



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 days¹. Combined treatments with non-steroidal anti-inflammatory drugs and antibiotics may offer significant benefits in the prevention of pain and infections associated with oral surgery². 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 surgery³.

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 resistance⁴⁻⁶. 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)^{7,8}.

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 ⁹.

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 ¹⁰.

Accumulating evidence suggests that activation of proteolytic enzymes, including the matrix metalloproteinase family, is responsible for the collagen destruction during inflammatory diseases ¹¹. 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 collagenase 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 - Dipyrone 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-inflammatories 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%

($P < 0.0001$) and 69.49% ($P < 0.0001$) lower in relation to pain, bleeding, edema, inactive days, trismus, and discomfort, respectively, when 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 dipyrone 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).

	Control	Experimental	P	CI*
Pain	3.93	2.50	0.01	0.27-2.16
Bleeding	2.07	1.11	0.04	0.05-1.87
Discomfort	4.21	1.29	< 0.0001	1.86-3.99
Edema	4.14	1.71	< 0.0001	1.50-3.36
Infection	0	0	-	-
Trismus	3.54	1.00	< 0.0001	1.55-3.52
Inactive days	1.96	0.57	< 0.0001	0.73-2.05

*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^{16,17}. In our study there was no clinical infection in both treatments.

Patients often suffer considerable post-operative pain, hyperemia, bleeding, edema, trismus, and discomfort¹⁸. Sub-antimicrobial dose doxycycline aims to modulate the host by suppressing the inflammatory response¹¹. 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 collagen¹. In our study pain, bleeding, edema, trismus, and discomfort were significantly lower when using the doxycycline gel in nanotubes, compared with conventional

treatment, which resulted in a reduction in the number of inactive days and treatment costs. Also, patient compliance to treatment was increased. For several reasons, this evaluation of the signs and symptoms after surgery was made by patients, previously trained, including the high demand for dental care in the hospital, which would compromise the care of patients not involved in the research, to avoid that patients had to travel to the hospital, since there was a need for rest, and because we consider that there would be greater fidelity to evaluate the intensity of symptoms. However, the intensity of some signals could be better assessed by a trained professional.

The statistically better results for the experimental group can be justified by the fact doxycycline, inoculated into the surgical cavity prior to closure, is inserted in a degradable

platform which allows controlled and extended release of the drug in a therapeutically relevant concentration. Other benefits include increased bioavailability, improved patient compliance, higher efficiency, low side effects, limited potential for systemic absorption and toxicity, reduced volumes of antibiotic use, and, possibly, less potential for the development of antibiotic resistance, e.g. bowel microbiota⁶.

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 costs⁶. Thus, it is possible to consider doxycycline gel in nanotubes an 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

1- PRESNAW PM, HEFTI AF, JEPSEN S, ETIENNE D, WALKER C, BRADSHAW MH. Subantimicrobial dose doxycycline as adjunctive treatment for periodontitis. A review. J Clin Periodontol. 2004; 31: 697-707.

- 2- GRAZIANI F, CORSI L, FORNAI M, ANTONIOLI L, TONELLI M, CEI S. Clinical evaluation of piroxicam-FDDF and azithromycin in the prevention of complications associated with impacted lower third molar extraction. *Pharmacol Res.* 2005; 52: 485-490.
- 3- ARTEAGOITIA I, RAMOS E, SANTAMARIA G, BARBIER L, ALVAREZ J, SANTAMARIA J. Amoxicillin/clavulanic acid 2000/125 mg to prevent complication due to infection following completely bone-impacted lower third molar removal: a clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2015; 119: 8-16.
- 4- FRIBERG Ö, SVEDJEHOLM R, SÖDERQUIST B, GRANFELDT H, VIKERFORS T, KÄLLMAN J. Local gentamicin reduces sternal wound infections after cardiac surgery: a randomized controlled trial. *Ann Thorac Surg.* 2005; 79: 153-161.
- 5- PARVIZI J, SALEH KJ, RAGLAND PS, POUR AE, MONT MA. Efficacy of antibiotic-impregnated cement in total hip replacement. *Acta Orthop.* 2008; 79: 335-341.
- 6- SINGH K, NAIR AB, KUMAR A, KUMRIA R. Novel approaches in formulation and drug delivery using contact lenses. *J Basic Clinic Pharm.* 2011; 2: 87-101.
- 7- MCHUGH SM, COLLINS CJ, CORRIGAN MA, HILL AD, HUMPHREYS H. The role of topical antibiotics used as prophylaxis in surgical site infection prevention. *J Antimicrob Chemother.* 2011; 66: 693-701.
- 8- MELO GB, MOREIRA MR. Antimicrobials: old tools, new approaches. In: *Science against microbial pathogens: communicating current research and technological advances*, vol. 1, 3rd ed., Badajoz: Formatex Microbiology Series, Badajoz, Spain; 2011. p. 631-635.
- 9- HANES PJ, PURVIS JP. Local anti-infective therapy: pharmacological agents. A systematic review. *Annals of Periodontology.* 2003; 8:79-98.
- 10- KIRKWOOD KL, CIRELLI JA, ROGERS JE, GIANNOBILE WV. Novel host response therapeutic approaches to treat periodontal diseases. *Periodontology 2000.* 2007; 43: 294-315.
- 11- BEZERRA MM, BRITO GAC, RIBEIRO RA, ROCHA FAC. Low-dose doxycycline prevents inflammatory bone resorption in rats. *Braz J Med Bio Res.* 2002; 35(5): 613-616.
- 12- MEIRA ALT, TODESCAN SMC, AZOUBEL E, BITTENCOURT S, AZOUBEL MCF. Use of local antimicrobials in periodontics: A critical approach. *Periodontia.* 2007; 17(1): 83-89.
- 13- FATTAH CMRS, ARANEGA AM, LEAL CR, MARTINHOJ, COSTA AR. Control of postoperative pain in oral surgery: literature review. *Rev Odontol Araçatuba.* 2005; 26(2): 56-62.
- 14- REN YF, MALMSTROM HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a metaanalysis of randomized controlled clinical trials. *J Oral Maxillofac Surg.* 2007; 65(10): 1909-1921.
- 15- SASKA S, SCARTEZINI GR, SOUZA RF, HOCHULI-VIEIRA E, FILHO VAP, GABRIELLI MAC. Tramadol/acetaminophen in the control of the postoperative pain for impacted third molar surgery. *Rev Cir Traumatol Buco-Maxilo-Fac.* 2009; 9(4): 99-106.
- 16- MCMANUS LM, PINCKARD RN. Paf, a putative mediator of oral inflammation. *Crit Rev Oral Biol Med.* 2000; 11: 240-258.
- 17- DEO V, BHONGADE ML. Pathogenesis of periodontitis: role of cytokines in host response. *Dent Today.* 2010; 29: 1-11
- 18- RICIERY CB, ARANEGA AM, TAKAHASHI A, LEMOS FR. Alveolite: ocorrência e tratamento em consultórios odontológicos de Araçatuba/SP (alveolitis: incidence and treatment in the dental office of Araçatuba/SP). *Rev Fac Odontol Lins.* 2006; 18: 33-40.