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Effect of Prednisolone Premedication on Postoperative Pain after Single Visit Endodontic Therapy: A Randomized Controlled Trial part (XIII)

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Abstract **Original Research Article**

This study was designated to evaluate the effect of Prednisolone as premedication in controlling post-endodontic pain after single visit treatment of acute irreversible pulpitis using in a randomized controlled trial. 40 Mandibular Molar teeth were treated using Revo S system, Patients were asked To sign a printed consent and obligated the patient to fill the pain diary 6,12,24 hours after root canal treatment. The patients were randomly divided into 2 groups: experimental group (A): prednisolone 40 mg and control group (B): placebo. The pain was measured using VAS measurement, a triple blind randomized study used to minimize bias and to allow sufficient comparison between groups. The outcome of this study showed that Prednisolone resulted in statistically significant reduction in post endodontic pain at 6, 12 hours post operatively which was considered as large and moderate effect size respectively. At 24 hours postoperatively; Prednisolone group didn't seem to differ significantly from placebo group with small effect size and this is may be due to prednisolone half life is from 3 hours to 4 hours. So, in absence of contraindications for corticosteroid administration, the use of single-dose prednisolone appears to be a safe and effective method to reduce postoperative pain. It is possible that these favorable results might help to prevent post-endodontic pain.

Keywords: Prednisolone, Patients, VAS measurement, postoperative pain.

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INTRODUCTION

Endodontic post-treatment pain continues to be a significant problem facing the dental profession, The incidence of this pain is of concern to both the patient and the dentist, Pain resulting from endodontic procedures may last from several hours to several days depending on the damage sustained by the periapical tissue and the nature of the damaging agent [1].

Postoperative endodontic pain is often linked to inflammatory mediators (such as prostaglandins, leukotrienes, bradykinin, and serotonin) that activate sensitive nociceptors, leading to both peripheral and central mechanisms of hyperalgesia. Among inflammatory mediators, prostaglandins play a critical role in the pathogenesis of pulpal and periradicular disease [2, 3].

Management of endodontic pain is multifactorial and directed at reducing the peripheral and central components of hyperalgesia through combined endodontic procedures (non-pharmacological strategies) and pharmacological strategies.

The pharmacological strategies include using long acting local anesthesia, antibiotics, analgesia and glucocorticoids. Corticosteroids are group of drugs that can be used for managing inflammation (and hence pain). Glucocorticoids have been used as an intracanal medication either alone or in combination with antibiotics/ antihistamines, and systemically as a means to decrease pain and inflammation in endodontic patients.

This review focuses on Prednisolone which is one of the synthetic glucocorticoids as they act at multiple sites to inhibit immune and inflammatory reactions by reduction of prostaglandin and leukotriene synthesis. It also suppresses the polymorphonuclear leukocyte chemotaxis.

The optimal oral prednisolone dosage for prevention and control of post- endodontic pain is yet to be determined. The purpose of this study is to evaluate the effect of prednisolone (40 mg) administered as a

single, preoperative oral dose for the prevention and control of postendodontic pain.

The aim of this study was to evaluate the effect of Prednisolone as premedication in controlling post-endodontic pain after single visit treatment of acute irreversible pulpitis using in a randomized controlled trial.

MATERIALS AND METHODS

1) Trial design: Parallel randomized controlled trial.

2) Participants:

2a) Sample size:

40 patients were selected from the outpatient clinic of the endodontic department, Tripoli University.

2b) Eligibility criteria for participants:

i) Inclusion criteria:

- Medically free patients, with good health.- Patient's age between 25-35 years.
- Mandibular molar teeth diagnosed clinically and radiographically as acute pulpitis without apical periodontitis. - Positive patient's acceptance for participation in the study.

ii) Exclusion criteria:

- Analgesic and anti-inflammatory drugs taken within 6 hours before the start of the treatment.- Acute Periodontitis.- Need for prophylactic antibiotic.- Pregnancy or lactation .- Systemic diseases: hypertension, diabetes. - Psychological disturbance.
- Infectious disease.

Patients were asked to follow general instructions:

- To sign a printed consent that explained the aim of the study and obligated the patient to fill the pain diary 6,12,24 hours after root canal treatment accurately and honestly and to return it to the operator due time.
- The patients were instructed basically not to take any analgesic or anti- inflammatory drugs and to report if they took any of them.
- Not to take antibiotics, as previous studies showed no increased incidences of infection following the administration of corticosteroids [4].

2c) Setting and location:

Patients were recruited from outpatient clinic of endodontic department of new building, Faculty of Dentistry, Tripoli University.

The diagnosis of acute pulpitis was depending on the basis of history as well as clinical and radiographic features.

Treatment in all cases was completed in a single visit as following:

Cleaning and shaping were done through rotary system using Revo-S™ files **(**MICRO-MEGA®+, BESANCON cedex, France):

1. The first step comprised an initial penetration of the canal, using a Conventional stainless steel hand instrument k files size 10, 15, and 20 (MANI- MANI, INC. Industrial Park, Utsunomiya, Tochigi, Japan.)
2. The rotation speed of the electric motor used was adjusted between 250-400 rpm and the torque adjusted to 0.8 (according to manufacture instructions).
3. The root canal cleaning and shaping instruments SC1,SC2,SU were used with slow and unique downward movement in a free progression and without pressure accordingly: SC1 till the two third of the working length, SC2 and SU till the whole working length. (according to manufacture instructions).
4. The AS30 and AS35 were used in all root canals till the whole working length in the same way as the cleaning and shaping instruments.
5. In case presented with one distal canal, the preparation was completed till AS40. - Obturation was carried out using the single cone technique with MM-GP Points.

3) Intervention:

The patients were randomly divided into 2 groups: experimental group (A): prednisolone 40 mg and control group (B): placebo . Both should be administrated orally 30 minutes before the root canal therapy.

4) Out comes:

Primary outcome was the degree of post operative pain which measured by visual analogue scale (VAS). It consisted of a 100 mm line (numerical value) anchored by 2 extremes "no pain" and "very severe pain" [5]. Immediately after session patients received pain diary and asked to make a mark on the line that represented their level of pain 6, 12, 24 hours after root canal treatment. After receiving pain diary from the patient, the assessor checked the marks to evaluate the amount of pain reduction.

5) Randomization

It depended on two interrelated aspects, adequate generation of an unpredictable allocation sequence and concealment of that sequence until the trial occurred. The treatment allocation system should thus be set up so that the person enrolling participants did not know in advance which treatment the next person would get. The process was termed as allocation concealment [6].

5a) sequence generation:

Computer sequence generation using site of www.Random.org. And then Random Sequence

Generator was selected to make the randomization.

5b) Allocation concealment mechanism:

Allocation concealment was the process that prevented any study participant or investigator from knowing in advance the treatment to which subjects would be assigned. It is important that the decision to enroll a participant was made in ignorance of the treatment to which they would be assigned, as this knowledge might influence the decision on whether or not to enroll [6].

5c) Implementation:

Mamdoh M generated the random allocation sequence. Ramadan M enrolled participants and assigned them to interventions.

6) Blinding (Masking):

The difference between blinding and allocation concealment was that allocation concealment was to prevent the selection bias (different subjects being entered into the different groups). In contrast, blinding was to prevent the performance and ascertainment bias (different response to treatment, or to measuring effect of treatment due to knowledge of which treatment was received) [6]. In this study blinding was triple blind (Patient, dentist, and assessor). Patient did not know what medication he was taking. Operator and assessor were blinded to the premedication given; the interventions (placebo, prednisolone) each packed in opaque identical containers.

RESULTS

Regarding age, sex, tooth number, number of canals, analgesics, broken file and placebo medication; there was no significant difference between the two groups except for the overextended obturation cases as presented in (Figure 1).

Statistical Analysis

The mean of visual analogue scale in group A was 49.9, 32.025 and 22.075 at 6, 12 and 24 hours respectively. In group B, the mean of visual analogue scale was 18.8, 18.2 and 19.77 at 6, 12 and 24 hours respectively. The standard deviation of group A was 33.14, 32.43 and 27.94 at 6, 12 and 24 hours respectively. In group B, the standard deviation was 33.14, 26.44 and 26.68 at 6, 12 and 24 hours respectively.

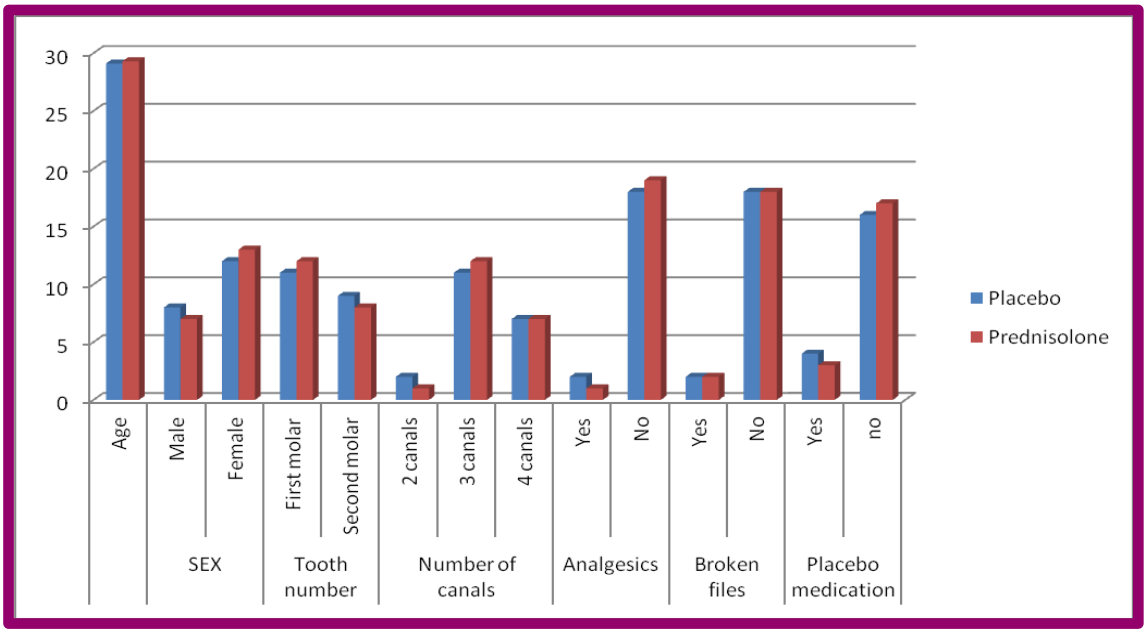

Figure 1: Showes Base line data (age, sex, tooth number, number of canal, analgesics, and broken files)

Comparison between groups at different follow up interval

Null hypothesis:

No difference was found in the Visual Analogue Scale scores between Prednisolone and Placebo groups at 6, 12 and 24 hours post operatively. Since data was not normally distributed, thus Man Whitney U test was used.

RESULTS

At 6 hours post operatively; Prednisolone group (Mdn=0.5) showed lower VAS score compared to placebo group (Mdn=52.5), and difference was statistically significant with large effect size, U=100.5, $p<0.01$, ($r=-0.6$) and (P=0.002*) thus null hypothesis was rejected.

At 12 hours postoperatively; Prednisolone group (Mdn=0.5) didn't seem to differ significantly from placebo group (Mdn=33.3) with moderate effect

size U=97, P<0.05, r=-0.39. (p=0.015*), thus null hypothesis was rejected.

At 24 hours postoperatively; Prednisolone group (Mdn=5.25) did not seem to differ significantly from placebo group (Mdn=7.25) with small effect size, U=132, P>0.05, r=-0.23. (P= 0.16), thus null hypothesis was not rejected as presented in.

CONCLUSION

There was a significant difference in the Mean Visual Analogue Scale scores between Prednisolone and Placebo groups at 6 hours and 12 hours post operatively. As presented in. There was no significant difference in the Mean Visual Analogue Scale scores between Prednisolone and Placebo groups at 24 hours post operatively. As presented in (Figure 2).

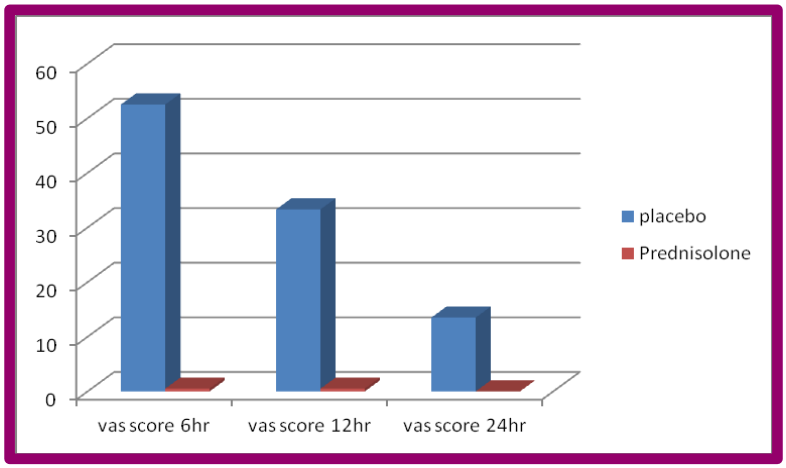

Figure 2: Median values of Visual Analogue Scale score at different follow up periods of Prednisolone and Placebo groups

Comparison within group through follow up interval
In Placebo group:
Null hypothesis:

No difference in Visual Analogue Scale score between follow up period of the same group. (Null hypothesis will be rejected at p value≤0.05).

RESULTS

Visual Analogue Scale score for placebo group decreased through follow up periods and difference was statistically significant p<0.001. Thus null hypothesis will be rejected.

Wilcoxon Signed Ranks Test was used as follow up test. Bonferroni correction was applied and so all effects are reported at 0.016 (significant value≤0.016).

There was n sig. difference between vas score at 6hr (*mdn*=52.5) and vas score at 12hr (*Mdn*=33.3) p>0.016. There was sig. difference between vas score at 12hr (*Mdn*=33.3) and vas score at 24hr (*Mdn*=13.5) p<0.016. There was no sig difference between vas score at 6hr (*Mdn*=52.5) and vas score at 24hr (*Mdn*=13.5) P<0.016.

As presented in Table 6 and Figure 19.

CONCLUSION

There was decrease in Visual Analogue Scale score through follow up period in placebo group and difference was statistically significant. As presented in (Figure 3).

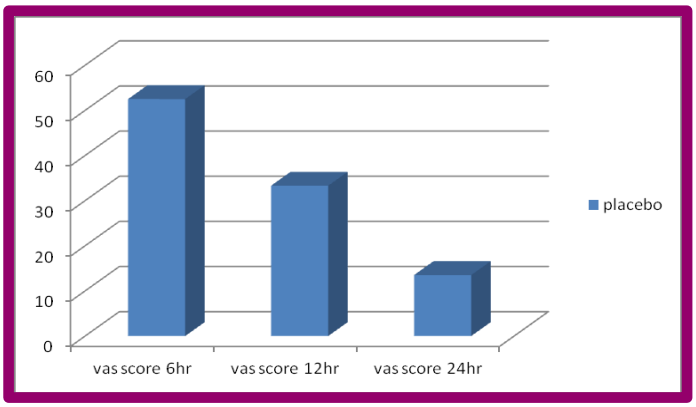

Figure 3: Median and Interquartile Range values of visual analogue scale score at different follow up periods of Placebo group

In Prednisolone group:

Null hypothesis:

No difference in Visual Analogue Scale score between follow up period of the same group. (Null hypothesis will be rejected at p value≤0.05).

RESULTS

There was no significant difference in Visual Analogue Scale score for Prednisolone group through follow up periods p>0.05. Thus null hypothesis will not be rejected.

CONCLUSION

The change in Visual Analogue Scale score for Prednisolone group was statistically non significant. As presented in table (Figure 4).

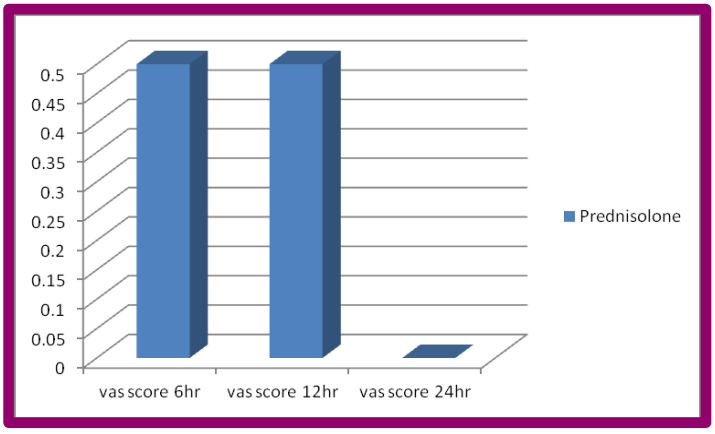

Figure 4: Median and Interquartile Range values of visual analogue scale score at different follow up periods of Prednisolone group

Time to Event Analysis

Null hypothesis:

No difference between Prednisolone and Placebo groups in developing the event of no pain. (Event was set with vas score below 20). Null hyposthesis reject at p value≤0.05.

RESULTS

For placebo group 11 patient developed event (vas score below 20), and 15 patient in prednisolone group.

- Mean time to event in placebo group was 18 hr and 12 hr for prednisolone group.
- 50% of patient in placebo group showed no pain after 24 hr and after 6 hr in prednisolone group.
- There was a significant difference between groups according to log rank test and Breslow test, P<0.05 thus null hypothesis was rejected.

CONCLUSION

There was significant difference between Prednisolone and Placebo groups in developing the event of no pain.

In Figure 5 as Prednisolone group was closer to the time border thus it had a high risk to the event of no pain while Placebo group had a lower risk to event as it was far from time border.

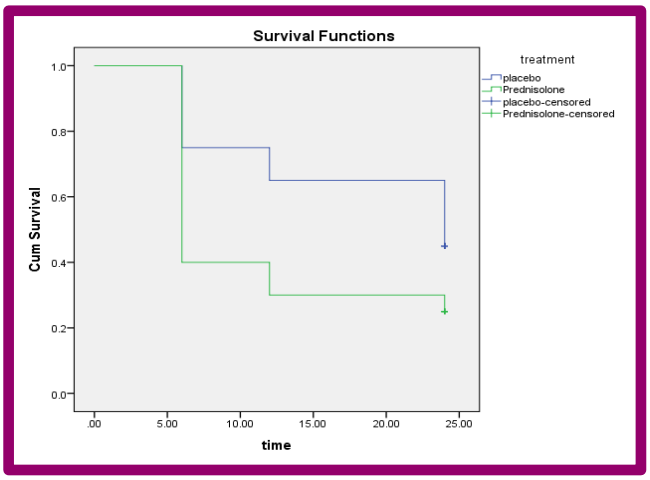

Figure 5: Time to Event Analysis in Prednisolone and Placebo groups

DISCUSSION OF METHODS

This study was conducted as a triple blind randomized study to minimize bias and to allow sufficient comparison between groups. This trial design methodology conforms to the CONSORT statement which is an international consensus guide and checklist to improve reports on randomized controlled trials.

Forty patients with acute pulpitis were enrolled from outpatient clinic of endodontic department, Patients were divided randomly in two experimental groups which received Prednisolone 40 mg (Intervention) and control group (Comparative) which received placebo.

The comparative group was placebo (powder milk packed in capsules). Placebos are pharmacologically inert substances that have no therapeutic effect. They act by alleviating anxiety and are fairly effective in high percentage of cases. A placebo does not have to be a medication it could be a person, a procedure, a place or ritual [7]. In this study, placebo was used to evaluate the effectiveness of prednisolone. It is usually used in drug efficacy studies.

In this study root canal treatment in all cases was completed in a single visit. There are several advantages for single visit root canal treatment as the reduction of chair time without reduction in the quality of treatment [8], absence of disturbance by additional anesthetic injections or replacement of the rubber dam or intracanal medication placement and removal, elimination of time spent by the clinician in refreshing his memory and tactile sensations regarding prepared canal anatomy, tooth lengths. No problem of inter visit leakage due to loss of temporary seal, or any of the accidents that can and do occur between visits. Also, the fees reduction is a welcome addition into day's inflationary society [9].

Oral administration of the treated drug was preferred as this technique was clinically effective and convenient; the use of intramuscular or intravenous injection might have led to discomfort and fear and was not well accepted by some patients [10].

Regarding the best time for drug administration, the pre-operative drug administration was better in pain control than the post operative drug administration [11]. Most patients and dentists would prefer to provide an anti- inflammatory agent immediately before or self administered as needed by the patient after anesthesia has worn off .However, in the present research, prednisolone was administered 30 minutes before conventional root canal therapy. This was due to when the endodontic instruments and irrigating solutions reach the periapical region; the drug will have achieved therapeutic levels in the tissues. According to Jalalzadeh *et al*., corticosteroids must be administrated before the infliction of tissue damage, not during or after endodontic treatment [5].

Root canal instrumentation in this study was done using rotary NiTi system (Revo S), as the effect of nickel-titanium rotary instruments in reducing post-operative pain was proven by Wei *et al*., [12]. The Revo S files were used according to manufacturer instructions in a crown down technique. This technique allowed elimination of debris and microorganisms from the coronal parts of the root canal system thereby minimizing inoculation of apical tissues with contaminated debris and well controlled gradual passive enlargement of the apical part of canal in an apical to coronal direction and created a flared, tapered preparation while reducing procedural errors.

In this study irrigation was accomplished by flushing the canal space with 5.25% NaOCl (diluted to 1:2 NaOCL: distilled water) which was used due to its strong antibacterial properties and its unique ability to dissolve organic tissues [13].

After treatment each patient was dismissed with a placebo (powder milk packed in green capsules) as an analgesic. The patient was instructed to take it

only in the presence of pain and not to take any other medication or antibiotic, If pain persisted Cataflam 50 mg was prescribed and patients who took it would be reported but not eliminated from the trial as intention to treat analysis was used in this trial.

A Visual Analogue Scale was used to evaluate pain intensity; this scale has been used in most of the previous studies that analyzed pain after endodontic treatment [14-16]. The VAS is more sensitive to small changes than simple descriptive ordinal scales.

Discussion of Materials

Prednisolone was the drug particularly selected for this study because of its favorable pharmacokinetic properties; Prednisolone has favorable anti-inflammatory activity than other steroids with low cytotoxicity which is six times lower than Dexamethasone [17].

Revo-S was used in this study due to its special design features which allowed better preparation. The asymmetrical cross section provides less stress on the instrument. The canal axis has 3 cutting edges located on 3 different radiuses. The smaller section allows more flexibility, and offers a better ability to negotiate curves. The asymmetrical cross section increases the available volume for upward debris elimination. The extended helical machining up to the coronal region increases the instrument flexibility. Reduction of the contact lengths of the blade on the dentine reduces stress.

Discussion of Results

The outcome of this study showed that Prednisolone resulted in statistically significant reduction in post endodontic pain at 6, 12 hours post operatively which was considered as large and moderate effect size respectively. This result may be due to that the prednisolone inhibits the production of multiple cells or factors that are important in the production of inflammatory response .This inhibition results from the effect of corticosteroids on gene transcription, and thus causes a reduction in the release of vasoactive and chemoattractive factors, secretion of lipolytic and proteolytic enzymes, extravasation of leukocytes to area of tissue injury and ultimately decreased fibrosis [18]. Which lead to reduction of post endodontic pain. The multiple sites of action of the glucocorticoids is the reason for their greater anti inflammatory and analgesic effects than non steroidal anti inflammatory drugs which are more selective and only act on one site [19].

At 24 hours postoperatively; Prednisolone group didn't seem to differ significantly from placebo group with small effect size and this is may be due to prednisolone half life is from 3 hours to 4 hours [20].

No difference in Visual Analogue Scale score between follow up period of the prednisolone group. In Placebo group visual analogue scale score decreased through follow up periods and difference was statistically significant between VAS score at 6hours and VAS score at 24hours with moderate effect size. No side effects were observed after Prednisolone treatment.

In Prednisolone group 15 patients developed the event of no pain with mean time to event 10 hours, 50% of these patient showed no pain after 6 hours. This is may be due to the favorable anti-inflammatory effect of prednisolone and the 3-4 hours half life of the drug. In Placebo group 13 patients developed the event with mean time to event 19 hours, 50% of these patients showed no pain after24 hours. This is may be due to effect of Placebo psychologically on patients by improving their emotions as feeling comfort as they thought they took an analgesic. There was significant difference between Prednisolone and Placebo groups in developing the event of no pain.

Despite the limitations of this study, it was found that oral administration of Prednisolone 40 mg 30 minutes before endodontic treatment is statistically significant and clinically relevant in controlling and reducing post endodontic pain by 6% at 6 hours and 39% at 12 hours post operatively and thus it is recommended to be used.

Conclusion

Conclusion, in absence of contraindications for corticosteroid administration, the use of single-dose prednisolone appears to be a safe and effective method to reduce postoperative pain. It is possible that these favorable results might help to prevent post-endodontic pain.

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