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Comparison of the Analgesic Efficacy of Two Medications in Patients Receiving Dental Implants: A Randomized Controlled Trial

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Abstract: The aim of this randomized control trial was to compare the analgesic efficacy of two commonly prescribed medications, mefenamic acid (Ponstan™ Forte) and lysine clonixinate (Dorixina®) in patients undergoing dental implant surgery. A total of 130 patients receiving dental implants were randomized into two groups: 75 Treated with Mefenamic Acid (MA) and 75 with Lysine Clonixinate (LC). The primary outcome was the change in pain scores according to a Visual Analog Scale (VAS) recorded by the patients on a questionnaire over 7 days post-operatively. Secondary outcome was analgesic consumption taken as a rescue medication. 102 patients (78.5%) completed questionnaires and were available for analysis. No significant difference was found for both outcome measures during the first 4 days post-operative. However, the mean VAS score was significantly lower in LC group at days 5, 6 and 7 compared to MA group. The results of this study suggests that there is no difference in the analgesic efficacy between MA and LC when prescribed as pain medications following dental implant surgery. The abovementioned findings will help clinicians to have a better understanding of the analgesic efficacy of two different medications in implant surgery. When anti-inflammatory drugs are contraindicated in patients undergoing implant treatment, LC can be safely prescribed with the same analgesic efficacy of an AINS.

Keywords: Analgesia, Dental Implantology, Nonsteroidal Anti-Inflammatory Drugs, Pain

Introduction

In dentistry, implant placement is a well-established and widely used treatment modality for the replacement of single and multiple missing teeth in both partial and complete edentulous cases. Management of postoperative pain following the surgical procedure is an inherent part of clinical practice. Therefore, practitioners often prescribe medications with analgesic and/or anti-inflammatory activities in order to reduce the postoperative pain. However, there are no conclusive guidelines for post-operative pain management (Misch and Moore, 1989). Therefore, postoperative pain and swelling are usually managed by Nonsteroidal Anti-Inflammatory Drug (NSAIDs) alone, or NSAIDs and analgesics (Misch and Moore, 1989; Al-Khabbaz *et al*., 2007; Karadottir *et al*., 2002; Sotto-Maior *et al*., 2011).

Mefenamic Acid (MA), one of many NSAIDs, provides also analgesic and antipyretic effect. It has been shown to inhibit prostaglandin activity and thus effectively relieve pain. NSAIDs produce analgesic and anti-inflammatory actions by inhibition of Cyclo-Oxygenase (COX-1 and COX-2), thereby reducing the synthesis of arachidonic acid metabolites, such as prostaglandins and thromboxanes, that play an essential role in provoking pain (Cimolai, 2013; Hargreaves *et al*., 2005).

Lysine-Clonixinate (LC) is a Nonsteroidal Anti-Inflammatory (NSAID) drug with mainly analgesic but also anti-inflammatory, antipyretic and anti-rheumatic activities (Seymour *et al*., 1983). It is a weak cyclooxygenase inhibitor and acts especially in blocking cyclooxygenase 2 and can be used as alternative to patients at risk for adverse upper gastrointestinal tract events. The structural formula of LC allows for rapid absorption and a good bioavailability after oral ingestion

(Santos *et al*., 2011; Krymchantowski *et al*., 2005; Eberhardt *et al*., 1995).

There is still some controversy regarding the best protocol to manage post-operative pain (Barasch *et al*., 2011). While several double-blind controlled clinical trials have proved the efficacy of LC compared to other standard medications in patients with pain of various etiology, no studies evaluated, to the best of our knowledge, the effect of LC in comparison to mefenamic acid after implant placement (Krymchantowski *et al*., 2005; Eberhardt *et al*., 1995; De los Santos *et al*., 1998a; 1998b).

The aim of this randomized controlled clinical trial was to compare the analgesic efficacy of two commonly prescribed medications, mefenamic acid (Ponstan™ Forte, MA) and lysine clonixinate (Dorixina®, LC) in patients undergoing dental implant surgery.

Materials and Methods

Study Population

Patients receiving from one to six dental implants at the periodontology department of the Faculty of Dental Medicine at the Saint Joseph University- Beirut, Lebanon between November 2014 and September 2015 were asked to participate in the study. Patients who had implant (s) placement concomitantly with a grafting surgery (e.g., bone grafting, sinus lift, gingival grafting) were excluded.

The study protocol complied with the requirements of the Declaration of Helsinki. Healthy patients, of either gender, aged between 18 and 80 years were included in this study. Any patient with the following condition was excluded: Local or systemic conditions that jeopardize implant therapy, allergy to any of the drug used in the study, hypertension, diabetes, gastro-intestinal complaints and intolerance to paracetamol.

All patients read and signed an informed consent form.

Surgical Procedure

All the surgical procedures were performed by the residents in the periodontology department of the faculty under the supervision of the same practitioner.

Medications and Groups

After each surgery, post-operative instructions were given to the patients by a single operator. At this step, a concealed envelope was opened to determine the allocation to one of the two medications groups: Lysine-Clonixinate (LC) or Mefenamic-Acid (MA). Accordingly, the consented patients received and were instructed to take the following medications:

- Groupe 1 (LC)
- Lysine-Clonixinate (Dorixina®, Roemmers, Argentina) 125 mg, 2 tablets three times a day for 3 days.
- One tablet of Paracetamol 1000 mg (if required) taken as “rescue medication”
- Amoxicillin 1g every 12 h or Clindamycin 600 mg every 12 h (in case of allergy to penicillin) for 7 days.
- Group 2 (MA)
- Mefenamic-acid (Ponstan™ Forte, Parke-Davis, Lebanon) 500 mg, 1 tablet three times a day for 3 days.
- One tablet of Paracetamol 1000 mg (if required) taken as “rescue medication”
- Amoxicillin 1g every 12 h or Clindamycin 600 mg every 12 h (in case of allergy to penicillin) for 7 days

Data Collection

All patients were asked to document and record the following data:

- The assessment of efficacy (intensity of pain) using a 100-mM Visual Analog Scale (VAS) (Fig. 1) with “0” being equivalent to “none” and “10” being equivalent to “very severe” pain three times per day for 7 days following the surgery
- The number and exact timing of Paracetamol tablets consumed each day for three days post-operation

Data were collected from the patients one week after the surgery at sutures removal. Patients who did not follow the instructed data collection protocol were eliminated from the study. The primary outcome measure was the change in pain scores, as measured by the visual analogue scale, over the post-operative days 1-7 in the Group 1 and 2. Additional analysis was performed on the analgesia consumption and timing between the two groups.

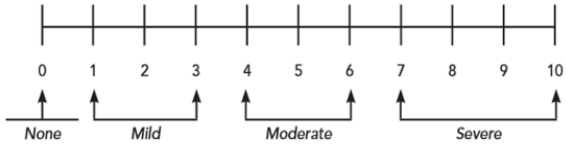

Fig. 1: Representation of the Visual analog scale (VAS) used by the patient

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 16.0. The alpha error was set at 0.05. The Kolmogorov-Smirnov tests were used to assess the normality of the distribution of each variable. The student t tests and the Mann Whitney tests were used for continuous variables. The Chi square test and the Fisher Exact test were used for categorical variables.

The comparison of the mean VAS score (8 am; 2 pm; 8 pm) among groups (Dorixina v/s Ponstan F) within time (days 1 to 7) was performed using repeated measure analysis of variance followed by univariate analyses and Bonferroni multiple comparisons.

Results

A total of 130 eligible patients participated to the study. Twenty-eight patients (14 from each group) were excluded due to lack of compliance. The remaining 102 patients, between the ages of 22 and 76, were included in this double-blind Randomized Controlled Trial (RCT).

Comparability Between Treatment Groups

206 implants were placed (106 implants in group 1 and 100 implants in group 2). The mean number of implants' distribution was not significantly different between the two groups (p-value = 0.745) Table 1.

Comparison of VAS Score at Different Days Between Groups

The mean VAS decreased significantly with time in participants treated with LC (p-value <0.0001) and MA (p-value <0.0001).

No significant difference was found between the two groups at day 1 (p-value = 0.644), day 2 (p-value = 0.988), day 3 (p-value = 0.484) and day 4 (p-value = 0.195). However, the mean VAS score was significantly lower in group 1 at day 5 (p-value = 0.018), day 6 (p-value = 0.025) and day 7 (p-value = 0.027) when compared to group 2 (Fig. 2) and (Table 2).

Comparison of Rescue Medication at Different Days Between the Two Groups

Over the study period, 41.2% of participants in group 1 and 39.2% of participants in the group 2 used rescue medication. No significant difference was found between both group (p-value = 0.840) Table 3.

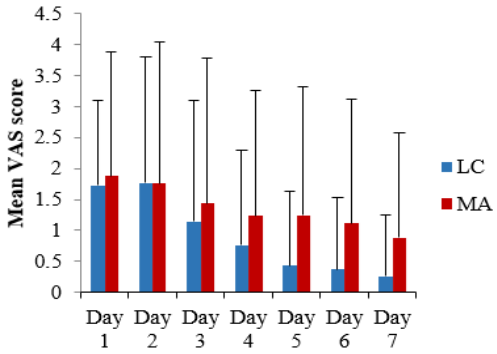

Fig. 2: Mean VAS scores per group for 7 days. (LC: Lysine clonixinate; MA: Mefenamic acid)

Table 1: Distribution of implants placed per group (LC: Lysine clonixinate; MA: Mefenamic acid)

Groups Number of implants	LC n = 51	MA n = 51	Total
1 implant	16(31.4%)	19(37.3%)	35(34.3%)
2 implants	21(41.2%)	20(39.2%)	41(40.2%)
3 implants	10(19.6%)	7(13.7%)	17(16.7%)
4 implants	3(5.9%)	5(9.8%)	8(7.8%)
6 implants	1(2.0%)	0(.0%)	1(1.0%)
Total of Implants	106	100	Sig. a 0.745

Table 2: Comparison of the VAS scores from Day 1 to Day 7 between the two groups (LC: lysine clonixinate; MA: mefenamic acid)

	LC(n = 51)	MA (n = 51)	Sig.
EVA Day1	1.73±1.361	1.88±1.996	*0.644*
EVA Day2	1.77±2.036	1.76±2.286	*0.988*
EVA Day3	1.14±1.959	1.44±2.343	*0.484*
EVA Day4	0.76±1.531	1.23±2.030	*0.195*
EVA Day5	0.43±1.204	1.24±2.073	*0.018*
EVA Day6	0.37±1.162	1.11±2.012	*0.025*
EVA Day7	0.26±.998	.88±1.684	*0.027*
Sig.	*<0.0001*	*<0.0001*	

Table 3: Comparison of rescue medication between the two groups (LC: lysine clonixinate; MA: mefenamic acid).

		Groups		
		LC n = 51	MA n = 51	Sig.
Rescue Med	Yes	21(41.2%)	20(39.2%)	0.840 Chi Square test
	No	30(58.8%)	31(60.8%)	

Discussion

The present randomized controlled trial presented herein comparing the analgesic efficacy of Mefenamic acid versus Lysine clonixinate showed no significant difference between both medications in patients treated with one to multiple implant placement. In fact, the pain scores (as measured objectively by visual analogue scores) and analgesic consumption (using a rescue medication) were statistically insignificant when prescribing randomly one of the two medications to a hundred and two patients receiving one to six dental implants.

Over the study period, only 41.2% of participants in group 1 and 39.2% of participants in the group 2 used rescue medication with no statistically significant difference between both groups. This means that approximately 60% of the patients did not use any rescue medication to control their pain after the placement of even multiple implants and only kept using the main medication prescribed (LC or MA). This proves the efficacy of both medications to control pain when used in dental implant placement since a rescue medication is only used by the patients when the pain is not controlled and persists even after the use of the main medication.

The mean VAS score reached the highest level eight hours after the implant surgery for both group 1 (VAS = 2.86) and group 2 (VAS = 3.00) and decreased progressively during the subsequent days. In fact, pain scores decreased significantly (p-value<0-0001) after the second day in participants treated with Lysine clonixinate (VAS <1.18) and Mefenamic acid (VAS <1.61). This is in

accordance with previous studies in which the maximum pain levels reported were at their highest 8 to 24 h post-operatively and then decreased significantly after the first two-days of implant placement (González-Santana *et al*., 2005; Muller and Calvo, 2001; Olmedo-Gaya *et al*., 2002; Noronha *et al*., 2009; Hashem *et al*., 2006).

Interestingly, while no significant difference was found between Lysine clonixinate and Mefenamic acid the first 3 days post-operatively, the mean VAS score was significantly lower in Lysine clonixinate group at days 5, 6 and 7 (-p-value = 0.018, 0.025 and 0.027 respectively) compared to Mefenamic acid group. While this finding can be hardly explained, it may speculate longer analgesic efficacy when using Lysine clonixinate in patients receiving dental implants. However, it is difficult to definitely correlate these results to the inherent properties of Lysine clonixinate. Further studies using Lysine clonixinate are needed in order to confirm this outcome.

It is also important to note that although 26 patients (25.5%) out of 102 received more than 3 implants, they reported only mild VAS scores, showing that patients receiving multiple dental implants might not perceive high degree of pain especially when adequate medications are prescribed. This observation is in agreement with previous reports that found that implant placement is generally a mild to moderately painful procedure with no major postoperative symptoms (Al-Khabbaz *et al*., 2007; Muller and Calvo, 2001; Hashem *et al*., 2006).

The performance of the surgeries by the residents in the periodontology department instead of a single practitioner with more expertise can constitute a drawback of this study. However, the authors wanted to include as many surgeries as possible for a more powerful statistics and thus a better outcome assessment. Moreover, the exclusion of patients who had implant (s) placement concomitantly with a grafting surgery (e.g., bone grafting, sinus lift, gingival grafting) can be a limitation of this study since most of implant cases include an extra procedure in order to correct or enhance the bony and/or gingival compartment around the implants. It would be interesting to test and compare the efficacy of the two medications used in this study in heavier surgeries that include bone grafting and sinus lifting simultaneously to implant placement.

To the best of the author's knowledge, this is the first study comparing Lysine clonixinate to Mefenamic acid in the management of post-operative pain in implant surgery. Considering the scarcity of studies with Lysine clonixinate in Dentistry, our study aimed at evaluating and comparing its analgesic efficacy with a commonly prescribed NSAID. In fact, inherent properties of LC render it attractive to use in oral surgery. Orally administered, Lysine clonixinate has excellent biological tolerance and low incidence of side effects in the treatment of painful syndromes, such as renal pain, neurogenic pain, muscle pain, tooth pain and migraine (Krymchantowski *et al*., 2005; Noronha *et al*., 2009; Krymchantowski *et al*., 2001; Gonzalez-Martin *et al*., 1996; Amorim *et al*., 2012; Marti *et al*., 1993). Since it is a weak cyclooxygenase inhibitor and acts especially in blocking cyclooxygenase 2 it can be used as alternative to NSAID in patients with a risk of adverse upper gastrointestinal tract events thus eliminating the risk of complications (bleeding, perforation or pain) (Santos *et al*., 2011; Klasser and Epstein, 2005). Thus, Lysine clonixinate could be recommended as a useful pharmacological alternative to NSAID for the management of postsurgical pain after one to multiple implant placement. Further studies with a bigger population and including surgeries of implant placement with bone grafting and/or sinus lifting would be interesting to confirm the findings of this study and the efficacy of Lysine clonixinate as a replacement of NSAID. Such findings could be very beneficial to patients that develop complications when using NSAID for pain management after dental surgeries.

Conclusion

The results of this study suggests that LC and MA are both efficient in reducing pain as measured by the Visual Analog Scale (VAS) scores following dental implant surgery. However, no difference in pain scores was found between them in the first 4 days. Interestingly, mean VAS scores were lower in LC group at day 5, 6 and 7 compared to MA.

Acknowledgement

All authors declare no conflict of interest with respect to authorship and publication of the article.

Author's Contributions

Alexander Saber: Wrote the protocol, participated in the experiment and data collection.

Abdel Rahman Kassir and Layal Bou Semaan: Wrote the manuscript.

Nada Naaman and Nadim Mokbel: Read the protocol and the article manuscript.

Maroun Dagher: Wrote the protocol and the manuscript, participated to the experiment and data collection.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved

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