamethasone was administered as intraoral or intra muscular injections. Study aimed to control post obturation pain.
5.	Alfredo Calderon	1993	The control group was treated with intra canal dexamethasone which did not fit in with the inclusion criteria. Obturation was completed in some of the cases and post operative pain was evaluated.
6.	L.R.G Fava	1998	Intracanal Corticosteroids were used in non vital teeth.
7.	Negm et al	2001	Corticosteroid antibiotic compound was used in the form of a paste instead of a solution.
8.	Khalid et al	2016	Compared the two corticosteroid solutions in the management of endodontic pain.

Table 2. General information of variables of included studies

No	Author and year	Study type	Study design	Outcome variable	Time of assessment	Statistical test	Intervention	Overall interpretation
1.	Moskow et al 1984	<i>In vivo</i>	Sample Size=50 (Study=24 Control=26)	Reduction in inter appointment pain.	24 th , 48 th and 72 nd hours	Chi square test	Study on vital teeth. Group 1- Dexamethasone solution. Group 2- Placebo	Corticosteroid cases had fewer subjective reports of pain than the saline controls.
2.	K Chance et al 1987	<i>In vivo</i>	Sample size=280 Study=147 Control=133	Reduction in inter appointment pain.	24 th hour	Chi square test	Study on vital teeth. Group 1- Prednisolone acetate solution Group 2- Normal saline.	Pain occurred less frequently in the corticosteroid group than in the control group and showed a statistical difference.
3.	L R Fava et al 1992	<i>In vivo</i>	Sample size=60 (n=30)	Reduction in inter appointment pain.	48 th hour and 7 th day	-	Study on vital teeth. Group 1- Otopsporin solution Group 2- calcium hydroxide	No significant difference in pain reduction between the two groups was seen.
4.	Rogers et al 1999	<i>In vivo</i>	Sample size=48 (n=12)	Reduction in inter appointment pain.	6 th , 12 th , 24 th and 48 th hours	Chi square test	Study done on vital teeth. Group 1- oral ibuprofen Group 2- Placebo Group 3- Intracanal dexamethasone Group 4- Intracanal ketorolac tromethamine	The intra canal ketorolac group showed maximum reduction in pain followed by intracanal dexamethasone, oral ibuprofen and placebo.

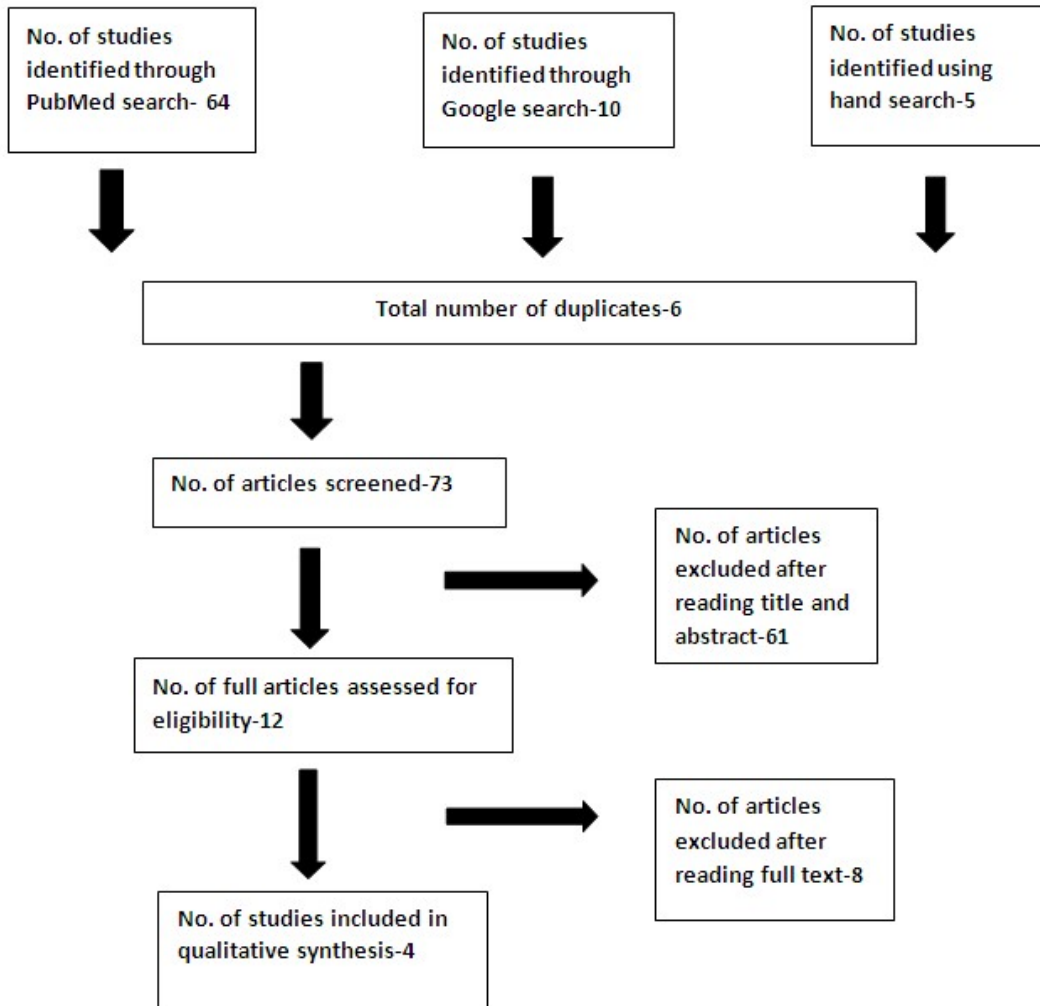


Fig. 1. PRISMA flow chart

Table 3. Depicts risk of bias (major criteria)

S.No	Author	Year	Randomization	Allocation concealment	Assessor blinding	Dropouts described	Risk of bias
1.	Moskow et al	1984	No	No	Yes	None	High
2.	K Chance et al	1987	Unclear	No	No	Unclear	High
3.	L R Fava	1992	No	No	No	None	High
4.	Rogers et al	1999	Unclear	No	No	None	High

Table 4. Indicates risk of bias (minor criteria)

S.No	Author	Year	Sample justified	Baseline comparison	I/E criteria	Method error
1.	Moskow et al	1984	No	Yes	Yes	No
2.	K Chance et al	1987	No	No	Yes	No
3.	L R Fava	1992	No	No	Yes	No
4.	Rogers et al	1999	No	Yes	Yes	No

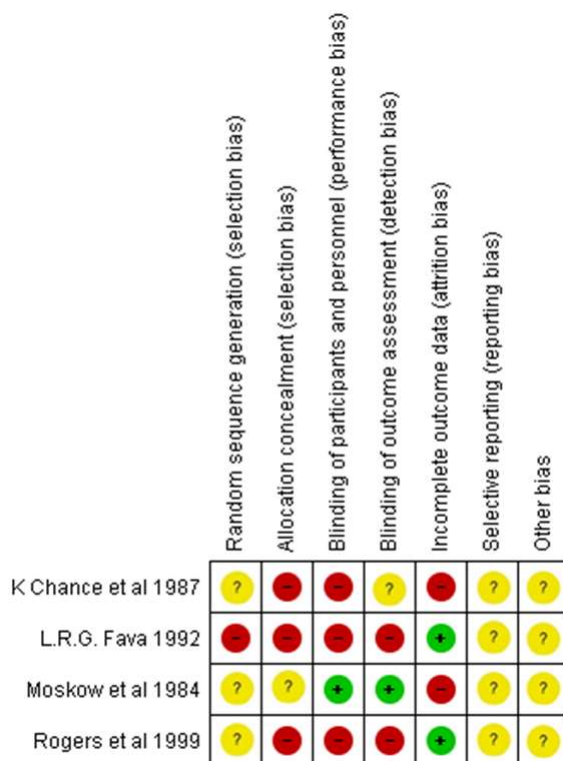


Fig. 2. Depicts the risk bias summary [Quality assessment results using risk bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)]

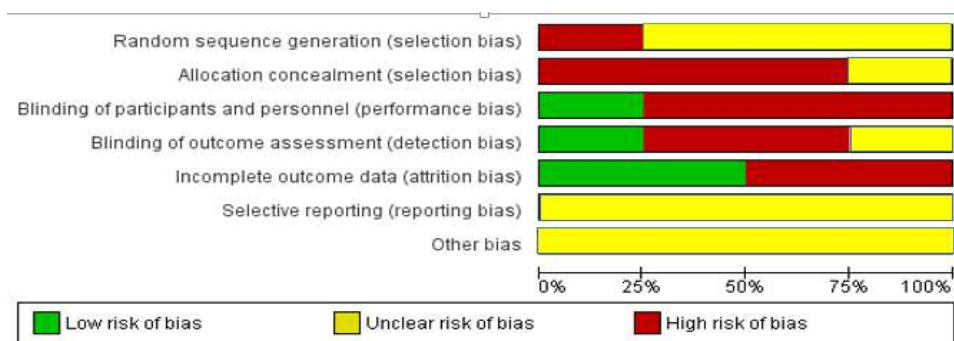


Fig. 3. Depicts overall assessment of risk bias [Quality assessment results using risk bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)]

studies such as sample size and follow up periods, meta-analysis could not be performed to summarize the data of included studies. Hence, only descriptive evaluation of data has been provided.

In the study conducted by Moskow et al in 1984, fifty patients who gave a positive reading to the

pulp test were included in the study. Two solutions were prepared, which were stored in identical bottles to achieve double blinding. The experimental solution was a corticosteroid, Decadron (Dexamethasone 4 mg/ml) and the control solution was physiologic saline solution. The patients received the experimental drug or the placebo within the root canal after cleaning

and shaping. Patients were asked to rate their pain on a scale of 0 to 100 at 24, 48 and 72 hours. The data was analyzed and statistical analysis was done using chi square test. The author noticed that corticosteroid cases had fewer subjective reports of pain when compared to control through the three postoperative time periods. At the end of 24 hours, the corticosteroid group showed better pain control when compared to the placebo group and the results were statistically significant [8].

Chance et al in 1987 conducted a clinical trial of intracanal corticosteroid in root canal therapy. Three hundred patients with both vital and non vital pulp were included in this study. The subjects were randomly allocated in two groups. The experimental group received a solution of prednisolone acetate (2.5%) and the control group received saline. These solutions were delivered into the root canal after cleaning and shaping. Eleven experimental and nine control patients dropped out. Therefore 280 patients were evaluated with 133 in the control group and 147 in the experimental group. The pain was recorded at the end of 24 hours into four categories: no pain, slight pain but no medication required, moderate pain that requires mild analgesia and severe pain that requires a narcotic. It was seen that pain occurred more frequently in the control group than in the experimental group in cases of vital pulps whereas there was no significant difference in pain reduction among the groups in case of non vital pulps. The analgesic effect of corticosteroid was explained to be due to its prostaglandin inhibition activity. This study proved the ineffectiveness of use of corticosteroid in case of necrotic pulps [21].

A study by L R G Fava in 1992 on controlling postoperative pain using two intracanal dressings used Otosporin solution (corticosteroid- antibiotic compound containing 10000 IU of polymixin B sulphate, 5mg of neomycin sulphate and 10mg of hydrocortisone) and calcium hydroxide paste. The study was conducted on sixty maxillary central incisors with vital pulps. Thirty teeth were assigned to each group. The experimental group received Otosporin solution and the control group received calcium hydroxide paste within the root canal after cleaning and shaping. The pain was assessed at the end of 48 hours and 7 days. Pain assessment was done subjectively as none to slight pain, moderate and severe pain. The study showed no difference in the incidence of pain in the both the groups and both the time

periods tested. The effectiveness of Otosporin is due to its corticosteroid component that inhibits prostaglandin synthesis and the aqueous nature of the preparation that enables better flow and penetration into the tissues. The effectiveness of calcium hydroxide can be attributed to its hygroscopic nature that absorbs the inflammatory exudate, formation of calcium bridges that blocks the seepage of exudates from blood vessels and tissues and phospholipase inhibition that prevents cellular lysis and prostaglandin synthesis [22].

Rogers et al in 1999 compared the effectiveness of intracanal ketorolac, intracanal dexamethasone and oral ibuprofen in controlling inter appointment pain during endodontic treatment. For this study, 48 patients with vital pulps were taken and allotted into 4 groups of 12 each. Group 1 received oral ibuprofen, Group 2 received oral placebo, Group 3 received intracanal dexamethasone solution and Group 4 received intracanal ketorolac solution. Pain evaluation was done at 6, 12, 24 and 48 hours with VAS 0-100 scale. It was seen that intracanal ketorolac showed significant reduction in pain followed by intracanal dexamethasone and oral ibuprofen. The effectiveness of ketorolac is believed to be due to its strong inhibitory activity on the cyclooxygenase pathway which inhibits prostaglandin release. Moreover the delivery of this agent locally at the site of action would bypass the first pass metabolism and give effective pain relief [23].

3.4 Interpretation of the Result

Of the four studies reviewed, two studies evaluated the effectiveness of intracanal corticosteroid solution as an analgesic in comparison to placebo, one studies used corticosteroid antibiotic solution locally for endodontic pain control in comparison to commonly used calcium hydroxide and one study assessed the effectiveness of intracanal corticosteroid, intracanal ketoprofen with oral ibuprofen and placebo.

It was observed in these studies that intracanal corticosteroid solution was effective in management of inter appointment pain in endodontics. Another observation was that corticosteroid- antibiotic solution was as effective as calcium hydroxide in managing pain. The last study that compared corticosteroid with analgesics showed that intracanal analgesic solution was more effective in pain control

compared to intracanal corticosteroid and oral analgesics.

3.5 Implications for Practice

Intracanal route of administration of corticosteroids can be taken as an alternative to conventional oral route of administration. Intracanal administration would result in delivery of the drug directly at the site of action and a lesser concentration of the drug would be required as first pass metabolism would be bypassed. This will not only reduce the systemic side effects caused due to oral intake of the drug but also results in faster and effective pain management.

3.6 Implications for Research

These studies that used the intracanal route of administration of corticosteroid solutions for analgesia were not standardized and had low quality of evidence. All the studies used commercial preparation of corticosteroids that were available for oral or intravenous use. Evaluation of the cytotoxicity of the drug at the site of action has to be evaluated and the dosages should be standardized for intracanal delivery. In teeth undergoing endodontic treatment, the pain site is very specific and the surface area is small which makes it possible for target oriented drug delivery so the dosage of drug required for intracanal administration would be much less than the oral dose. Therefore further studies have to be carried out to standardize the safe and effective concentration of corticosteroids for intracanal use.

4. CONCLUSION

With the available evidence, this review concludes that the studies reviewed here have a high risk of quality bias. Therefore, this review draws no conclusion regarding the use of intracanal corticosteroid solutions for inter appointment pain control in endodontics. The studies here were not properly designed with respect to size of samples, standardization and statistical analysis. Further studies have to be conducted with a proper design, standardization of the drug and appropriate statistical analysis to obtain accurate results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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Both the authors have equal contribution in bringing out this research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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