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USE OF TOPICAL CLINDAMYCIN IN THE TREATMENT OF ROOT SURFACE IN DELAYED TEETH REPLANTATION – STUDY IN RATS

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ABSTRACT

This study aims to evaluate dentoalveolar repair after topical use of clindamycin as root surface treatment of replanted teeth. Fourteen Wistar rats had the right maxillary incisor extracted and stored dry. The periodontal ligament was removed chemically by immersion in 1% sodium hypochlorite. Specimens were distributed into an experimental group (immersion in clindamycin solution for 5 minutes) and a control group (no topical antibiotic treatment) and then replanted. After 90 days, specimens were examined histologically, and variables were analyzed using the Fisher exact test ($p<0,05$).Showed no inflammatory infiltrate or up to 10% of the field in both groups. In the control group, periodontal ligament fibers were reinserted in a disorganized way, and there were areas of replacement and inflammatory resorption and ankylosis. In the experimental, there was no reinsertion of the periodontal ligament fibers, and there were few areas of inflammatory resorption, but extensive areas of replacement resorption and ankylosis. Chemical removal of periodontal ligament together with topical use of clindamycin resulted in few and small areas of inflammatory resorption, but marked ankylosis along the root surface.

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INTRODUCTION

Replantation is the treatment of choice for tooth avulsion because it responds, for an undetermined period of time, to the immediate psychological needs of patients and their families (FLORES *et al.,* 2007; SUÁREZ; GUITART, 1988). Immediately repositioning the tooth after avulsion is not always possible. If the tooth is kept for a long time out or its socket, the periodontal ligament (PDL) on the root surface may dry and necrotize (TROPE; FRIEDMAN, 1992). In such cases, replantation should be delayed and the treatment of the root surface should include the removal of the necrotic PDL to preserve root structure and to prevent the action of bone resorption cells (FLORES *et al.,* 2007; ANDREASEN; KRISTERSON, 1981; FILIPPI; POHL; VON ARX, 2001; IQBAL; BAMAAS, 2001).

Different chemicals have been used in the topical treatment of the root surface, such as: sodium fluoride (ANDREASEN, 1994), calcium hydroxide (OKAMOTO *et al.,* 1998), sodium hypochlorite (KANNO *et al.,* 2000), dexamethasone, citric acid (KEUM *et al.,* 2003), acetazolamide (MORI; GARCIA, 2002), adenosine triphosphate solution (ZANETTA-BARBOSA; de CARVALHO, 1990), stannous fluoride (SAAD-NETO *et al.,* 1984), bisphosphonate compounds, such as alendronate (LUSTOSA-PEREIRA *et al.,* 2006), vitamin C, and propolis (PANZARINI, 2005). Tooth replantation failure may be assigned to the difficulty in preventing the contamination of avulsed teeth by bacteria. Bacteria seem to promote inflammatory root resorption, and lead to severe sequelae in cases of replanted avulsed teeth. To inhibit or minimize their action, the use of systemic antibiotics has been suggested, particularly those derived

from penicillin (SAAD-NETO; PINTO; COLLIBOATTO, 1991) or topical antibiotics, such as: rifamycin (OKAMOTO, 2003), tetracycline (MA; SAE-LIM, 2003; BRYSON *et al.,* 2003), and lincosamides (SILVA *et al.,* 2009). The major lincosamides are lincomycin and clindamycin. Recent studies showed that lincomycin, evaluated for the treatment of the surface of avulsed teeth, maintained PDL integrity and its reinsertion in cementum, and local inflammation was reduced (SILVA *et al.,* 2009). Clindamycin is a semi-synthetic derivative of lincomycin chloride, largely used clinically. It is about 20 times more powerful than lincomycin in inhibiting the growth of *Escherichia coli* (VERDIER *et al.,* 2000) and more active in the treatment of bacterial infections, particularly those produced by anaerobic species (SPÍZEK; REZANKA, 2004). This study aims to evaluate tissue response to the topical use of clindamycin phosphate in the treatment of the root surface of rat teeth intentionally avulsed and replanted.

MATERIAL AND METHODS

This study was approved by the Ethics Committee on the Use of Animals local. The Ethical Principles in Animal Experimentation were adopted, recommended by the Brazilian Society of Science in Laboratory Animals, an institution affiliated to the International Council for Laboratory Animal Science and respecting the precepts presented by the Brazilian Legislation on Experimental Animals, Law nº. 11.794, of October 9, 2008. Fourteen male Wistar rats 120 days old and weighing 250-300 g were used in this study. After weighing, the animals were anesthetized using an intraperitoneal injection of ketamine 100 mg/kg (ketamine®, Cristália Produtos Químicos Farmacêuticos Ltda., Itapira, SP, Brazil) and xylazine 10 mg/kg (Calmiun®, Agener União, Embu-Guaçu, SP, Brazil). After intra and extraoral antisepsis with 2% chlorhexidine digluconate (FGM Ltda., Curitiba, PR, Brazil), incisions to release the ligament, luxation and tooth avulsion were performed so that trauma was kept to a minimum. After extraction, the dental papilla was removed using a #15 scalpel blade.

The teeth were fixed by the crown to sterile bone wax (Bone wax, W31, 2,5g, sterile, Ethicon®, Johnsons do Brasil SA, São José dos Campos, SP) pads and were exposed to room conditions for 30 minutes. After that time, the pulp was removed with a slightly pre-curved #15 Flexofile (Flexofile endodontic files – size 15; 21 mm. Dentsply – Maillefer Instruments, Ballaigues, Switzerland.). The canal was cleaned with saline solution and a disposable syringe. PDL was removed chemically by immersion in 1% sodium hypochlorite (Carbocloro S/A Indústrias Químicas, Cubatão, SP, Brazil) for 30 minutes. The animals were randomly divided into two groups (n = 7) and received the following treatments: experimental group – immersion in 5 mL of clindamycin phosphate solution for 5 minutes; control group – no topical antibiotic treatment. The teeth were washed with 0.9% saline solution, the root canal contents were aspirated with a suction cannula, and the canal was dried with absorbing paper points. Immediately after that, the canals were filled with a calcium hydroxide paste, the sockets were carefully examined, and the teeth were then replanted. No splinting was used because the curvature of a rat's maxillary incisor (that has a C shape) is sufficient for the necessary stability for the replanted tooth (OKAMOTO *et al.,* 1995; LUSTOSA-PEREIRA *et al.,* 2006). The animals received a single intramuscular (IM) dose of penicillin G benzathine 20,000 units/kg immediately after replantation, and IM acetaminophen 80 mg/kg in the first 3 days postoperatively. The animals were fed ground Nuvital®and water ad libitum so that they would not need to gnaw their feed, which would overload the tooth and might affect results. After 90 days, the animals were euthanized. The side of the maxilla that contained the replanted tooth was removed, fixed in 10% buffered formalin for 24 hours and decalcified in 5% nitric acid. After that, the specimens were rinsed and embedded in paraffin to prepare blocks that were later cut into 6-µm sections with a microtome longitudinally to the incisor. Sections were stained with hematoxylin-eosin for histological analysis under light microscopy. A sample composed of a left incisor, which had not undergone treatment, from each group was used as a standard reference for histological analyses. Histological analysis was made by the same, previously calibrated examiner. Microscopic analysis was performed in the middle and apical thirds of the palatal surface of the root because in rats the PDL is found only on this surface (MARKS; SCHROEDER, 1996). The light microscope magnifications to evaluate the histological fields were 100 x and 400 x. Slide description included: inflammation intensity – granulation tissue, neutrophils, eosinophils, lymphocytes, plasma cells, macrophages, giant cells and mast. Each element was used to define the value of a total score: 1 = 0 or up to 10% (slight); 2 = 11 to 50% (moderate); 3 = greater than 50% (intense) (JURISIC *et al.,* 2008; de OLIVEIRA; RIBEIRO-SILVA; ZUCOLOTO, 2007); PDL reinsertion (yes/no); distribution of PDL fibers – organized (parallel, oblique) or disorganized; presence or absence of resorption – surface, replacement or inflammatory; and ankylosis. Data were analyzed using tables, graphs, descriptive statistics and the Fisher exact test at a level of significance of 5% (VIEIRA, 2004; de OLIVEIRA; RIBEIRO-SILVA; ZUCOLOTO, 2007).

Table 1. Comparison of inflammation intensity between control and experimental groups

Variable	Control group				Experimental group				p*
	Score 1		Score 2		Score 1		Score 2		
	n	%	n	%	n	%	n	%	
Middle third									
Granulation tissue	7	100	-	-	6	100	-	-	-
Neutrophils	7	100	-	-	6	100	-	-	-
Eosinophils	7	100	-	-	6	100	-	-	-
Lymphocytes	6	85.7	1	14.3	6	100	-	-	1.000
Plasma cells	7	100	-	-	6	100	-	-	-
Macrophages	7	100	-	-	6	100	-	-	-
Giant cells	7	100	-	-	6	100	-	-	-
Mast cells	7	100	-	-	6	100	-	-	-
Apical third									
Granulation tissue	6	85.7	1	14.3	4	66.7	2	33.3	0.559
Neutrophils	7	100	-	-	6	100	-	-	-
Eosinophils	7	100	-	-	6	100	-	-	-
Lymphocytes	6	85.7	1	14.3	4	66.7	2	33.3	0.559
Plasma cells	7	100	-	-	6	100	-	-	-
Macrophages	7	100	-	-	5	100	-	-	-
Giant cells	7	100	-	-	6	100	-	-	-
Mast cells	7	100	-	-	6	100	-	-	-

*Fisher exact test. Statistically significant p<0,05.

RESULTS

One animal in the experimental group died in the study; therefore, the sample comprised 13 animals, six in the experimental group and seven in the control group.

Table 2. Comparison of resorption, ankylosis, and PDL reinsertion between control and experimental groups

Variable	Control group		Experimental group		p*
	n	%	n	%	
Middle third					
PDL reinsertion	3	42.9	-	-	0.192
Surface resorption	-	-	-	-	-
Replacement resorption	4	57.1	6	100	0.192
Ankylosis	4	57.1	6	100	0.192
Inflammatory resorption	2	28.6	1	16.7	1.000
Apical third					
PDL reinsertion	2	28.6	-	-	0.462
Surface resorption	-	-	-	-	-
Replacement resorption	5	71.4	5	83.3	1.000
Ankylosis	5	71.4	5	83.3	1.000
Inflammatory resorption	4	57.1	2	33.3	0.592

PDL = periodontal ligament. *Fisher exact test. Statistically significant p<0,05.

The analysis of healing included the alveolar bone, the PDL space, cementum and dentin on the palatal surface of the root.

Control group: Inflammatory intensity had a score of 1 in most specimens. PDL reinsertionwas seen in half of the specimens, mostly disorganized (Figure 1), although a little more organized in the middle third. No surface resorption was found. There was replacement root resorption characterized by direct connection between alveolar bone and tooth, without interposition of periodontal ligament (Figure 2) and ankylosis. Inflammatory resorption was seen in 50% of the specimens, but it was associated with the apical third (Figure 3). Bone showed organized trabeculae away from PDL, and there were clots and granulation tissue in the apex of all specimens.

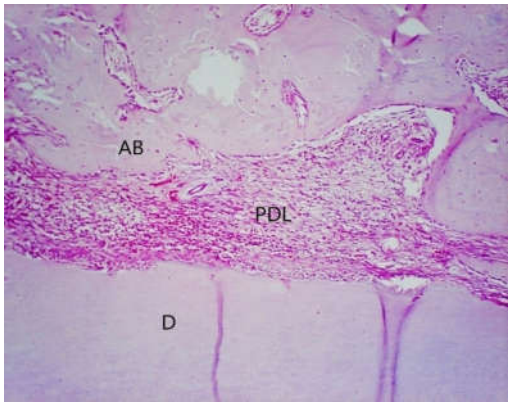

Figure 1. Control group - Periodontal ligament (PDL), with disorganized fibers in root middle third, between dentin (D) and alveolar bone (AB). H.E. 40X magnification

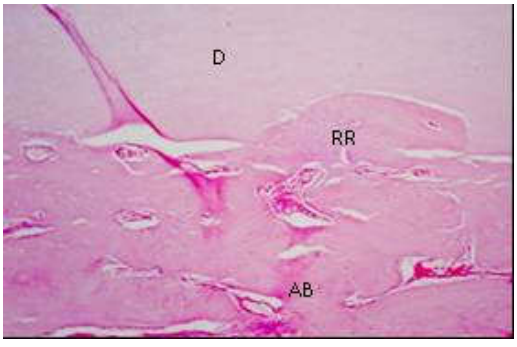

Figure 2. Control group - Replacement resorption (RR) in root apical third. Note direct connection between alveolar bone (AB) and dentin (D), without interposition of periodontal ligament. H.E. 40X

Experimental group: The intensity of inflammation had a score of 1 in four specimens, and, in two specimens, a score of 2 in the root apical third. There was no PDL reinsertion, and no surface resorption, although some inflammatory resorption was seen only in the apical third of two specimens and the root middle third of another. Replacement resorption (Figure 4) and ankylosis were present. Bone tissue was abundant due to intense new tissue formation.

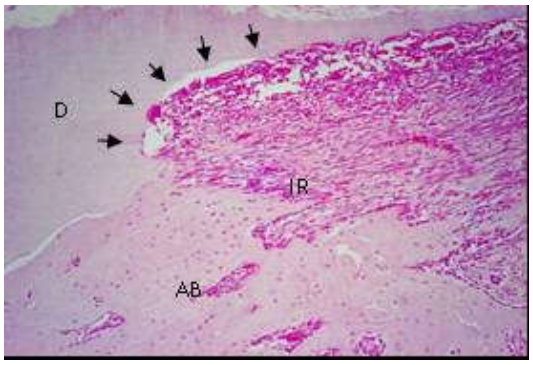

Figure 3. Control group - Note inflammatory resorption (IR) in the root apical third (arrow), between dentin (D) and alveolar bone (AB). H.E. 40X magnification

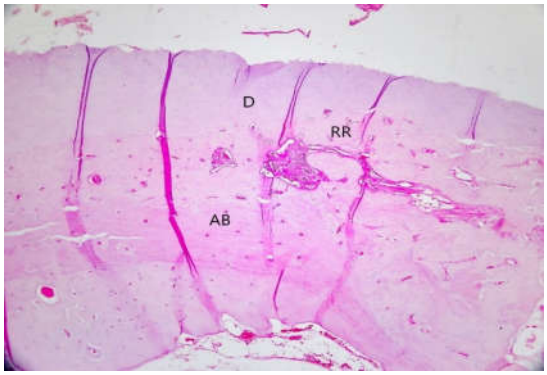

Figure 4. Experimental group - Replacement resorption (RR) in root middle third. Absence of periodontal ligament between dentin (D) and alveolar (AB). H.E. 40X magnification

Although abundant, newly formed bone was organized all over the palatal surface in all specimens. The comparison of inflammatory intensity between the two groups revealed that, in delayed replantation, only a few or no inflammatory cells were seen, and most specimens had a score of 1 in both the middle and the apical thirds. The results of the Fisher exact test did not show any significant association between the variables compared (Table 1). The comparison of surface, replacement and inflammatory resorption, ankylosis and PDL healing between groups did not show any significant association (Table 2). The comparison of distribution of PDL reinsertion between groups did not reveal any significant association between the variables, whether they were organized, disorganized or showed no healing without fibers. The inflammatory process parameters did not score 3.

DISCUSSION

Replantation should be performed immediately after avulsion. When performed up to 15 minutes after it, it is classified as immediate; at

extra alveolar times greater than 15 minutes, it is called delayed replantation (ANDERSSON; BODIN, 1990). In this study, the use of clindamycin was tested in delayed replantation, in which dry storage lasted 30 minutes. PDL removal has been suggested for cases in which extra alveolar time is long, and the tooth is kept in dry or inadequate wet storage, because it may necrotize and the PDL cells may become less viable (ANDREASEN; ANDREASEN, 2001; CONSOLARO, 2005). Necrotic PDL that remains on the root surface may promote external root resorption, the main cause of replanted tooth loss (OKAMOTO; HANADA; SAAD-NETO, 1986; ANDREASEN *et al.,* 1995). Removal or treatment of necrotic PDL results in less root resorption and a greater area of ankylosis (PERCINOTO *et al.,* 1988; SONODA, 2000). Root resorption, therefore, is associated with the preservation of PDL and the cementoblast layer. Ankylosis occurs due to PDL removal; the tooth is fixed to the bone, and may stay there for years. Progressive resorption may also lead to dental loss (SUÁREZ; GUITART, 1988). Failed tooth replantation may be assigned to the difficulty in preventing the contamination of avulsed teeth by bacteria (ANDREASEN; KRISTERSON, 1981). In cases of avulsion, the vascular and nervous bundles are severed, which may lead to pulp necrosis and bacterial contamination. Therefore, endodontic treatment should be performed to avoid that bacteria in the root canal, combined with other factors (such as damage to cementum and PDL) promote inflammatory resorption. In this study, endodontic treatment was performed by removing the pulp and filling the root canals with calcium hydroxide paste to control resorption (FLORES *et al.,* 2007; GULINELLI *et al.,* 2008). Bacterial contamination of avulsed teeth may have adverse effects on dental replantation (SAAD-NETO; PINTO; COLLIBOATTO, 1991) and, therefore, trigger or accelerate resorption. The use of systemic antibiotics to inhibit or control resorption has been used routinely in cases of avulsion and replantation and is part of the guidelines of the American Association of Endodontic for the treatment after replantation (FLORES *et al.,* 2007). In this study, IM penicillin G benzathine was used immediately after replantation in all animals. Systemic antibiotic treatment should be used because, in addition to the contamination due to pulp necrosis, there is another contamination path, the exposed root surface during extra alveolar time (CVEK *et al.,* 1990; ANDERSSON; BODIN, 1990). Not using treatment with antibiotics might result in infection and increased inflammatory resorption. Several topical antibiotics have been tested as treatment of the root surface: rifamycin (SAAD-NETO; PINTO; COLLIBOATTO, 1991; OKAMOTO, 2003), derivatives of tetracycline, such as minocycline (MA; SAE-LIM, 2003; BRYSON*et al.,* 2003), and doxycycline (CVEK*et al.,* 1990), and derivatives of lincosamides, such as lincomycin (SILVA *et al.,* 2009).

The effect of rifamycin on the surface and root canal of replanted rat teeth was superior to the use of saline solution. It promoted the fast proliferation of connective tissue and new bone formation in the PDL area, prevented inflammatory root resorption, did not affect PDL remains in the initial period, but did not prevent surface resorption and ankylosisreplantation (SAAD-NETO; PINTO; COLLIBOATTO, 1991). Okamoto (2003), also evaluated the repair of delayed dental replantation followed by topical use of 1% stannous fluoride and sodium rifamycin, and found that PDL removal with sodium hypochlorite and surface treatment with fluoride and rifamycin ensured the preservation and integrity of cementum and dentin. Minocycline, applied topically to the tooth surface, did not prevent or reduce external resorption of the root surface of dog teeth (BRYSON*et al.,* 2003). However, studies using rats as an experimental model found beneficial effects of the topical use of minocycline in healing of delayed replantation, and greater incidence of complete healing than in the control group, which did not receive any topical antibiotic treatment, but the difference was not statistically significant (MA; SAE-LIM, 2003). Doxycycline was tested as topical medication in the treatment of the root surface of monkey teeth. It showed benefits even at low dosages, as high doses of some antibiotics may be toxic for the PDL. It promoted a greater frequency of pulp revascularization, a decrease in the number of microorganisms, and a lower incidence of ankylosis and inflammatory root resorption when used before replantation in monkey incisors (CVEK *et al.,* 1990). Lincomycin as treatment of the surface of avulsed teeth before replantation preserved PDL integrity, promoted its reattachment to cementum, and reduced local inflammation. However, root resorption and ankylosis were observed (SILVA *et al.,* 2009). Despite the good results of lincomycin in the decontamination of the root surface, it has been replaced in the market with clindamycin, which led us to conduct this study. Clindamycin was chosen for this study because lincosamides are antibiotics largely accepted for use in human beings and animals. It has affinity to bone and acts predominantly against Gram-positive microorganisms in the oral microbiota (RAJESWARAN; SRIKRISHNAN, 2004). Moreover, clindamycin is recommended in case of infections by gram-positive aerobic and gram-positive and negative anaerobic microorganisms as it inhibits bacterial protein synthesis, is bacteriostatic or bactericide, depending on the dose, inoculum and bacterial species (WANNMACHER; FERREIRA, 1999). When used systemically, clindamycin has similar effects to those achieved with penicillin, in terms of both microbiological and clinical parameters. It has been recommended as an alternative drug for the prevention and treatment of patients allergic to beta-lactam antibiotics (ANDREASEN *et al.,* 1995). It has good tissue penetration and its bone concentration is particularly high when compared with serum levels (WANNMACHER; FERREIRA, 1999). Both groups had replacement resorption and ankylosis. Inflammation was mild or absent. In patients, the replacement resorption is a less unfavorable factor. In case the tooth is lost, which is not rare in patients with dental avulsion, there will be bone enough for rehabilitation with a dental implant without the use of bone grafts.

There was no significant association between variables under comparison. Histological analysis revealed that, in the control group, there was disorganized ligament healing and inflammatory resorption, especially in the root apex. However, in the experimental group, topical clindamycin reduced inflammatory resorption to a minimum, that is, it was found only in 1 of the 6 specimens in the middle third and in 2 of 6 specimens in the apical third. Vogt et al. (2015), found similar results when PDL was removed chemically in association with the topical use of 6% propolis. Therefore, the chemical action of 1% sodium hypochlorite for 20 minutes might have removed PDL completely, which was positive for repair as a whole. The determination of hypochlorite concentration was based on studies in the literature (OKAMOTO *et al.,* 1998; LUSTOSA-PEREIRA *et al.,* 2006; VOGT *et al.,* 2015). Surface resorption was not found in any of the specimens. As this type of resorption may be seen as transitory (self-limiting) or progressive (beginning of a more destructive resorption, either inflammatory or replacement) due to the long observation time, resorption might have occurred, but at time points subsequent to replantation. In face of the knowledge available in the literature about repair in cases of dental replantation and the progression of biological events, efforts should be made to prevent inflammatory resorption by controlling contamination with endodontic treatment, systemic antibiotics and root surface treatment. Replacement resorption and ankylosis will be expected while no PDL replacement is developed to fulfill its function (GULINELLI *et al.,* 2008; HERNÁNDEZ *et al.,* 2020). Studies should investigate possible treatments to make the root surface more resistant to resorption, or to delay resorption so that the tooth remains in the mouth for the longest possible time. Moreover, extra alveolar time is fundamental for the prognosis of an avulsed tooth, and campaigns should inform the community about the importance of replanting the tooth as early as possible.

CONCLUSION

There was no difference between the topical use of clindamycin and the control group, in the histological parameters of inflammatory process intensity, resorption, ankylosis and PDL reinsertion.The chemical removal of PDL à with sodium hypochlorite associated to topical use of clindamycin phosphate resulted in fewer areas of

inflammatory resorption and larger areas of replacement resorption and dentoalveolar ankylosis.

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