Efficacy of Nano-Pulsed Magneto Infrared Laser Therapy with a Fixed Dose Combination Tablet of Oral Ibuprofen and Paracetamol on the Reduction of Postendodontic Pain: A Clinical Study

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ABSTRACT

Introduction: The occurrence of mild pain is relatively common after post-endodontic therapy. The combination of analgesics offer enhanced pain relief and improved tolerability. Cold laser therapy has been reported to be significantly effective in the reduction of post- endodontic pain. The purpose of this study was to evaluate the effect of fixed dose combination of ibuprofen and paracetamol with low level laser therapy in patients with post-endodontic pain.

Material and Methods: One hundred twelve patients (mean age=35years) with mild to moderate postendodontic pain (VAS score of ≥30 mm) were selected. Patients were randomly assigned into four groups. Group 1(n=30) received 400 mg of ibuprofen+ 500 mg paracetamol orally. Group 2(n=30) irradiation of a Magneto-Infrared Nano Pulsed Cold Laser therapy (MILTA-DENT™) in analgesic mode for 10 min extra orally. Group 3(n=30) 400 mg of ibuprofen+ 500 mg paracetamol followed with laser for 10 min. Group 4(n=30) received no ibuprofen and no laser irradiation. The patients were dismissed with a VAS chart to be filled out at 4, 8, 12, 24 and 48 hrs after initiation of therapy.

Results: The test groups were compared using Kruskal-Wallis and Mann-Whitney U tests. The combination of laser and fixed dose combination drug resulted in better pain relief and the difference was statistically significant at 4 and 8 hours (P= <0.001). The difference was also statistically significant when comparing group 2 and 3 with placebo at all time periods.

Conclusion: Magneto-Infrared Nano Pulsed Cold Laser therapy had a significant role in the relief of postendodontic pain and can be advocated as a non- pharmacological approach in patients experiencing mild to moderate postendodontic pain.

Keywords: Low Level Laser, Post-Endodontic Pain, NSAIDs.

INTRODUCTION

The relief of pain has been described as a universal human right but is not always easily achieved.[1] Endodontic treatment should ideally eliminate all pain that exists in the offending tooth, but the physiodynamics of inflammatory process do not allow for pain to immediately disappear once the source of pain is removed. The occurrence of mild pain is relatively common even when the treatment has followed the highest standards and should be expected and anticipated by patients.[2] The incidence of postendodontic pain, mainly mild discomfort, has been reported to range from 3% to 58%.[3] The reasons for postendodontic pain can be many including chemical, mechanical or microbial injuries to the periapical tissues that result in acute inflammation.[5] Postendodontic pain is often linked to inflammatory mediators such as prostaglandins, leukotrienes, bradykinin, and serotonin.[6] Nonsteroidal anti-inflammatory drugs (NSAIDs), preferably Ibuprofen is the commonly used NSAIDs for postendodontic pain control having a good efficacy and a safety profile.[7] Prescribing fixed dose combination of ibuprofen and paracetamol together is common in clinical practice.[8] The combination of analgesics with different modes of action has the potential to offer enhanced pain relief with reduced dosage and consequently improved tolerability.[9] Ibuprofen is a NSAID that inhibits cyclooxygenase enzymes.[10] Paracetamol is thought to inhibit a subclass of cyclooxygenase enzyme isoforms in the central nervous system, which may involve cyclooxygenase 3, and some cyclooxygenase 2 inhibition.[11]

Rapid developments in laser technology and better understanding of bio-interactions of different laser systems have broaden new horizons for clinical use of laser in contemporary endodontics.

Low-level laser therapy (LLLT) is well established in clinical dentistry because of its anti-inflammatory, anti-infective and analgesic effects.[12] Unlike other lasers used in dentistry, LLLT has also shown non-thermal and bio-stimulatory effects and the energy output of the device is low enough not to exceed an irradiated tissue temperature of 36.5°C.[13] LLLT can assist with endodontic procedures by reducing postoperative pain and swelling, eliminating the need for analgesics, and reducing pulp hyperemia.[14] Low level laser therapy has been reported to be significantly effective in the reduction of post endodontic pain control.[15,16] Nevertheless, none of the studies have been reported on the effect of the fixed combination drug in a single dose with low level laser therapy (LLLT) on post endodontic pain. The purpose of this study was to evaluate the effect of fixed dose combination of ibuprofen and paracetamol with LLLT in patients who received a standard single visit endodontic treatment for

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symptomatic irreversible pulpitis. Null hypothesis tested that there exists no significant difference among the groups in post endodontic pain control.

MATERIAL AND METHODS

This study was designed to be randomized, single blind, parallel-group, placebo-controlled clinical study. Sixty eight male patients and fifty two female patients (age 18-64 years, mean age 35years) participated in the study. The gender and age distribution was not significant among the groups (*P*=0.965). Patients who reported with mild to moderate postendodontic in well obturated canals pain just within two days after obturation, that were previously diagnosed and treated for symptomatic irreversible pulpitis using standard single visit endodontic protocol by endodontists, were eligible for the study. Written informed consent was taken from every patient before performing the study. Permission from the institutional ethical committee was also taken. A score of ≥30 mm for pain on the 100-mm visual analog scale (VAS) was necessary for enrollment into the study. Patients were excluded if they had a history of hypersensitivity to the study medications, any gastrointestinal disorder or if they were taking medications that might confound the assessment of pain relief. Patients were randomly assigned into four groups. Group 1(n=30) patients were orally administered a single dose of the fixed dose combination drug containing 400 mg of ibuprofen+ 500 mg paracetamol. Group 2(n=30) patients received irradiation of a Magneto-Infrared Nano Pulsed (905nm) Cold Laser therapy (MILTA-DENT™ / PhysioQuanta, Montpellier - France) at 50 Hz for 5 min at periapical region extra orally (Figure 1) with a power density of 37mW/cm^2. Group 3(n=30) patients were administered single dose of the fixed dose combination drug containing 400 mg of ibuprofen+ 500 mg paracetamol followed with extraoral Magneto-Infrared Nano Pulsed Cold Laser therapy at 50 Hz for 5min. Group 4(n=30) patients received no ibuprofen and no low level laser irradiation. The patients were dismissed with a VAS chart to be filled out at 4, 8, 12, 24, and 48 hrs after initiation of therapy. Each patient was given an "escape envelope" containing 650 mg of paracetamol in case of continued pain while taking the test medication in question. The patients were instructed to indicate in the pain survey if this additional medication was required and record the time it was taken. Ten patients required additional medication for postendodontic pain and one patient did not return the pain survey and were excluded.

STATISTICAL ANALYSIS

The VAS pain scores for each group at each time were analyzed. Statistical calculations were made through the Statistical Package for Social Science (SPSS) version 17. The test groups were compared at baseline for age using one-way analysis of variance (ANOVA); for gender and tooth location using Pearson chi-square test; and for VAS score of pain using Kruskal-Wallis (K-W) test. When K-W test showed significant difference, Mann-Whitney U test was applied for pairwise comparisons. *P*-value less than 0.05 were considered statistically significant.

RESULTS

Median pain VAS scores were plotted in relation to time after administration of the drugs/ laser therapy (Figure 2). At 4 and 8 hour periods there was no significant difference in the pain relief in group 1, 2 and 3, while it was statistically significant(P = 0.002) at 12-, 24 and 48 hours. However, there was a statistically significant difference when compared with the placebo at 4- and 8- hours, but non-significant at 12, 24 and 48hours (Table 1and 2). Therefore the fixed dose combination of ibuprofen and paracetamol significantly reduced pain at 4 and 8 hours. When comparing group 2 with group 3, the combination of laser and fixed dose combination was better in reducing pain and the difference was statistically significant at 4 and 8 hours (P= 0.04) but the difference was not statistically significant at 12, 24 and 48hrs. Also the difference was statistically significant (P =0.001) when comparing group 2 and 3 with placebo at all time periods (Table 3). The best pain relief was given by ibuprofen paracetamol with laser combination.

DISCUSSION

Alleviating pain is of utmost importance when treating

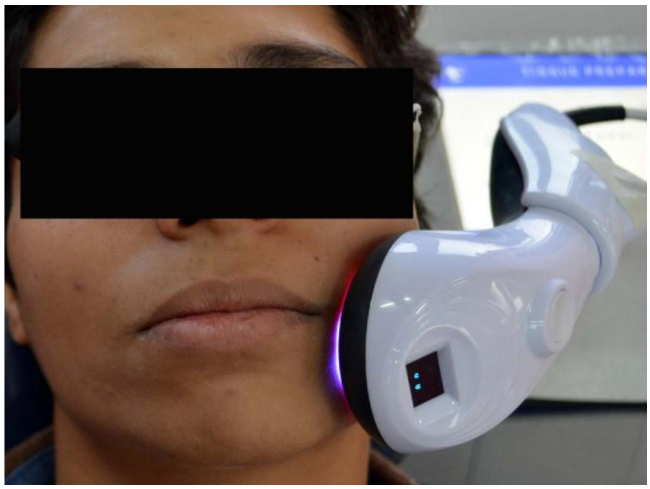

Figure-1: Extraoral application of laser at the periapical region of the offending tooth.

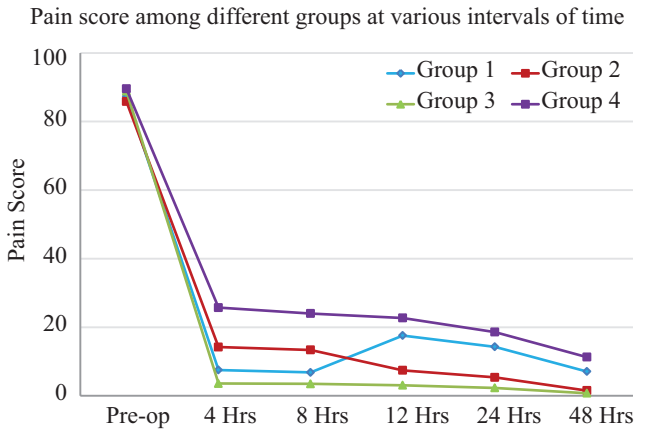

Figure-2: Pain score among different groups at various intervals of time

Time	Group 1	Group 2	Group 3	Group 4	P-value
Preop	87.3±29.81	85.8±29.19	88.9±28.29	89.6±20.83	0.953
4 Hrs	7.5±14.19	14.2±23.76	3.6±10.99	25.7±32.39	0.001*
8 Hrs	6.8±13.72	13.4±20.08	3.5±9.31	24±28.84	<0.001*
12 Hrs	17.6±25.67	7.4±12.97	3.1±7.95	22.7±21.97	<0.001*
24 Hrs	14.3±18.9	5.4±9.89	2.3±7.02	18.6±26.5	0.001*
48 Hrs	7.1±13.47	1.5±5.84	0.8±4.2	11.3±18.93	0.003*
*Statistically Significant Difference (P-value<0.05)					

Table-1: Pain score among different groups at various intervals of time

Group Comparison	P-value					
	Preop	4 Hrs	8 Hrs	12 Hrs	24 Hrs	48 Hrs
1 vs 2	0.845	0.241	0.195	0.036*	0.040*	0.047*
1 vs 3	0.832	0.490	0.508	0.003*	0.009*	0.044*
1 vs 4	0.731	0.002*	0.001*	0.285	0.340	0.184
2 vs 3	0.678	0.041*	0.039*	0.363	0.495	0.808
2 vs 4	0.564	0.035*	0.036*	0.002*	0.004*	0.002*
3 vs 4	0.914	<0.001*	<0.001*	<0.001*	<0.001*	0.001*
*Statistically Significant Difference (P-value<0.05)						

Table-2: Intergroup comparison based on pain score at various intervals of time

Time	Group 1 (Mean±SD)	Group 2 (Mean±SD)	Group 3 (Mean±SD)	Group 4 (Mean±SD)
Pre-op	87.3±29.81	85.8±29.29	88.9±28.29	89.6±20.83
4 Hrs	7.5±14.19*	14.2±23.76*	3.6±10.99*	25.7±32.39*
8 Hrs	6.8±13.72*	13.4±20.08*	3.5±9.31*	24.0±28.84*
12 Hrs	17.6±25.67*	7.4±12.97*	3.1±7.95*	22.7±21.97*
24 Hrs	14.3±18.90*	5.4±9.89*	2.3±7.02*	18.6±26.50*
48 Hrs	7.1±13.47*	1.5±5.84*	0.8±4.20*	11.3±18.93*
*Statistically Significant Difference from preoperative pain (P-value<0.05)				

Table-3: Intra-group comparison of pain score

dental patients, as it has far reaching effects for both the patient and the clinician alike. Postoperative endodontic pain control continues to be a significant challenge in endodontic therapy. Amongst all dental procedures, endodontic treatment produces more frequent and severe postoperative pain.[17] Endodontic treatment itself can trigger production of prostaglandins which results in postoperative pain.[18] Post-endodontic pain is more likely to occur within the first 24 h following endodontic treatment.[19] The prevalence of post-endodontic pain has been reported to be as high as 40%.[20] Hence, successful management of post-endodontic pain is an important concern for patients and clinicians. Management of post-endodontic pain is multifactorial and should be aimed at reducing the peripheral and central components of hyperalgesia. For the treatment of mild to moderate pain nonsteroidal anti-inflammatory drugs (NSAIDs) continue to be the most appropriate options. NSAIDs have been the traditional treatment for moderate pain and inflammation. NSAIDs diminish postoperative hyperalgesia peripherally.[21] NSAIDs act primarily through inhibition of cyclooxygenase (COX) enzymes 1 and 2. COX-1 is distributed throughout the body and has a role in protection of stomach mucosa, platelet action and kidney function. COX-2 is important in the production of prostaglandins and is expressed in only a few specialized tissues and is induced during inflammation. In the present study the combination of ibuprofen and paracetamol was taken as it has been reported that the combination may be more effective than individual drug alone for the management of postoperative endodontic pain.[22] Ibuprofen is the most frequently used NSAID for control of pain associated with endodontic treatment.[23] Ibuprofen blocks both COX-1 and COX-2 enzymes with highly effective analgesic and anti-inflammatory action for post-endodontic pain.[24] Ibuprofen has been reported to be the most effective and widely used nonsteroidal anti-inflammatory drugs (NSAID).[25] A limitation to this drug, however, is the 'ceiling effect', in which the patient may not experience sufficient relief with administration of increased dosages of the medication.[26] Supplementing the initial dosage with a second drug that acts in an alternative manner may allow sufficient analgesia to be achieved. Another commonly used analgesic to control dental pain is paracetamol. The mechanism of action of paracetamol (acetaminophen) is still not clearly understood. Although various biochemical studies point to inhibition of central COX-2 activity, the existence of a COX activity that is selectively susceptible to paracetamol (COX-3) and stimulation of the activity of descending 5-HT pathways that inhibit nociceptive signal transmission in the spinal cord have been reported.[6] Hence, a combination of ibuprofen with paracetamol in fixed doses may be more effective than ibuprofen alone for the management of postoperative endodontic pain. This was the reason for the selection of

this combination in the present study. The combination of ibuprofen and paracetamol in a fixed-dose tablet does not significantly alter the pharmacokinetic profiles of either drug alone, although the rate of paracetamol absorption is enhanced; offering potential therapeutic benefits in relation to the onset of analgesia.[27] Inhibition of COX-1 attenuates its gastro protective action causing gastrointestinal toxicity with long-term use of NSAIDs.[28] Inhibition of both COX-1 and COX-2 by NSAIDs also has been associated with renal toxicity on long-term use.[29] NSAIDs also have been shown to interact with several antihypertensive agents, which may compromise blood pressure control. The most common short-term side effects of NSAID usage are dyspepsia, diarrhea and abdominal pain.[30,3]

The goal of combining analgesics with different mechanisms of action is to use lower doses of the component drugs, thereby improving analgesia without increasing adverse effects. This can be achieved by targeting different pain pathways simultaneously which may allow "balanced analgesia "for lower doses.[32,33] In this study, fixed drug combination showed significantly lower pain ratings at 4-and 8-h post therapy when compared with the placebo. However, the 12-h pain rating for fixed drug combination was significantly higher than its rating at 8 h. This could be attributed to the drugs metabolic half-life, which is between 4 and 6 h. Fixed drug combination and placebo gave similar pain ratings at 12- and 24-h post therapy. This was expected, because the endodontic procedure should have reduced the pain by this time. Moreover, fixed drug combination's maximal analgesic effect would not have lasted for more than 8 h. Our results were consistent with the studies done by Mehlisch et al,[34] Po and Zhang[35] and Cooper et al.[36] Our results are also consistent with the other studies where the therapy with FDC ibuprofen 200 mg/paracetamol 500 mg or ibuprofen 400 mg/paracetamol 1000 mg was significantly more effective than comparable doses of either drug alone in the management of moderate to severe acute dental pain in the immediate postoperative period.[37] Despite the most preferred drugs for pain control, NSAID's have limitations and disadvantages. This necessitates a better alternative to be sought for post-endodontic pain control.

There is strong evidence that low level laser therapy (LLLT) modulates the inflammatory process and relieves acute pain in the short-term.[38] Laser is a monochromatic, collimated, coherent and intense beam of light produced by stimulated emission of radiations of light source. LLLT can modulate inflammatory processes and can significantly induce dose dependent reduction of acute inflammatory pain in clinical settings.[39] LLLT is reported to be an effective non-pharmacological approach for reduction of post endodontic pain which has been attributed to anti-inflammatory and neural effects of LLLT including stimulation of nerve cell and lymphocyte respiration, stabilization of membrane potentials, and the release of neurotransmitters in the inflammatory tissue.[40] Low level laser therapy, in a dose dependent manner, may reduce pain related to inflammation by lowering levels of prostaglandin E2, prostaglandin-endoperoxide synthase 2, interleukin 1-beta, tumor necrosis factor-alpha, the cellular influx of neutrophil granulocytes, oxidative stress, edema, and bleeding. The appropriate dose appears to be 5 joules per day.[41] The present study compared the immediate postoperative pain reduction using LLLT due to healing of periapical wound or inflammation caused after biomechanical preparation and obturation of root canal. Various factors have been reported to elicit post-endodontic pain such as the existence of preoperative pain, infection retreatment, intracanal medications, physical and chemical damage to periapical tissue.[42] LLLT is referred to as ''low level' 'or ''cold laser'' therapy because of its use of light at energy densities that are low compared to other forms of laser therapy that are used for ablation, cutting, and thermally coagulating tissue as the power densities used are lower than those needed to produce heating of tissue. LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation.[40] When a photon of light is absorbed by a chromophore in the treated cells, an electron in the chromophore within mitochondria can become excited and jump from a low-energy orbit to a higher-energy orbit.[43] This stored energy can then be used by the system to perform various cellular tasks. The pulsed electromagnetic field also has been reported to have beneficial effects in bone healing.[44]

In the present study a new generation of low level laser, MILTA-DENT(Physioquanta /34000 Montpellier-France) was used. According to the manufacturer, MILTA-DENT is a pan-spectral magneto infrared nano pulsed cold laser device (Class 3R) belonging to the visible and infrared technology. The device can be programmed for wavelengths (from 470 to 905nm) to obtain the whole spectrum of light. The presence of a steady magnetic field (200mT) incorporated in the MILTA- DENT transforms by a quantic mechanism into a "tunnel effect", kind of energy and information teleportation penetrating human physiology up to 13cms. This was the reason for extraoral application of the laser in the present study. This enhances lymphatic drainage which facilitates the elimination of the metabolic waste linked to cellular regeneration. MILTA- DENT comes with two circular shower emitter probes with active surface area of 9.6cm2, mounted on easy to maneuver telescopic arms. Each Shower emitter has three polychromatic diodes RGB (400 to 650nm, 50W), three infrared diodes (850nm, 22W) and three infrared soft lasers (850nm, 30W). In the present study the effects of laser on pain reduction can be explained by the fact that laser light absorbed by nociceptors, exert an inhibitory effect on A and C pain fibers, which slows conduction velocity, reduces amplitude of compound action potentials and suppresses neurogenic inflammation. Results from the present study indicate that pain was significantly reduced in all treatment groups. Fixed drug combination (FDC) showed significant pain relief as compared to control group which is consistent with the study of Arslan et al.[45] Group 2 showed significant pain reduction at 12, 24 and 48 hours post treatment as compared to group 1, while it was not significant at 4 and 8 hrs. Group 3 showed a significant

difference at 4 and 8 hrs when compared to group 2 and group 1, which is consistent with other studies.[15,16] In this study, Ibuprofen showed significantly lower pain ratings at 4-and 8-h post therapy when compared with the placebo. However, the 12-h pain rating for ibuprofen was significantly higher than its rating at 8 h. This could be attributed to the drugs metabolic half-life, which is between 4 and 6 h. Ibuprofen and placebo gave similar pain ratings at 12- and 24-h post therapy. Moreover, ibuprofen's maximal analgesic effect would not have lasted for more than 8 h. The combination of laser and fdc showed the best effect on postendodontic pain relief for all time intervals as compared to control, while significantly better at 12, 24, and 48hrs as compared to the fixed dose combination.

Conclusion:

Within the limitations of this study, it can be concluded that the single session of MILTADENT therapy in addition to single dose of ibuprofen and paracetamol proved to be an effective approach for the reduction of post endodontic pain at 4, 8, 12 and 48hrs after treatment unlike the combination of ibuprofen and paracetamol alone which lasted only for 4 to 8 hrs post treatment. On the basis of the present study, Single dose of MILTADENT therapy can be recommended as a non-pharmacological alternative in patients presenting with mild to moderate postendodontic pain.

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