ANTIMICROBIAL MODULATOR OF INFLAMMATORY RESPONSE IN THIRD MOLAR SURGERY COMPARED WITH CONVENTIONAL MEDICATION

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ABSTRACT

Surgeries performed in retained third molars occur in the contaminated field, bringing post-operative problems such as pain, bleeding, discomfort, swelling, infection, trismus, and inactive days. This study evaluated the differences between conventional medication and topical doxycycline in third molar surgery. Twenty-eight patients were selected requiring removal of four third molar. Half of the mouth was randomly selected to undergo surgery with the use of conventional medication (analgesic, anti-inflammatory and antimicrobial) and after 25-30 days, the other half of the mouth was subjected to surgery using doxycycline delivered through gel nanotubes. The results showed that in both treatments there was no clinical infection. The other evaluations were significantly lower in relation to pain, bleeding, edema, inactive days, trismus, and discomfort when compared with conventional therapy.

KEYWORDS: Doxycycline, Drug delivery, Modulation of inflammatory response, Oral and maxillofacial surgery.

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INTRODUCTION

Surgeries performed in retained third molars occur in the contaminated field, bringing post-operative problems such as pain, bleeding, discomfort, swelling, infection, trismus, and inactive days. Combined treatments with non-steroidal anti-inflammatory drugs and antibiotics may offer significant benefits in the prevention of pain and infections associated with oral surgery. However, there is no consensus on the use of antibiotics to minimize infectious complications and despite the increase in the rates of bacterial resistance, prophylactic use of antibiotics is very widespread in this type of surgery.

Incorporating drug-delivery platforms into medical devices offers the benefits of controlled release and localized delivery of drugs, which can improve efficacy of treatments for dentistry, cardiology, ophthalmology, and orthopedic applications, among others, minimizing adverse reactions and bacterial resistance. The progress in drug-delivery technology has thrust degradable platforms into the spotlight in recent years, as the key enabler of degradable drug-delivery systems, the bioabsorbable polymer poly (lactic-co-glycolic acid).

Topical antibiotics have certain benefits such as high concentrations, topical application and persistence in place since physiological
changes in the region may compromise the efficacy of systemic antibiotics \(^7\).

Another very important advantage is the low systemic absorption and low toxicity, which consequently reduces the intake of systemic antibiotics and, invariably, the possibility of developing a systemic side effect \(^8\).

In 1985, tetracyclines were discovered to have anticollagenolytic activity and were proposed as a host-modulating agent. Initial studies demonstrated that doxycycline was the most potent tetracycline in the inhibition of collagenolytic activities \(^9\).

Accumulating evidence suggests that activation of proteolytic enzymes, including the matrix metalloproteinase family, is responsible for the collagen destruction during inflammatory diseases \(^10\). Apparently, an imbalance between activation of matrix metalloproteinase and down regulation of their endogenous inhibitors leads to pathologic breakdown of the extracellular matrix \(^11\).

Tetracyclines have long been used as adjuncts in the treatment of periodontal diseases \(^11, 12\). Although initially attributed to its antimicrobial properties, the clinical efficacy of tetracyclines in periodontitis has been recently suggested to be due to their intrinsic anti-inflammatory activity, since low doses (subantimicrobial) of doxycycline decrease attachment loss and excessive collagense activity in the crevicular fluid of periodontitis patients \(^11\). Considering the anti-inflammatory properties of doxycycline, the aim of this study was to evaluate the differences between conventional medication and topical doxycycline delivered through gel nanotubes in the postoperative of retained third molar surgery class II.

**MATERIALS AND METHODS**

A split-mouth prospective clinical trial was performed on 28 patients requiring class II removal of four third molars in the Dental Hospital of Uberlândia Federal University, Minas Gerais, Brazil, to evaluate the occurrence of pain, bleeding, discomfort, swelling, infection, trismus, and inactive days during the postoperative period. The patient received explanations on how to identify each of these signs and symptoms. The discomfort was seen when there was a feeling of heaviness in the side where the surgery was performed and the infection would be investigated if there was purulent discharge in the suture site. The surgeries were performed, randomly, by three surgeons dentists, residents of the residency program in oral and maxillofacial surgery and traumatology, which also contributed to the objectives and design of this study. The patients agreed with the research and signed an informed consent form, according to the protocol 274/2011 of the Ethics Committee for Human Research of Uberlândia Federal University, which could be provided upon request. This committee approved the study, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Half of each patient’s mouth was randomly selected to undergo surgery and used conventional medication according to the residency program protocol for dental surgery (analgesic - Dipyrrone Sodium 500 mg every six hours while there is pain; anti-inflammatory - Diclofenac Sodium 50 mg every eight hours for five days and antimicrobial - Amoxicillin 4g one hour before the surgical procedure and 500 mg every eight hours, for seven days) and this, was considered the control situation \(^13-15\).

After 25 to 30 days, the other half of the mouth was subjected to surgery using 10mg doxycycline (Pharma Nostra, Anápolis, Goiás, Brazil) gel (HPMC - hydroxypropyl methylcellulose) handled and packaged aseptically in a laboratory, under license from national health surveillance agency - ANVISA No. 28023) delivered through gel nanotubes, after the toilet of surgical site and prior to suture, and this situation being considered experimental; on both sides, an ostectomy was necessary. Doxycycline was used only when the patient returned to perform the surgery in the other half of the mouth. No other antibiotics or anti-inflammatory were used concomitantly with the use of doxycycline. At the time of removal of sutures, the patients assigned grades from zero to ten, with zero being the absence of signs or symptoms. At the end of the study, the mean score for the controls was compared with the cases.

**STATISTICAL ANALYSIS**

The \(t\) test was performed comparing the scores given by patients after the use of conventional medication and after topical doxycycline delivered through gel nanotubes. \(P \leq 0.05\) was considered statistically significant.

**RESULTS**

A total of 110 surgeries were performed, 55 experimental and 55 controls, since in one patient were only two. The results showed that, in both treatments, there was no clinical infection. The other evaluations were 36.36\% (\(P = 0.01\)), 46.55\% (\(P = 0.04\)), 58.62\% (\(P < 0.0001\)), 70.91\% (\(P < 0.0001\)), 71.72\%
activities matrix metalloproteinases, many of which are produced by infiltrating neutrophils, mediate this tissue destruction by degrading plasma membrane proteins and extracellular matrix proteins such as collagen. In our study pain, bleeding, edema, trismus, and discomfort were significantly lower when using the doxycycline gel in nanotubes, compared with conventional therapy (Table 1). Regarding the evaluation of pain, five patients who used doxycycline reported the need to take a single dose of dipyrrone after the end of the anesthetic effect.

Table 1: Average score (0-10) assigned by the 28 patients undergoing surgery for extraction of third molars using conventional therapy (control) or topical doxycycline gel (experimental).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Experimental</th>
<th>$P$</th>
<th>CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>3.93</td>
<td>2.50</td>
<td>0.01</td>
<td>0.27-2.16</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.07</td>
<td>1.11</td>
<td>0.04</td>
<td>0.05-1.87</td>
</tr>
<tr>
<td>Discomfort</td>
<td>4.21</td>
<td>1.29</td>
<td>&lt; 0.0001</td>
<td>1.86-3.99</td>
</tr>
<tr>
<td>Edema</td>
<td>4.14</td>
<td>1.71</td>
<td>&lt; 0.0001</td>
<td>1.50-3.36</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trismus</td>
<td>3.54</td>
<td>1.00</td>
<td>&lt; 0.0001</td>
<td>1.55-3.52</td>
</tr>
<tr>
<td>Inactive days</td>
<td>1.96</td>
<td>0.57</td>
<td>&lt; 0.0001</td>
<td>0.73-2.05</td>
</tr>
</tbody>
</table>

*Confidence Interval

**DISCUSSION**

In infectious processes, microorganisms take the host cells to produce pro-inflammatory cytokines which may induce destructive processes that attack the soft and/or hard tissues of the oral cavity leading to tissue damage and the onset of the disease. In our study there was no clinical infection in both treatments.

Patients often suffer considerable post-operative pain, hyperemia, bleeding, edema, trismus, and discomfort. Sub-antimicrobial dose doxycycline aims to modulate the host by suppressing the inflammatory response. Additionally, it has long been known that members of the tetracycline family possess the ability to inhibit matrix metalloproteinases, independently of their antimicrobial activities. Matrix metalloproteinases, many of which are produced by infiltrating neutrophils, mediate this tissue destruction by degrading plasma membrane proteins and extracellular matrix proteins such as collagen. In our study pain, bleeding, edema, trismus, and discomfort were significantly lower when using the doxycycline gel in nanotubes, compared with conventional therapy (Table 1). Regarding the evaluation of pain, five patients who used doxycycline reported the need to take a single dose of dipyrrone after the end of the anesthetic effect.

**CONCLUSION**

We conclude that the use of doxycycline gel in nanotubes was more effective in reducing postoperative signs and symptoms, as well as post-surgical comfort and adherence to therapy, does not interfere with the normal microbiota of the patient, and provides a considerable reduction in treatment costs. Thus, it is possible to consider doxycycline gel in nanotubes as alternative medication to modulate the inflammatory response in retained third molar surgery class II and other dental surgical procedures. However, the sample size is not enough to ensure the power of the study and sophisticated tools are needed to examine some of these findings, and not all the different crystalline forms of a drug will behave the same way in terms of their activity rate.

**REFERENCES**


