

# Prostaglandin E2 in Apical Tissue Fluid and Postoperative Pain in Intact and Teeth with Large Restorations in Two Endodontic Treatment Visits

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## SUMMARY

**Introduction** Acute periapical inflammation is the most common cause of postoperative pain developing as a result of mechanical, chemical and/or microbial injury of periapical tissue. The major inflammatory event responsible for periapical pain is increased vasodilatation and vascular permeability, partly caused by prostaglandin E2, with consequent edema, which leads to the compression of nerve fibers.

**Objective** The aim of this study was to determine the concentrations of prostaglandin E2 in apical tissue fluid after endodontic treatment of intact and teeth with large restorations and to compare it with the occurrence and intensity of postoperative pain.

**Methods** Single-rooted teeth of 24 patients, selected for this study, were distributed into two groups: intact (group 1, n=27) and asymptomatic teeth with large restorations (group 2, n=20). Clinical examination of the involved teeth included the electric pulp test, recording pain on percussion, spontaneous pain, and a radiographic examination. Samples of apical tissues fluid were obtained from root canals at two treatment visits, and prostaglandin E2 concentrations were measured using radioimmunoassay. Pain intensity was assessed by visual analogue scale.

**Results** Prostaglandin E2 concentrations at the second visit, in teeth with large restorations, was significantly higher (36%) than at the first treatment visit (Wilcoxon signed rank test,  $p < 0.05$ ). Occurrence and intensity of spontaneous pain after the first visit were significantly higher in group 2 ( $p < 0.05$ ) than in group 1.

**Conclusion** These results suggest that the increased prostaglandin E2 concentration, caused by endodontic treatment of teeth with large restorations, is well correlated with the intensity of postoperative pain.

**Keywords:** prostaglandin E2; endodontic treatment; pain; vital teeth

## INTRODUCTION

Postoperative pain after endodontic procedures is defined as pain of any degree that occurs after the initiation of root canal treatment [1]. Acute periapical inflammation is the most common cause of postoperative pain developing as a result of mechanical, chemical and/or microbial injury of the pulpal and periapical tissues [2]. Mechanical and chemical injuries are usually associated with iatrogenic factors, such as over instrumentation, apical extrusion of irrigants or medications. Microbial insult can be coupled with iatrogenic factors, and it can sometimes occur even when the root canal procedures have been judicious and careful [3].

When periapical tissues are injured various kinds of inflammatory mediators, such as histamine, cytokines, neuropeptides, lysosomal enzymes, nitric oxide, oxygen derived free radicals, plasma derived factors, including prostaglandins are released [4]. Some mediators can cause pain by direct effects on sensory nerve fibers, such as histamine [5], while others modulate pain through decreased threshold of nociceptors, such as prostaglandin E2 (PGE2) and prostaglandin F2 $\alpha$  (PGF2 $\alpha$ ) [4]. It has been stated that the ma-

ior inflammatory event responsible for periapical pain is the increased vasodilatation and vascular permeability – partly caused by PGE2 and PGF2 $\alpha$ , with consequent edema, which leads to compression of nerve fibers [6, 7]. Cyclooxygenase (COX) catalyses the prostaglandin synthesis from arachidonic acid. Whereas the constitutively expressed COX-1 is important for homeostasis, COX-2 is up-regulated in inflammation and diseases. Increased tissue COX-2 expression and PGE2 production are frequently used as markers of inflammation [8, 9, 10]. Periapical tissues exudates taken from root canals contain locally produced mediators and should reflect the immune processes that occur as a result of endodontic treatment or injured periapical tissue [11].

Several studies investigated the presence of PGE2 in periapical exudates as the diagnostic marker of periapical periodontitis in teeth with or without periapical lesions [12, 13, 14]. In experimentally induced inflammation of rat dental pulps, it has been demonstrated that healthy and inflamed pulps respond differently, where inflamed pulps are characterized with increased production of PGE2 in contrast to healthy pulps [15]. On the other hand, Mohorn et al. [16] showed that after pulp extirpation and instru-

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mentation of the root canals of healthy dog teeth, the pressure at the apices of the teeth characteristically fluctuated over an eight-hour period as a result of the fluid emanating from the periapical area.

However, there are no data concerning the relationship between the presence of PGE2 in apical tissues fluid caused by endodontic treatment of intact teeth or vital teeth with large restorations and the presence of postoperative pain in humans. Interestingly, endodontic treatment of such teeth is indicated only for prosthodontic reasons and the study of De Quadros et al. [17] has shown that such treatment accounts for 9% of endodontic treatments.

## OBJECTIVE

Objective of this study was to measure PGE2 concentrations in apical tissue fluids after two-visit endodontic treatment of teeth with vital pulps, intact or with large restorations indicated for prosthetic restorations, and to correlate it with the incidence and intensity of postoperative pain.

## METHODS

### Patients

Patients scheduled to undergo endodontic treatment due to prosthodontic indications at the Department of Restorative Odontology and Endodontics, Faculty of Dental Medicine, University of Belgrade were selected for this study. The medical histories of all patients were noncontributory. A total of 47 single-rooted vital teeth of 24 patients were clinically examined. Of 24 patients, 11 were male and 13 were female; mean age was 56.5 years with a range of 32 to 75 years. Official approval from the Faculty of Dental Medicine Ethic Board was obtained, and all participants gave written consent to participate in the study.

### Clinical findings

Clinical examination of the involved teeth included the electric pulp test, recording pain on percussion, spontaneous pain, and radiographic examination. Only vital symptom free teeth were selected for this study. Two investigators with similar clinical experience collected all clinical data and apical tissue fluids.

Teeth were divided into two groups. Group 1 contained 27 intact teeth. The teeth were placed into this group based on the following criteria: a verbal history confirmed no history of pulpal pain; a clinical and radiographic examination assured that these teeth had no caries, restorations, wear facets, or periodontal disease; and the teeth tested vital with an electric pulp tester (Digitest TM, Parkell Inc, Edgewood, NY, USA). Group 2 consisted of 20 asymptomatic teeth with large restorations. Teeth were placed into this group based on the following criteria: a verbal history confirmed no history of pulpal pain, clinical and radiographic exami-

nation determined the presence of large amalgam or composite restorations, no pulp exposure, no signs of periapical pathosis, and there was no sensitivity to percussion.

### Sampling of apical tissue fluid

After administering local anesthesia the involved tooth was isolated with a rubber dam. Penetration of the pulp chamber and unroofing were made using low speed round burs (Jota AG, Rüthi, Switzerland). Working length was established using apex locator, Root ZX (J. Morita, Kyoto, Japan). Following the measurement of working length, the root canal was instrumented with ProTaper® (Dentsply Maillefer, Ballaigues, Switzerland) nickel titanium rotary files. EDTA gel (Canal+, Saint-Maur-des-Fossés Cedex, France) was used and the root canal was irrigated with 1% NaOCl.

Apical tissue fluid samples were taken from the tooth at two treatment visits in a 3-day interval during the root canal treatment. After the root canal was dried with sterilized paper points, sequentially two #40 paper points (absorbent paper points, Kerr Manufacturing Co, Romulus, MI, USA) were inserted into the root canal at the working length and each paper point was held for 30 s. The wetted length of each paper point was measured immediately upon removal. Each paper point was placed in a microfuge tube (SARSTEDT AG & Co, Germany) containing 150 µl of 10 mM phosphate-buffered saline, and the tube was vortexed for 30 s. After centrifugation for 10 min at 5000×g, 4°C, the supernatant was collected and stored at -80°C until the measurement of PGE2 concentrations. The second visit was scheduled in three days time, when the sampling procedure was repeated as described above. The presence of spontaneous pain after the first treatment visit and pain on percussion at the second treatment visit were recorded.

### Pain assessment

Subjects were asked to rate their perception of worst postoperative pain on the visual analogue scale (VAS) once the effect of anesthesia wore off after the first treatment visit. For this reason, subjects were given a printed questionnaire and asked to place a mark on a 100-mm line labeled from “No pain” to “Maximum imaginable pain”. They were asked to adjust the length of VAS line in respect to an anchor point, so that the line length and pain intensity were proportional. Presence of pain on percussion was registered at the second treatment visit.

### Measurement of PGE2 concentrations

The PGE2 concentrations in the collected supernatants were measured by Prostaglandin E2 (125I) RIA Kit (PerkinElmer Life Sciences, Boston, MA, USA) according to the manufacturer's instructions at the Institute for the Application of Nuclear Energy – INEP, Belgrade, Serbia. The apical tissue fluid samples were diluted in an assay buffer to appropriate

dilution and incubated with [<sup>125</sup>I] PGE<sub>2</sub> and rabbit anti-PGE<sub>2</sub> antibody overnight at 4°C in a polypropylene tube (Spektar, Čačak, Serbia). The antigen-antibody complex was precipitated by the addition of 1 ml of 16% polyethylene glycol in 50 mM PBS (pH 6.8) and centrifuged for 30 min at 2000 g. The radioactivity incorporated into the precipitate was counted in a gamma counter (Wallac Wizard 1470, PerkinElmer, Boston, USA). The PGE<sub>2</sub> concentration of each sample was determined by the standard curve.

### Statistical analysis

Wilcoxon signed-ranks test with continuity correction was used to compare PGE<sub>2</sub> concentrations within the groups between two treatment visits. To evaluate statistical difference among different groups, Fisher exact test and Wilcoxon rank-sum test with continuity correction were used. All statistical analysis were performed using R version 2.8.1 software.

### RESULTS

Table 1 shows PGE<sub>2</sub> concentrations in the apical tissue fluids for the two groups at two treatment visits. In intact teeth (group 1) the concentration of PGE<sub>2</sub> in apical tissue fluid was for 21% higher at the second treatment visit than at the first treatment visit. The observed increase was not statistically significant. However, in teeth with large restorations (group 2) the concentration of PGE<sub>2</sub> at the second treatment visit was significantly higher (36%) than at the first treatment visit (Wilcoxon signed-ranks test,  $p < 0.05$ ). Also, when the entire population of treated patients was taken into account, the change in PGE<sub>2</sub> concentrations in apical tissue fluid at the second treatment visit was found to be significant by the Wilcoxon signed-ranks test ( $p < 0.05$ ). There were no significant differences in the concentration of PGE<sub>2</sub> in apical tissue fluid between the groups at either treatment visits (Table 1).

Table 2 shows the presence and intensity of spontaneous pain, measured by VAS after the first treatment visit,

and also the presence of pain on percussion at the second treatment visit in both groups. After the first treatment visit spontaneous pain was present in about 15% in group 1 and 45% in group 2. The observed difference in the occurrence of pain between the studied groups was statistically significant (Fisher exact test,  $p < 0.05$ ). The intensity of spontaneous pain after the first treatment visit was found to be significantly higher in group 2 than in group 1 (Exact Wilcoxon rank-sum test,  $p < 0.05$ ). The difference between the groups in the presence of pain on percussion at the second treatment visit was not statistically significant. Spontaneous pain at the second treatment visit was absent (Table 2).

### DISCUSSION

Some data show that pulps of asymptomatic human teeth, with large restorations and/or caries, have a significantly higher concentration of PGE<sub>2</sub> than the pulps of intact teeth [18]. The present study shows no significant differences in the concentration of PGE<sub>2</sub> in apical tissue fluids between the intact and teeth with large restorations. This may be the consequence of strict inclusion criteria employed in the recruitment of clinical cases. Namely, in the group of teeth with large restorations the inclusion criteria excluded teeth with clinical signs of pulp inflammation, which may have yielded higher levels of PGE<sub>2</sub>.

Comparing the concentrations of PGE<sub>2</sub> at the first and the second treatment visit, an increase in PGE<sub>2</sub> at the second with respect to the first treatment visit was observed, which was significant in teeth with large restorations, but not in the intact teeth. It was postulated that this increase of PGE<sub>2</sub> is primarily the result of mechanical injury of the periodontal ligament during endodontic instrumentation. It is of interest that animal studies have suggested that mechanical and inflammatory injuries of periodontal ligament cause increased expression of COX-2 in ligament fibroblasts which are responsible for PGE<sub>2</sub> production [10, 19, 20]. Moreover, Shimizu et al. [21] demonstrated that tension force induced expression of COX-2 in human periodontal ligament cells and that this induction was responsible for the augmentation of PGE<sub>2</sub> production. In the study of human teeth, with or without periapical lesions, Schimauchi et al. [13] found decreased concentration of PGE<sub>2</sub> in periapical exudate samples taken during the course of root canal treatment as the result of endodontic treatment. In another study, Alptekin et al. [14] have reported increased PGE<sub>2</sub> level in periapical exudates at the second treatment visit in endodontically treated teeth, and postulated that canal instrumentation is the cause of exacerbation of apical inflammation.

The main goal of endodontic treatment includes removal of remaining pulp tissue to the level of the apical foramen. Clinicians are guided by radiographs and apex locators, but it is impossible to know where the pulp tissue terminates and if all pulpal cells are removed, especially at the level of the apical ramifications. A recent study of Ricucci and Siqueira [22] demonstrated that histological

**Table 1.** PGE<sub>2</sub> concentrations in apical tissue fluids of two groups

Teeth	Number of teeth	First visit (mean±SD, pg/0.1 ml)	Second visit (mean±SD, pg/0.1 ml)
Group 1	27	3.99±1.6	4.82±2.1
Group 2	20	3.62±1.2	4.92±1.2*
Total	47	3.83±1.5	4.86±1.7**

\*  $p < 0.05$ , Wilcoxon signed rank test with continuity correction:  $V = 284.5$

\*\*  $p < 0.05$ , Wilcoxon signed rank test with continuity correction:  $V = 41$

**Table 2.** Spontaneous pain and pain on percussion at two treatment visits

Teeth	Pain after the first visit			Pain on percussion at the second visit (N)	
	VAS (mean±SD)	Spontaneous pain (N)		Present	Absent
		Present	Absent		
Group 1	1.04±2.5	4	23	15	12
Group 2	5.2±7.3*	9**	11	11	9

N – number of teeth

\*  $p < 0.05$ , Exact Wilcoxon rank sum test:  $W = 178.5$

\*\*  $p < 0.05$ , Fisher exact test

condition of the tissue contained in the apical ramifications reflected the condition of the pulp in the main canal. Having in mind these relevant clinical and histological data, the significantly increased level of PGE2 in the apical tissue fluid from teeth with large restorations, at the second treatment visit, could also be attributed to the increased synthesis of PGE2 by pulpal cells that remained within the apical ramifications after endodontic treatment. At the same time, there is no significant increase of PGE2 concentration in the apical tissue fluid in intact teeth, where, according to Ricucci and Siqueira [22], when healthy pulp tissue is present in the main canal, healthy tissue is found throughout apical ramifications. On the other hand it is interesting to note that weak expression of various types of adhesion molecules for leukocyte migration is observed in the microvascular endothelium in both healthy and inflamed human pulps, indicating that apparently healthy dental pulp may be mildly inflamed [23].

Results have also shown that tendency of increasing level of PGE2 in apical tissue fluid in teeth with large restorations between two treatment visits correlates well with a significantly higher incidence and severity of spontaneous pain in these teeth after the first treatment visit. Prostaglandins are known to induce pain by sensitizing nociceptive neurons via PG-receptors [24]. Moreover, it has been recently reported that PGA2, a derivate of PGE2,

can directly activate nociceptive neurons through the transient receptor potential A1 (TRPA1) channel [25]. The pulp-innervating trigeminal nociceptors express both PG receptors and TRPA1 [26, 27]. The correlation between the elevated PGE2 levels in periapical exudate and the clinical symptoms such as spontaneous pain and pain on percussion was suggested earlier by Takayama et al. [12] and Shimauchi et al. [13]. VAS has been selected as the method of assessing pain because it is reliable, reproducible and scientifically valid [28].

## CONCLUSION

This study showed a direct correlation between the increased level of PGE2 in apical tissue fluid, caused by endodontic treatment of teeth with large restorations, and postoperative endodontic pain. It is clinically relevant indicating the need for postoperative pain control in endodontic treatment of vital teeth with large restorations.

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## Простагландин E2 у течности апикалног ткива и постоперациони бол код интактних и зуба с великим ресторацијама у два ендодонтска третмана

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### КРАТАК САДРЖАЈ

**Увод** Акутно периапикално запаљење је најчешћи узрок постоперационог бола који се јавља као резултат механичке, хемијске и/или микробне повреде периапикалног ткива. Главни запаљењски процес одговоран за периапикални бол је повећана вазодилатација и васкуларна пропустљивост, делимично узрокована простагландином E2, с последичним едемом, што доводи до компресије нервних влакана.

**Циљ рада** Циљ рада је био да се утврди концентрација простагландина E2 у течности апикалног ткива после ендодонтског лечења интактних и зуба с великим ресторацијама, а затим упореди с појавом и интензитетом постоперационог бола.

**Методe рада** Једнокорени зуби 24 одабрана пацијента сврстани су у две групе: интактни зуби (група 1, 27 зуба) и асимптоматски зуби с великим ресторацијама (група 2, 20 зуба). Клинички преглед зуба састојао се од електроте-

ста, регистрација бола на перкусију или спонтаног бола и радиографског испитивања. Узорци течности апикалног ткива сакупљани су из канала корена током две посете стоматологу, а концентрација простагландина E2 мерена је радиоимунесej анализом. Интензитет бола је одређиван на визуелној аналогној скали.

**Резултати** Концентрација простагландина E2 код зуба с великим ресторацијама приликом друге посете била је значајно већа (36%) него током прве посете (Вилкоксонев тест,  $p < 0,05$ ). Интензитет спонтаног бола после прве посете био је значајно већи у групи 2 ( $p < 0,05$ ) него у групи 1.

**Закључак** Резултати показују да је повећана концентрација простагландина E2 узрокована ендодонтским лечењем зуба с великим ресторацијама у корелацији с интензитетом постоперационог бола.

**Кључне речи:** простагландин E2; ендодонтско лечење; бол; витални зуби