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Lidocaine subgingival irrigation modulate the levels of prostaglandin E_2 in gingival crevicular fluid after periodontal therapy

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The aim of this study was to evaluate if lidocaine 2% with 1:100.000 epinephrine, used as subgingival irrigation, has anti-inflammatory effect after periodontal therapy. Seventeen patients were selected to this paired split mouth randomized, subject-blind study. Each patient had a minimum of two sites labeled and alleatory separated, both with probe depth ≥ 5 mm. Each site were separated in two groups: scaling and root planing + lidocaine 2% with 1:100.000 epinephrine used as subgingival irrigation (LD); and scaling and root planing + saline solution (SRP), both groups were blinded to the examiner. Clinical periodontal parameters were recorded: plaque index (PI), bleeding on probe (BOP), probing depth (PD), gingival recession (GR) and clinical attachment level (CAL). Levels of GCF-PGE_2 were analyzed by enzyme-linked immunosorbent. All parameters were recorded at baseline (1 and 3 months) after periodontal treatment. The results indicated reduction of PI, BOP, PD, CAL for LD and SRP groups and GCF-PGE_2 levels were reduced in LD group after 3 months periodontal therapy. The LD and SRP groups were equally efficacious to control the periodontal disease after 3 months. However, LD improved the reduction of PGE_2 levels and maintains the inhibitory anti-inflammatory effect on PGE_2 after 3 months of periodontal treatment.

Key words: Lidocaine, periodontal treatment, prostaglandin E2.

INTRODUCTION

Lidocaine is local anesthetics of amino amide type and it has been used in dental practice to block peripheral nerves and to prevent pain in dental procedures (McLure and Rubins, 2005). Epinephrine is a vasoconstrictor used

as adjunct of lidocaine, which promotes arterial; reducing bleeding and also delays the resorption of lidocaine, almost doubling the duration of anesthesia (Cepeda et al., 2010). Lidocaine has limited allergenicity and rare incidence of hypersensitivity reactions. It is formulated in cartridges as 2% lidocaine with 1:50.000, 1:100.000 and 1:200.000 epinephrine. The 2% lidocaine with 1:100.000 epinephrine is considered the standard for comparison with newer anesthetics. Lidocaine with epinephrine rapidly induces oral anesthesia and provides surgical anesthesia that last 90 to 180 min (Hawkins and Moore, 2002).

However, local anesthetic has not only effect on pain control, but it can also promote anti-inflammatory and antibiotic systemic effects. Local anesthetics have shown to be potent inhibitors of inflammation, reduce edema formation in various conditions (Winning et al., 2012; Garutti et al., 2014). The anti-inflammatory effect of local anesthetics has not been totally elucidated, but it should possess a wide range of anti-inflammatory actions through their effects on cells of the immune system, as well as microorganisms, thrombocytes leukocytes and erythrocytes (Ohsaka et al., 1994; Cassuto and Tarnow 2003; Lan et al., 2005). Garutti et al. (2014) confirm the anti-inflammatory effect of lidocaine. The authors reported that the expression tumor necrosis factor α (TNF-α) decreased after systemic administration.

Periodontal disease is a group of inflammatory disease that started with periodontal pathogenic biofilm that destroyed supporting tissues: Cement, periodontal ligament and caused bone loss (Offenbacher, 1996). In addition, pro-inflammatory cytokine mediate host defense and are frequently present in higher levels in periodontal tissues. Chemokines are cytokines that play an important role in leukocyte recruitment and may directly or indirectly modulate osteoclast formation.

Prostaglandin E_2 (PGE_2) is one of pro-inflammatory products that can mediate tissue destruction in periodontal disease (Offenbacher, 1996). It is present in high levels at sites with inflammation and pain (Funk, 2001). It has been associated with changes in fibroblast metabolism and bone resorption (Offenbacher and Heasman, 1993). In addition, PGE_2 levels have been noted to be elevated in the gingival crevicular fluid (GCF) from patients with gingivitis and chronic periodontitis (Salvi and Lang, 2005).

After periodontal treatment, the levels of PGE_2 should be decreased due to re-establishment of healthy periodontal (Sánchez et al., 2013). For several years, studies have been made to improve the outcomes of scaling and root planing using laser application, antibiotic systems, irrigation solutions, chlorhexidine digluconate, povidone-iodine, sodium chloride, etc (Krück et al., 2011). However, there are few reports about the effects of the local anesthetic in inflammatory process after periodontal treatment. Derman et al. (2014) used anesthesia gel to treat periodontal pockets and found benefits, less pain and discomfort during procedures and similar attachment gain comparing local anesthetic gel and injection. Based on this report, this study intends to test whether lidocaine 2% with 1:100.000 epinephrine used as subgingival irrigation as adjunct to scaling and root planing can promote greater attachment gain and reduction of the levels of PGE_2 of gingival crevicular fluid compared with control group after 3 months of periodontal therapy.

MATERIALS AND METHODS

Seventeen patients (mean aged 38.5 ± 8 years old), both genders (48% male) were selected to this paired split mouth randomized, subject/examiner-blind study. All subjects were recruited from the Department of Periodontology, School of Dentistry, Fluminense Federal University, Nova Friburgo, Rio de Janeiro State, Brazil, over a period of 6 months between 2011 and 2012. The study protocol was approved (protocol number: CAAE-0157.0.258.000-10) by the ethics committee of the Medicine School, Fluminense Federal University. Prior to participation, the purpose and procedures were fully explained to all patients, who consequently gave written informed consent in accordance with the Helsinki Declaration. Medical and dental histories were taken and patients received clinical evaluation at prescreening visits. Inclusion criteria were: presence of periodontal disease in unirradicular teeth, bleeding on probing in sites where probing depth was ≥ 5 mm in a minimum of two teeth in different arch; and radiographic bone loss ranging from 30 to 50%. Exclusion criteria were: patients with systemic diseases; diabetes; osteoporosis; pregnant lactating females; use of immune suppressive medication, phenytoin, cyclosporine, calcium channel blockers or any use of antibiotics or nonsteroidal anti-inflammatory drugs in the past 3 months; and any medical conditions requiring immunotherapy or diagnosed as HIV + or with AIDS, that could interfere with the periodontum.

An experienced periodontist evaluated the clinical parameters and selected two unirradicular teeth for the protocol procedure. Each selected tooth were measured by periodontal parameters: Plaque index (PI), bleeding on probe (BOP), probing depth (PD), gingival recession (GR), clinical attachment level (CAL) using a periodontal probe PCP15 (PCP- UNC15, Hu-Friedy, Chicago, IL), six sites (mesio-buccal, mediobuccal, disto-buccal, mesio-lingual, medio-lingual, disto-lingual) were recorded. One site with PD ≥ 5 mm was selected and labeled in sites number 1 or 2 to receive subgingival irrigation labeled in 1 or 2.

Gingival crevicular fluid (GCF) was sampled 1 week after clinical examination, by a blinded researcher to clinical parameters, in order not to alter the nature of the GCF. GCF samples were taken from two different sites labeled as 1 or 2, both sites with the deepest PD was ≥ 5 mm and BOP were chosen for sampling the same patient. After removal of the supragingival biofilm with sterile cotton pellets, the sites were isolated with sterile cotton rolls and dried with an air syringe to eliminate the possibility of contamination with saliva. GCF was collected by inserting microcapillary 5 µl approximately 2 mm into the sulcus. GCF visually contaminated

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with blood was discarded. The GCF was immediately placed into separate microcentrifuge tubes containing 250 µl phosphate-buffered saline. The samples were stored at -20°C for subsequent assays. The samples were analyzed by a single-blinded examiner using a commercial PGE_2 specific enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA).

After clinical parameters were recorded, periodontal treatment was performed using Gracey curets to scaling and root planing associated with 50 µl of blinded solution labeled as 1 or 2. After periodontal treatment, each patient received subgingival irrigation once a week until one complete month and received oral hygiene instructions. GCF samples, clinical parameters measurements and periodontal treatment were recorded at baseline, 1 and 3 months. After the study had finished, the solutions were revealed by a blinded pharmacologist to this study: number 1 was identified as LD (Lidocaine group, containing lidocaine 2% with 1:100.000 epinephrine (Alphacaine 100®, DFL-Brazil) and number 2 was identified as scaling and root planing + saline solution (SRP; placebo group, containing saline solution).

Statistical analysis

Required sample size was determined by G*Power (G*Power, Franz Faul, Kiel University, Germany, Version 3.1.2, 2009) and was calculated to detect a 0.5 difference between BOP, LD and SRP groups at the 0.05 probability level with a power of 92%. The power calculation analysis revealed that the required sample size was a minimum of 17 subjects for each study group. The primary efficacy variables were whole-mouth mean BOP LD and SRP groups. Statistical analysis was performed on data obtained from all patients who completed the trial.

The decision about whether to use parametric or non-parametric tests was made based on the results of Shapiro-Wilk Normality Test for normal distribution.

Statistical tests were performed using the Statistix software (Analytical Software, Tallahassee, FL, USA, Version 8.0, 2003). A Repeated Measures - ANOVA was performed to compare clinical parameters (PI, BOP, PD, GR, CAL and GCF) among LD and SRP groups. All variables were normally distributed, except GCF-PGE_2. The Mann Whitney test was used to analyze differences in GCF-PGE_2 levels among LD and SRP groups and among baseline, 1 and 3 months. Statistical significance for all variables was defined as $p \leq 0.05$.

RESULTS

The mean ± standard deviation (± SD) of LD and SRP groups after periodontal treatment are presented in Table 1. Both groups had similar means of clinical parameters, no statistically significant differences of mean were found to PD and CAL between LD and SRP groups. Percentage of PI and BOP were also similar between the groups. No differences were found to GR and CGF parameters during baseline, 1 and 3 months. Comparison between times, baseline and 1 month and baseline and 3 months were also tested (Repeated Measures - ANOVA). All clinical parameters reduced after 1 and 3 months. This result shows that both therapies were efficient for periodontal disease control.

The GCF-PGE_2 levels were compared between LD and SRP groups and treatment intervals (baseline × 1 month and baseline × 3 months) after periodontal treatment. No differences were found between LD and SRP groups. Although, LD group had statistically significantly reduction at 1 month and 3 months to GCF-PGE_2 levels (Mann Whitney Test, $p \leq 0.05$). No difference was found to SRP group when compared 1 month and 3 months to GCF-PGE_2 levels. Lidocaine delivery shows to interfere with GCF-PGE_2 levels probably due to anti-inflammatory effects; however it did not improve clinical results (Figure 1).

DISCUSSION

This study evaluates the effect of lidocaine subgingival irrigation as adjunct of scaling and root planing in modulate PGE_2 responses after periodontal therapy. This study reveals that LD group had similar result to the clinical parameter to SRP group after 3 months periodontal therapy. Indeed, LD group revealed significant improvement to control PGE_2 levels compared to control group, 1 month and 3 months after periodontal treatment, suggesting that lidocaine subgingival irrigation can modulate inhibitory effect on inflammatory process. Recently, studies have correlated the high levels of PGE_2 in sites with periodontal disease and suggested that PGE_2 can mediate tissue destruction during periodontal disease (Chen et al., 2013; Sánchez et al., 2013). Kumar et al. (2013) reported that chronic periodontitis subjects treated by non-surgical periodontal therapy-SRP have mean PGE_2 concentrations in GCF and statistically it reduced significantly after periodontal therapy.

These results are in accordance with the results of this study that found reduced levels of PGE_2 after 1 and 3 months of periodontal therapy for both groups. According to Kumar et al. (2013), these results are associated with and are responsible for at least in part, inflammatory changes in the affected tissues. Levels of GCF PGE_2 can be used as a marker of gingival inflammation in order to determine the effect of periodontal therapy. The authors explain that most inflammation and periodontal destructive changes that occur in PD such as gingival redness, edema, collagen degradation and bone loss could be caused solely by the presence and direct actions of PGE_2. PGE2 can induce vasodilatation and increased capillary permeability, which elicit clinical signs of redness and edema. The vasoactive effects of PGE_2 are also enhanced by synergistic interactions with other inflammatory mediators such as bradykinin, cleavage fragments of the complement cascade and histamine (Salvi and Lang, 2005). PGE_2 can induce bone resorption and increase the number of osteoclasts, elevate Adenosine-3, 5-monophosphate (cAMP) levels of osteoblasts and osteoclasts (Dziak, 1993). The osteoclastic bone resorption is regulated through the stimulation of osteoclasts by PGE_2 (Chambers and Dunn, 1983). There is overwhelming body of evidence, which correlates with PGE_2 levels within the periodontal tissues

Table 1. Means, standard deviations and comparisons of LD (lidocaine delivery) and SRP groups at baseline, 1 month and 3 months after periodontal therapy.

	LD (n = 17)	SRP (n = 17)
PI		
Baseline	46.06 ± 48.43	28.6 ± 43.08
1 month	29.40 + 12.12	11.76 + 33.21†
3 months	26.47 ± 43.72	8.82 ± 26.43‡
BOP		
Baseline	98.00 ± 8.24	95.05 ± 14.23
1 month	49.00 + 4.49	62.70 + 41.46†
3 months	56.82 ± 41.29	69.58 ± 36.45‡
PD (mm)		
Baseline	5.05 ± 0.24	5.47 ± 0.51
1 month	3.17 + 0.63	3.35 + 0.82†
3 months	3.11 ± 0.69	3.05 ± 0.55‡
GR (mm)		
Baseline	0.64 ± 1.53	0.39 ± 0.68
1 month	0.70 + 1.82	0.35 + 0.86
3 months	0.88 ± 2.31	0.58 ± 1.32
CAL (mm)		
Baseline	5.70 ± 1.53	5.52 ± 0.62
1 month	3.88 + 1.96	3.76 + 1.74†
3 months	3.76 ± 1.82	3.81 ± 1.51‡
GCF (µl)		
Baseline	0.40 ± 0.12	0.39 ± 0.11
1 month	0.39 ± 0.14	0.38 ± 0.12
3 months	0.37 ± 0.16	0.36 ± 0.12

*P values represent statistically significant differences between LD and SRP (Repeated Measures - ANOVA) $p \leq 0.05$; †P values represent statistically significant differences between baseline and 1 month (Repeated Measures - ANOVA) $p \leq 0.05$; ‡P values represent statistically significant differences between baseline and 3 months (Repeated Measures - ANOVA) $p \leq 0.05$.

and within the crevicular fluid to the clinical expression of PD (Offenbacher and Heasman, 1993). Lidocaine 2% with 1:100.000 epinephine was selected to this study because it is easy to be purchased, inexpensive and commonly found in dental offices. It is a local anesthetic, well documented, that causes a nerve blocking effect, acting in pain prevention during dental procedures (Cassuto et al., 2006). Actually, it is also known to possess anti-inflammatory actions through their effects on cells of the immune system. The potent anti-inflammatory properties of local anesthetics, superior in several aspects to traditional anti-inflammatory agents of the NSAID and steroid groups and with fewer side-effects, has prompted clinicians to introduce them in the treatment of various inflammation-related conditions and diseases. They have proved to be successful in the treatment of burn injuries, interstitial cystitis, ulcerative proctitis, arthritis and herpes simplex infections. The detailed mechanisms of action are not fully understood but it seems to involve a reversible interaction with membrane proteins and lipids thus regulating cell metabolic activity, migration, exocytosis and phagocytosis (Cassuto et al., 2006).

Over the years, many chemical agents have been used as adjunct to SRP to improve the outcome; these substances are commercially available in the form of gel, strips and chips. These materials in high concentration, have improved the clinical results (Greenstein and Polson,

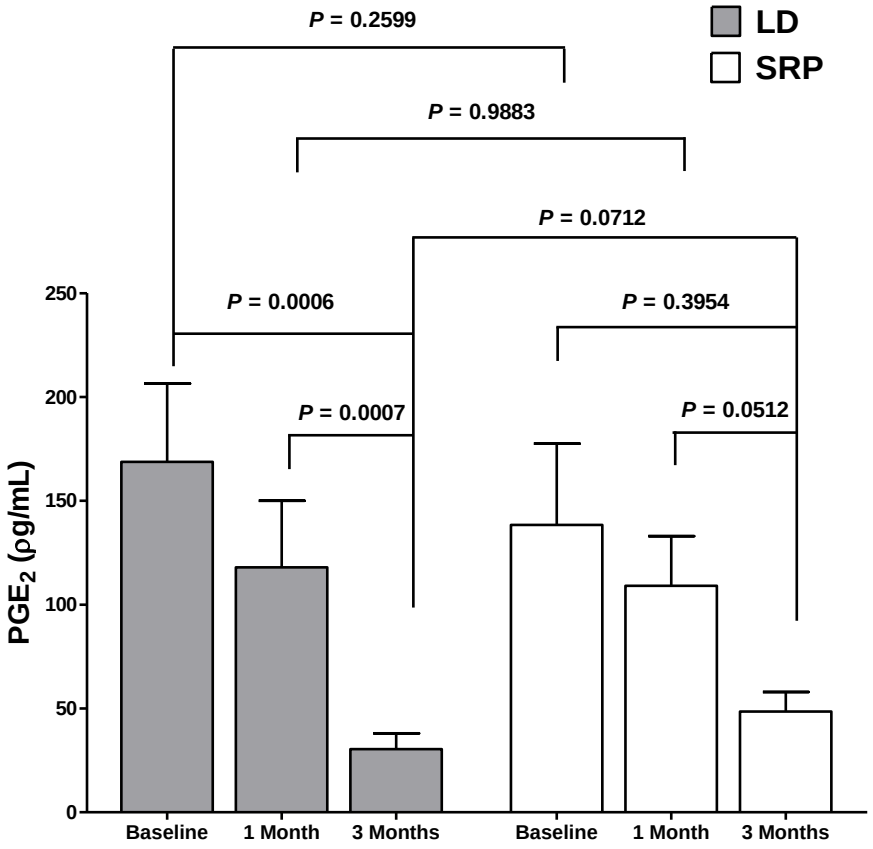

Figure 1. Modulation of GCF-PGE_2 levels of LD and SRP groups. Statistically significant difference between baseline and 1 month and baseline and 3 months after periodontal treatment to LD group and 1 month and 3 months to SRP group ($P \leq 0.05$ Mann Whitney Test). No Statistically significant differences to GCF-PGE_2 levels were detected to baseline, 1 month and 3 months between LD and SRP groups ($P > 0.05$ Mann Whitney Test).

Polson, 1998). However, irrigation solutions, such as chlorhexidine digluconate, povidone-iodine and sodium chloride, without SRP, have failure to demonstrate better results than SRP alone, but they were satisfactory to control periodontal disease when it is associated to SRP (Krück et al., 2011). These findings were in accordance with this study that used SRP as adjunct to lidocaine and saline solutions. Both groups, LD and SRP, were efficient to the control of periodontal disease after 3 months periodontal therapy. Table 1 shows reduction of CAL means 5.70 to 3.76 mm to LD group and 5.52 to 3.81 mm to SRP group after 3 months intragroup analysis. Although between groups LD and SRP groups, no difference were found. These local anti-inflammatory effects of lidocaine 2% with 1:100.000 epinephine were in agreement with Derman et al. (2014) that compare gel and injection lidocaine in periodontal pocket.

Other studies have been using lidocaine as adjunct of scaling and root planing to reduce a painful procedure (Svesson et al., 1994; Friskopp et al., 2001; Pandit et al., 2010). These authors suggested that gel is highly acceptable and can easily be administered into the periodontal pocket. Their results also show that gel does not interfere with the SRP procedure and no clinical signs of mucous membrane irritation were recorded, taste also does not affect the patients' willingness to have the gel at their next visit. So this study suggested that new researches should be made to investigate the anti-inflammatory effect of lidocaine gel in longitudinal evaluation of SRP.

Early studies have shown that inhibitory effects on PGE_2 have been reported after anesthetics administration (Cassuto et al., 1995, Jönsson et al., 1999; Cassuto and Tarnow, 2003). Lidocaine administration significantly secret IL-8 and IL-10 in cell culture experiments and this effect can mediate inhibition of NFkb via decrease IkB phosphorylation (Lang et al., 2009). In a recent study a potent inhibition of PGE_1 and PGE_2 release was

demonstrated when treating the burned skin in the intact animal with a topical local anesthetic cream (Yregård et al., 2001), thus confirming an earlier report showing reduced PGE_2 release from isolated pieces of gastric mucosa by lidocaine (Goel et al., 1994). These inhibitory effects on PGE_2, known to play a significant role in the mechanisms responsible for inflammatory pain, could account for some of the potent analgesic effects of intravenous lidocaine reported in burn patients (Jönsson et al., 1999, Cassuto and Tarnow, 2003) and in patients having undergone surgery (Cassuto et al., 1995; Chen et al., 2013).

This study did not test the effect of lidocaine in pain after periodontal treatment but suggested new approach to use lidocaine subgingival irrigation, as adjunct of periodontal treatment based on LD can reduce PGE level (Jönsson et al., 1991; Cassuto et al., 1995; Cassuto and Tarnow, 2003). PGE_2 is present in tissue destruction with periodontal disease (Offenbacher, 1996). This study suggested that LD group improved statically significant reduction of GCF-PGE_2 levels at 1 month and 3 months after periodontal therapy and confirm that after administration, lidocaine can reduce the level of PGE_2 and it was able to maintain these results during the 3 months.

Within limits of this study, the lidocaine irrigation substance used as adjunct of SRP was efficacious to control periodontal disease and reduces GCF-PGE_2 levels after 3 months of periodontal therapy. However, further research should be improved to confirm LD dosage or tested biochemical potential to suggest new approach to lidocaine to improve clinical periodontal parameters and contribute to reduce tissue destruction. This study also suggested that new research should be done to test the anti-inflammatory efficacy of lidocaine used as adjunct of SRP after periodontal treatment and verify if these outcomes should be maintained over the times.

Conclusion

Based on these findings, the LD and SRP groups were equally efficacious to control the periodontal disease after 3 months. LD group improved the reduction of GCF-PGE_2 levels at baseline and 1 month and 3 months after periodontal treatment, suggesting that the lidocaine 2% with 1:100.000 epinephrine can maintain inhibitory effect of PGE_2 after administration and it suggested that it can contribute to improve the reduction of this biochemical parameters connected to tissue destruction.

Conflicts of interest

The authors declare that they have no conflict of interest.

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