Postoperative Pain After the Use of a Dexamethasone Rinse as an Irrigant Prior to Obturation

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Recommended Citation

Mahajan, Sushant, "Postoperative Pain After the Use of a Dexamethasone Rinse as an Irrigant Prior to Obturation" (2012). Master's Theses (2009-). Paper 137.
http://epublications.marquette.edu/theses_open/137
POSTOPERATIVE PAIN AFTER THE USE OF A DEXAMETHASONE RINSE AS AN IRRIGANT PRIOR TO OBTURATION

by

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A Thesis submitted to the Faculty of the Graduate School, Marquette University, in Partial Fulfillment of the Requirements for the Degree of Master of Science

Milwaukee, Wisconsin

May 2012
ABSTRACT
POSTOPERATIVE PAIN AFTER THE USE OF A
DEXAMETHASONE RINSE AS AN
IRRIGANT PRIOR TO
OBTURATION

Sushant Mahajan, D.M.D.
Marquette University, 2012

Purpose: This randomized, single-blind pilot study was to determine the effect of
dexamethasone on post-operative pain when used as an intracanal rinse prior to
obturation.

Materials and Methods: Ten adult volunteers were enrolled. They presented to
the Marquette University School of Dentistry for endodontic treatment and experienced
pain from irreversible pulpitis. The patients were randomly assigned to either the control
group that received standard of care treatment or the experimental group that received the
rinse with 4 mg/mL dexamethasone solution prior to obturation. Before and after
treatment, the patients recorded their pain level on the numeric rating scale (NRS).
Recordings were made at baseline, 3, 6, 12, and 24 hours post-operatively. Means and
standard deviations were calculated. Treatment effects were analyzed using repeated
measures ANOVA. Statistical significance was set at $p<0.05$.

Results: Mean pain levels at baseline were 7.2 and 5.6 for the experimental and
control groups, respectively. Patients who received the dexamethasone rinse had mean
post-operative pain levels of 1.4, 0, 0, and 0 at 3, 6, 12 and 24 hours, respectively. The
control group had mean post-operative pain levels of 4.2, 2.6, 2.8, and 1.2 at 3, 6, 12, and
24 hours, respectively. Pain level reductions over time were statistically significant
($p=0.0014$). The overall difference between treatment groups was also statistically
significant ($p=0.0198$).

Conclusion: Endodontic treatment using the standard of care approach lead to
substantial pain relieve within 24 hours. This was further enhanced if the treatment was
followed by a rinse with dexamethasone.
ACKNOWLEDGMENTS

Sushant Mahajan, D.M.D.

I would like to thank my family and friends for their support during the residency. I would also like to thank my co-residents Reid Wycoff, D.D.S. and Erik DeYoung, D.D.S. for making the last 2 years an enjoyable experience. I must thank both Drs. Jim Bahcall and Kris Olsen for their work as program heads. I would also like to thank Dr. Daniel J. Nencka, Dr. Lance Hashimoto, and Dr. Arthur Hefti for their help in editing and revising this manuscript.
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INTRODUCTION

Dentists are employing sedation, nitrous oxide, adequate anesthesia, and oral anxiolytics to aid in relaxing their patients and therefore making the treatment less threatening and more comfortable. Postoperative pain following endodontic treatment, however, continues to be a frequently observed, detrimental sequela. In fact, the prevalence of moderate to severe postoperative endodontic pain was estimated to be between 16 to 25 percent (1-3). There is also a strong relationship between preoperative and postoperative pain. More than 35 years ago, O’Keefe (1) showed that patients with moderate to severe pain prior to treatment were five times more likely to experience moderate to severe pain postoperatively.

Postoperative endodontic pain has been linked to inflammatory reactions that last for several days after treatment. The mechanisms involved in the development of postoperative pain are complex; however, it is generally understood that the inflammatory response to over instrumentation is one of the major contributing factors (4). Over instrumentation during mechanical debridement can introduce irritants such as, microorganisms, bacterial toxins, pulpal degeneration products, as well as caustic intracanal irrigants and medicaments into the surrounding periapical tissues (4).

Inflammation is a defense reaction to the presence of a harmful stimulus. It is characterized by a series of vascular events that depend more upon the severity of the injury than the kind of stimulus. The reaction usually starts with a brief period of vasoconstriction that is followed by vasodilation leading to hyperemia and exudation of plasma proteins. Mediators linked to the vascular response and to the initiation of pain include prostaglandins, leukotrienes, bradykinin, substance P, and serotonin (5).
Glucocorticoids are potent anti-inflammatory agents that suppress the acute phenomena of inflammation, such as, edema, fibrin deposition, capillary dilation, and migratory and phagocytic activity of leukocytes. They also stem the chronic manifestation of inflammation by reducing proliferation of capillaries, fibroblast, and collagen deposition (5). Glucocorticoids inhibit the synthesis and release of arachidonic acid and its metabolites, such as, prostaglandins, thromboxane A₂, prostacyclin, and leukotrienes. Along with the above they also inhibit platelet activating factor, tumor necrosis factor and interleukin (5).

Dexamethasone is a synthetic form of the glucocorticoid class of steroid drugs. It is 25 times more potent in reducing inflammation than the naturally occurring cortisol hormone (6). It acts as an anti-inflammatory and immunosuppressant (7). Like most glucocorticoids, it inhibits phospholipase A₂ from converting phospholipids to arachidonic acid, which is a critical first step in the inflammatory pathway (7). The ability of glucocorticoids to directly and indirectly prevent pain is determined by their capacity to suppress the precursors of inflammation and to suppress tissue levels of bradykinin (5, 7). The suppression of these mediators prevents the increase in vascular permeability, thereby reducing tissue fluid accumulation with a resultant reduction in tissue pressure and pain (8, 9).

Due to its anti-inflammatory properties, dexamethasone has been used to reduce post-treatment swelling and pain following endodontic treatment. Dexamethasone has a plasma half-life of 200 minutes and a tissue half-life of 75 hours (10). No adverse reactions were reported with the use of dexamethasone in a variety of endodontic applications (11-15). Several administration modes of dexamethasone were reported in
the past. Krasner and Jackson (11) tested the oral administration (p.o.) of dexamethasone or a placebo. In comparison to patients who received the placebo, the patients who were prescribed dexamethasone reported reduced post-treatment endodontic pain 8 and 24 hours later. Marshall and Walton (12) injected 4mg/mL of dexamethasone intramuscularly (i.m.) at the completion appointment of the endodontic treatment and showed significant reduction in post-treatment pain. They found that significant pain reduction occurred after 4 and 24 hours but not after 48 hours. The recurrence of pain led them to conclude that the therapeutic effect of dexamethasone may diminish over time. Glassman et al. (13) compared interappointment administration of dexamethasone p.o. and a dextrose placebo p.o. in patients with asymptomatic inflamed pulps. They found that dexamethasone effectively inhibited pain between appointments. Moskow et al. (14) were among the first to place a corticosteroid within the root canal to deliver the medication locally. They found a statistically significant difference between the dexamethasone group and the placebo group after 24 hours. Chance et al. (15) also placed the medicament within the root canal. In contrast to the previously mentioned authors (11-14), they used prednisolone. Although prednisolone is less potent inhibitor of inflammation than dexamethasone, the results were still encouraging. Furthermore, Chance et al. (15) determined that patients with vital pulp tissue before treatment responded to the steroid with less postoperative pain than patient who used placebo.

The most important difference between the study presented in this thesis and the ones conducted by Moskow et al. (14) and Chance et al. (15) is that all endodontic treatment was completed in a single appointment. Along with the advent of rotary nickel-titanium systems, improvements in irrigation dynamics and delivery systems have
facilitated mechanical instrumentation and disinfection of the root canal. A recently conducted randomized clinical trial compared the more convenient single visit with the multiple-visit endodontic treatment. The study focused on bacteriological outcomes and showed no difference in treatment success between the modalities (16).

Therefore, the purpose of the present study was to determine the effect on post-operative pain of standard of care endodontic treatment in comparison to standard of care plus dexamethasone when used as an intracanal rinse prior to obturation as part of a single-visit procedure.
MATERIALS AND METHODS

A convenience sample of 2 male and 8 female volunteers, with an average age of 35 years (range: 23-56 years), participated in this prospective, randomized clinical pilot study. Participants were determined to be in good health as per health history and oral questioning. Qualifying patients met the following criteria:

Inclusion:

- Older than 18 years of age;
- Being a patient of record;
- Vital tooth with a pulpal diagnosis as symptomatic irreversible pulpitis;
- A pain level of 4 or higher on the numeric rating scale (NRS);
- Single appointment root canal therapy;
- Potential to achieve patency in all canals as determined by pre-operative radiograph;
- Able to understand and provide informed consent.

Exclusion:

- Radiographic evidence of periapical pathology;
- Female patients who were pregnant or nursing;
- History of peptic ulcer or gastrointestinal bleeding;
- Known hypersensitivity or allergic reactions to non-steroidal anti-inflammatory drugs or corticosteroids;
- At risk for renal failure or renal impairment;
- History of significant medical conditions (American Society of Anesthesiologist class II or higher excluded),
• Having a recent history of or currently taking anti-inflammatory, antibiotic, or narcotic drugs.

The Marquette University Institutional Review Board approved the study (Protocol HR-2195, see Appendix), and written informed consent was obtained from each patient prior to enrollment. Any endodontic treatment was completed in the morning between 9 a.m. and 4 p.m. to facilitate data collection requirements.

Teeth included in this study had a diagnosis of symptomatic irreversible pulpitis with moderate to severe preoperative pain. Candidate teeth were tested with Endo-Ice (Hydenic Corp, Akron, OH) to determine the pulpal status. A preoperative radiograph was taken at the treatment appointment to rule out periapical pathology. In addition, a comprehensive clinical examination was completed to rule out intra/extraoral swelling, presence of a sinus tract, or other major pathology.

Prior to anesthetizing the treatment area, each patient was asked to rate his or her pain on a numeric pain intensity scale otherwise known as a numeric rating scale (NRS) (Figure 1). The scale was from 0, being no pain, to 10, being the worst possible, unbearable, excruciating pain. The NRS score was considered the baseline pain level of the patient.
Patients who met all inclusion and none of the exclusion criteria were randomly assigned to one of two groups:

- Group 1 was the experimental group that received the dexamethasone rinse in addition to standard of care therapy;
- Group 2 was the control group who received standard of care therapy only.

Randomization tables were generated with the aid of the (pseudo) random number generator in Microsoft® Excel® for Mac 2011 (Microsoft Corp., Redmond (WA)). A formula was set to randomly select an integer between 1 and 10 without replacement. Drawing an even number indicated that the patient would be assigned to Group 1 while drawing an odd number resulted in the assignment to Group 2.

At the initiation of treatment, patients were anesthetized using 1.7-5.1 mL of 2% lidocaine with 1:100,000 epinephrine (Xylocaine; AstraZeneca LP, DENTSPLY, York (PA)) via local infiltration or inferior alveolar nerve block, depending on tooth location. Prior to beginning the endodontic therapy, anesthesia was confirmed by retesting the tooth with Endo-Ice. After confirmation of complete anesthesia, a rubber dam was placed, the occlusion was adjusted and the tooth was accessed. The working length of
the root canal instruments was determined and the canal(s) were prepared with hand and rotary instruments. Each canal was prepared to at least a size #20 hand file, along with 5.25% sodium hypochlorite (NaOCl) irrigation. A modified crown-down technique was employed to enlarge the canal in the coronal, middle and apical thirds using RaCe (Brasseler USA, Savannah (GA)) and EndoSequence (Brasseler USA, Savannah (GA)) rotary files. After the chemo-mechanical cleaning was completed, a final irrigation with 5.25% NaOCl, 17% ethylenediaminetetraacetic acid (EDTA), and 2% chlorhexidine (CHX) was performed. This was followed by ultrasonic agitation using a size #15 ultrasonic K-file (Satelec, Merignac, France). Then, the canal was dried with sterile paper points. In Group 2, the canals were obturated as described below. In Group 1, prior to obturation, each canal was rinsed with 1mL of 4 mg/mL dexamethasone sodium phosphate aqueous solution (Luitpold Pharmaceuticals, Shirley (NY)). Patency of the canals was rechecked at this point with a hand file of size #10 or greater. The dexamethasone solution was then agitated with a size #15 ultrasonic K-file for 30 seconds. The canals were dried again with sterile paper points.

Obturation was completed by vertical condensation with Brasseler EndoSequence .06 ISO sized gutta-percha (Brasseler USA, Savannah (GA)) and AH Plus sealer (DeTrey, Dentsply, Ballaigues, Switzerland). A sterile cotton pellet was placed in the pulp chamber and the access opening was sealed with Cavit temporary filling material (Cavit G; 3M ESPE, Seefeld, Germany). All treatment was provided by five residents enrolled in the advanced specialty education program in Endodontics at Marquette University School of Dentistry.
After completion of the endodontic treatment, patients were given post-operative forms that included rescue medication instructions, explanation of possible adverse events, and pain level score collection instructions. As rescue medication, all patients received 4 tablets of 600mg ibuprofen each, to be taken only if pain levels reached or exceeded 6 on the NRS. In addition, if pain was not manageable, patients were informed to contact the principal investigator by phone. Patients were instructed to report also any swelling, fever, or persistent infection. For data collection, patients were requested to record NRS values at exactly 3, 6, 12, and 24 hrs post-operatively. They were also instructed to record the amount of rescue medication and when it was taken. The principal investigator contacted the patients 24-hours post-operatively for data collection.

In view of the small sample size of this pilot study, statistical analyses were limited to computation of means and standard deviations. In addition, a repeated measure analysis of variance was used to investigate overall statistical between-group trends and to generate information that could be used for the planning of a pivotal randomized clinical trial. The patient was used as unit for all statistical calculations. Microsoft Excel® for Mac 2011 (Microsoft Corp., Redmond (WA)) and JMP® 9 (SAS Institute Inc. Cary (NC)) were used for data analyses and presentations.
RESULTS

All patients who enrolled on the study also completed it and could be reached 24 hours post-operatively to obtain all pertinent data. Teeth available for endodontic treatment included 6 molars and 4 premolars. The patients assigned to the control group reported a mean pre-operative pain level of 5.6 ± 1.5 (mean ± 1 standard deviation) as assessed using the NRS. The patients who were randomized to the experimental group reported a mean pre-operative pain level of 7.2 ± 1.6. The difference between treatment groups in mean pain levels at baseline was statistically not different ($p=0.148$). Nine patients reported preoperative percussion sensitivity. Self-reported pain levels at various time intervals over the 24-hour observation period are presented in the table.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>3hrs</th>
<th>6hrs</th>
<th>12hrs</th>
<th>24hrs</th>
<th>Rescue medication taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Patient 2</td>
<td>8</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Patient 3</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patient 4</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient 5</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Control Group**

| Patient 6 | 5        | 0    | 0    | 0     | 0     | 0                      |
| Patient 7 | 8        | 3    | 0    | 0     | 0     | 1                      |
| Patient 8 | 9        | 4    | 0    | 0     | 0     | 1                      |
| Patient 9 | 8        | 0    | 0    | 0     | 0     | 0                      |
| Patient 10| 6        | 0    | 0    | 0     | 0     | 0                      |

**Experimental Group**

Table. Pain level data for patients over a 24-hour period.

The mean NRS pain levels of each treatment group, as registered over the 24-hour observation period, are shown in Figure 2. Patients in the experimental group reported fewer pain incidents and less post-operative pain than patients in the control group.

Overall, the mean pain levels of the two treatment groups were statistically significantly
different ($p=0.0198$). In addition, the pain reduction achieved in response to endodontic intervention was clinically and statistically highly significant ($p=0.0014$).

Figure 2. Mean pain levels at the observation intervals for the dexamethasone and control group.

In the experimental group, 3 patients reported they were pain-free at 3 hours post-operatively. The other two patients reported mild pain. All 5 patients reported as being pain-free for the remaining observation periods. Figure 3 represents the NRS pain levels as reported by each patient over the 24-hour observation period. Patients of the control group and the experimental group are displayed in the panels on the left side and right side, respectively.
Figure 3. Tracking of pain over observation period for individual patients
Five patients reported taking the rescue medication, including 3 patients in the control group and 2 patients in the experimental group. Two of the control group patients reported taking the rescue medication twice, once between treatment and 3 hours and the second time during the interval between 3 and 6 hours post-operatively. The third patient reported taking the rescue medication also between 3 and 6 hours post-operatively. The patients in the experimental group reported taking the rescue medication between treatment and the time they recorded the 3-hour NRS scores.

All 5 patients of the control group reported mild to moderate pain 3 hours post-operatively. Only 2 patients were completely pain-free 24 hours after receiving the endodontic treatment. The other 3 patients reported of mild pain still present.

The endodontic treatments of all patients were completed uneventfully. The dexamethasone rinse was tolerated well. No acute adverse side effects, such as swelling, were reported during the 24-hour observation period of the study.
DISCUSSION

The goal of endodontic therapy is to relieve pain and prevent the systemic spread of infections. Post-operative pain following endodontic treatment of vital teeth most likely is caused by a combination of residual inflammatory mediators still present immediately following treatment. Such mediators can be the result of pulpal damage, but they can occur also due to over-instrumentation. Therefore, to control the initiation of pain clinically, an effective method would be to inhibit the inflammatory process.

With the above in mind this pilot study was conducted to determine if the use of dexamethasone as a pre-obturation rinse is effective in reducing post-operative pain. By itself, this is not a novel approach to manage post-operative endodontic pain. In the past, several studies were conducted with the use of a corticosteroid as an intracanal medicament (14,15). However, in these studies the medication was administered at the first treatment appointment, after which the tooth was obturated during a second appointment, allowing extended contact of the medicament with the periapical tissue. The studies clearly showed that post-operative pain was reduced when compared to a placebo. A survey of the members of the American Association of Endodontists showed that 55.8 percent of endodontists completed root canal obturation on the first visit in cases that presented with irreversible pulpitis (17). Hence, the novelty of the present study as compared to earlier experiments was to conduct the full endodontic treatment, including medication and obturation, in a single appointment. Therefore, the present study was conducted to determine if the use of a corticosteroid rinse was still an effective treatment modality with the hypothetical reduced contact time with the periapical tissue.
The results of the present study suggest that the proposed incorporation of a dexamethasone rinse can reduce post-operative pain level and duration in comparison to a non-medicated control group. All subjects of the dexamethasone group showed complete pain relief 6 hours post-operatively. Patients in the control group, on the other hand, reported pain present throughout the observation period.

At baseline, the mean pain level was slightly higher for the experimental group than for the control group. Although the difference was quite large, it was statistically not significant and can be explained by chance. However, this should not be interpreted as a failure of the random allocation process used in the study. Random assignment can lead to poorly balanced treatment groups at baseline, in particular when the sample size is very small, as was the case in the present study.

The present study’s findings agree with the results published by Moskow et al (14). They found that 84 percent of the patients on dexamethasone medication reported no pain at the end of the first 24-hour period of observation. Similarly, Chance et al. (15) found that 63 percent of the patients reported no pain after 24 hours even though the less potent prednisolone was used. In both studies, patient monitoring started 24 hours post-operatively, and therefore the short-term effect of the medication was not studied.

In the present study, patients in the experimental group noted complete pain relief as early as 3 hours post-operatively. The effect continued until the end of the 24-hour observation period. Even though the observation period was of limited duration, it can be hypothesized that the pain relief could last up to 75 hours. The half-life time (t½) of dexamethasone in connective tissue is about 75 hours, i.e., about 12-times greater than its t½ in plasma. This would indeed support the use of dexamethasone locally as opposed to
its systemic administration via plasma delivery. However, additional studies, extending the observation period beyond 72 hours, would be required to validate the claim.

Adverse effects inherent to the use of corticosteroids must be considered before using the drugs in endodontic practices (18-21). For example, corticosteroids can increase the risks of infection. In response to this concern, antibiotics have been prescribed in combination with steroids (18-21). However, such an approach appears to bear even more risk than using steroids or antibiotics alone. To minimize the risks of infection, this study was restricted to teeth with vital pulps. Teeth showing periapical radiolucency were also excluded because corticosteroids affect bone healing. In the present study, no patient reported fever, malaise, lymphadenopathy, or fluctuant swelling with or without the use of the rinse. However, a much larger study would be needed to assess this and other steroid-associated risks.

A shortcoming of this study was its small sample size. In fact, at the onset of study planning, a much larger available patient cohort was anticipated. In hindsight, the difficulty to recruit a larger sample was the result of extremely carefully chosen inclusion and exclusion criteria, which eliminated many potential study candidates. One way to improve on the recruitment could be to provide an incentive for patients to participate in the study. Another possible improvement to the study would be the use of a double-blinded treatment approach. This could be achieved by adding a placebo rinse in the control group, such as sterile saline. Another shortcoming of this study was the selected short observation period of 24 hours. It should be extended to determine the full extent of the therapeutic effect of the drug, i.e., to at least 96 hours, assuring that the majority of the drug has been eliminated from the periapical tissues. Similarly, a longer-term follow
up on patients would allow studying whether any signs of recurring infection, attributable to the use of dexamethasone, can be observed. Last but not least, the collection of patient-generated study information should not be handled over the phone and by the principal investigator to assure full compliance with good clinical research practice.
CONCLUSION

The findings of this study are encouraging, and corroborate those of similar, previously published studies. The patients on the dexamethasone rinse appeared to show a greater decrease in pain levels over the observation period when compared to the control group. A larger study is necessary to allow a more precise assessment of dexamethasone-associated effects and side-effects.
BIBLIOGRAPHY


December 9, 2011

Dr. Sushant Mahajan
School of Dentistry

Dear Dr. Mahajan:

Your protocol number HR-2195, titled, “Postoperative Pain after the Use of a Dexamethasone Rinse as an Irrigant Prior to Obturation,” received full approval with contingencies on June 16, 2011 from the Marquette University Institutional Review Board, and final approval of all IRB requested changes on September 29, 2011. The Office of Research Compliance received the mandatory training documentation on December 8, 2011.

Your IRB approved consent form is enclosed with this letter. Use the stamped copies of this form when recruiting research participants. Each research participant should receive a copy of the stamped consent form for their records. Each participant must also sign a HIPAA Authorization form.

Subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when conducting your research. This study is currently approved for 130 subjects.

If you need to increase the number of subjects, add research personnel, or make any other changes to your protocol you must submit an IRB Protocol Amendment Form, which can be found on the Office of Research Compliance web site: http://www.marquette.edu/research/compliance/research/irb/forms.shtml. All changes must be reviewed and approved by the IRB before being initiated, except when necessary to eliminate apparent immediate hazards to the human subjects. Any public advertising of this project requires prior IRB approval. If there are any adverse events, please notify the Marquette University IRB immediately.

Your approval is valid until June 15, 2012. Prior to this date, you will be contacted regarding continuing IRB review.

If you have any questions or concerns, please do not hesitate to contact me. Thank you for your time and cooperation.

Sincerely,

Amanda J. AHMAD
IRB Manager & Interim Compliance Officer

cc:  Dr. Christopher Okunseri, IRB Chair
     Dr. Kris Olsen, DENT
     Dr. Arthur Heff, DENT

Attachment