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ORIGINAL ARTICLE

Healing process after surgical treatment with scalpel, electrocautery and laser radiation: histomorphologic and histomorphometric analysis

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Abstract The aim of this study was to evaluate and compare the healing process after surgical treatment of chemically induced lesions in the lateral edge of tongue of hamsters performed with scalpel, electrocautery, carbon dioxide (CO_2) laser radiation or neodymium:yttrium–aluminum–garnet (Nd:YAG) laser radiation. Eighty hamsters of both sexes were used and examined at postoperative days 7, 14, 21 and 28 by histological and histomorphometric analysis of the skeletal muscle fibers. In the histological analysis it was observed that the dynamics of the healing process was faster in the group treated by scalpel than in the other groups. The histomorphometric observation of the skeletal muscle fibers was submitted to one-way analysis of variance (ANOVA) and Tukey's multiple comparison test, with a level of significance set at $P<0.05$, which showed that the amount of skeletal muscle fiber formed had significantly increased in the group treated by scalpel in comparison with that in the groups treated by electrocautery ($P<0.01$), CO_2 laser irradiation ($P<0.001$) and Nd:YAG laser irradiation ($P<0.01$) on the 14th postoperative day. A gradual increase in skeletal muscle fibers formed during the healing process was observed in all groups. When the laser irradiated groups were compared, it was possible to conclude that tissue organization and vascularization were faster and more intense in the Nd:YAG laser irradiated group than in the CO_2 laser irradiated group.

Keywords Lasers · Carbon dioxide · Neodymium:yttrium–aluminum–garnet (Nd:YAG) · Wound healing

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Introduction

When there is tissue loss, it is restored by regeneration or cicatrization. Regeneration is the replacement of damaged cells or tissue by tissue similar to the original, re-establishing the function, whereas cicatrization or repair is characterized by the formation of new connective tissue with substitution of the damaged cells and alteration of the architecture of the tissue [1]. However, this results in a satisfactory functional and structural condition but not like that previous to the injury [2].

High-power laser radiation, particularly by carbon dioxide (CO_2), diode, argon, erbium:yttrium–aluminum–garnet (YAG) and neodymium:yttrium–aluminum–garnet (Nd:YAG), has been utilized for surgical procedures such as incision, vaporization and coagulation, including, in traumatic wounds, application to benign neoplasm, proliferative processes, potentially premalignant lesions, and selective cases of malignant neoplasms [3–5]. For several authors the use of laser radiation did not increase the repair capacity of buccal wounds when compared with the surgical techniques carried out with scalpel, electrocautery and cryosurgery. However, the authors observed diminution of the time required for surgical procedures and that the application could be controlled with precision, with less tissue destruction associated with minimal contraction of the postoperative wound. These results justify the utilization of laser radiation, with detach for the lasers CO_2 and Nd:YAG, as a helpful tool in surgery on soft buccal tissue [6–10].

Regarding the use of electrocautery in the incision and coagulation of soft tissue, Sinha and Gallagher [11] and Camacho-Alonso and López-Jornet [12] considered some advantages when it was compared with the scalpel technique; among the advantages cited were diminution of surgery time, depletion of blood loss during surgery, and better visibility. However, this technique also can cause complications, such as electric burn, increase of postoperative pain, weight loss, repair delay, fumes from toxic gases, and electromagnetic interference with other instruments in the area. causing deficiency in the operation of implanted cardiac devices or in cochlear implants.

The purpose of this research was to evaluate the developmental process of tissue repair, after surgical treatment with scalpel, electrocautery and laser irradiation with CO_2 and Nd:YAG, by histomorphologic examination and statistical analysis of the histomorphometry of the skeletal muscle fibers.

Materials and methods

Animals

After approval by the Ethics in Research Committee of Pontifical Catholic University of Rio Grande do Sul, Brazil (protocol no. 06/03494), 80 Syrian hamsters (*Mesocricetus auratus*) of both sexes, weighing an average 150 g and approximately 8 weeks old, were kept in natural conditions of temperature and luminosity and fed with standard laboratory diets and water ad libitum.

Lesion induction

A wound in the left lateral border of the tongue was chemically induced by the infiltration of an aqueous solution of mono-ethanolamine oleate 5% (Ethamolin, Zest Farmaceutica Ltd., Rio de Janeiro, Brazil) in a single dose of 10 mg/kg body weight per 0.2 ml. For this procedure the animals were anesthetized with an intraperitoneal injection of xylazine (5 mg/kg body weight) (Rompum®, Bayer, Sao Paulo, Brazil) and ketamine (25 mg/kg body weight) (Dopalen®, Vetbrands, Sao Paulo, Brazil).

Surgical procedure

Seventy-two hours after induction, each lesion was clinically observed. The animals were divided into four groups of 20 and, once again, were anesthetized by intraperitoneal injection of xylazine (10 mg/kg body weight) and ketamine (50 mg/kg body weight) for surgical removal of the induced lesion.

Group treated by scalpel In the group treated by scalpel (SG) the lesion was removed with a steel scalpel (blade number 15, Solidor, Lamedid, Sao Paulo, Brazil). After the exeresis, the surgical area was cleaned with a sterile solution of 0.9% sodium chloride (NaCl) (Laboratory Sanobiol Ltd., Pouso Alegre, Brazil), and a simple suture was made with silk 4-0 (Ethicon®, Johnson & Johnson, Sao Paulo, Brazil) to approach the surgical borders.

Group treated by electrocautery In the group treated by electrocautery (EG) the lesion was removed by electrocautery (BM-560, Medical Cirurgica Ltda., Sao Paulo, Brazil) with 4 W of power and a 6-mm-diameter electroprobe, in incision mode.

Group treated by CO_2 laser irradiation In the group treated by CO_2 laser (CO_2) the lesion was removed by CO_2 laser radiation (Sharplan 15F, Israel/Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), protocol no. 97/07645-2) with 0.8 mm focus, 4 W of power, with 469 W/cm^2 of power density, and in continuous mode.

Group treated by Nd:YAG laser irradiation In the group treated by Nd:YAG laser (Nd:YAG) the lesion was removed by Nd:YAG laser radiation (Pulse Master 600IQ®, Dental Laser System, American Dental Technologies Inc., MI, USA) at 30 Hz, 200 mJ/Hz, 6 W of power, with 0.77 J/cm^2 of power density, and delivery by a 300 μm optic fiber in continuous and contact modes.

Wounds in the groups treated by electrocautery, CO_2 and Nd:YAG laser were sutured.

All surgery was performed on the same day and by the same individual, and all personnel participating in the surgery and vaporization process wore protective safety glasses, masks, and gloves. Vaporization was done under

constant aspiration of the fumes (Surgfresh, Texas, USA–FAPESP 97/07645-2).

Wound healing in each animal was histomorphologically evaluated over the following time sequences: 7 days, 14 days, 21 days and 28 days after the surgical procedure. Five animals from each group were killed at the end of each observation period with an overdose of anesthetic. The tongue fragment was removed en bloc, fixed in 10% formaldehyde for 72 h and embedded in paraffin. Histological sections approximately 5 μm thick were cut, sectioned in a transversal plane, and were stained with hematoxylin–eosin. All samples were studied by the same observer. These sections were then examined by light microscopy, and alterations in the tongue mucosa (epithelium and lamina propria) and muscle layer were observed.

Histomorphologic analysis

Histomorphologic examination of the surgical pieces was carried out, with regard to the evolution of the healing process, the cells involved, and the skeletal muscle fibers. The histological laminae were examined with a light microscope (Axioskop 40®, Carl Zeiss, Germany) under ×5, 10x, ×20 and ×40/0.63 objectives (Achroplan®, Carl Zeiss) and ×10 ocular lens (W-PI, Carl Zeiss).

Histomorphometric analysis

We used randomization as previously described by Gomes et al. [13] for selection of the sections for histomorphometric analysis, to eliminate sampling bias. Tongue fragments were sliced in a microtome (Leica RM2255, Nussloch GmbH), and ten histological sections were obtained. From these, three sections were randomly chosen for histomorphometric examination of the skeletal muscle fiber density, and, from each one three histological fields were taken, subjacent to the exeresis area of the lesion, to give nine fields per animal and a total of 720 fields to be quantified (the area of each histological field was equivalent to 14,275.18 μm^2). All the histological fields were collected by a digital system composed of a light microscope (Axioskop 40®, Carl Zeiss) with a ×40/0.63 objective (Achroplan®, Carl Zeiss) and a ×10 ocular lens (W-PI, Carl Zeiss), and a digital camera (AxioCam MR5®, Carl Zeiss) connected to a computer (Fujitsu Siemens) with AxioVision Release 4.6 software, 2007 version (Carl Zeiss).

Statistical analysis

Histomorphometric results were submitted to one-way analysis of variance (ANOVA) and Tukey's test using GraphPad Prism software (GraphPad, version 4.02, San Diego, CA, USA). The level of significance used was $P<0.05$.

Results

Histomorphologic analysis

After 7 days

SG There was substitution of muscle tissue by loose connective tissue in the median portion of the fragment, rich in cells and vascularized, with intense infiltrate of inflammatory cells, predominantly mononuclear, and edema (Fig. 1a).

EG Necrotic tissue with seen, with coagulation and extensive areas of hyaline in some histological views. An intense infiltrate of inflammatory cells was observed, predominantly mononuclear. In this same region the presence of muscle fibers in degenerative processes were verified (Fig. 1b).

CO_2 There was an extensive ulcerated area covered by a serofibrin membrane, with intense infiltrates of polymorphonuclear and mononuclear inflammatory cells on the surface and in the deep region of the fragment, respectively. Giant cells also were observed. Some areas showed skeletal muscle fibers in degenerative processes. Hyaline areas and preserved nerve branches completed the histological view (Fig. 1c).

Nd:YAG There was an extensive ulcerated area covered by a thick hyaline layer. Substitution of the muscle tissue by loose connective tissue rich in cells and vascularized, and the presence of muscle fibers in degenerative processes. There were intense infiltrates of polymorphonuclear and mononuclear inflammatory cells (Fig. 1d).

After 14 days

SG Loose connective tissue replacing the pre-existing muscle tissue in the exeresis was seen, with a moderate inflammatory cell infiltrate, predominantly mononuclear. In addition, we observed new atrophic muscle fibers , in a disorganized distribution. We observed re-epithelization in the damaged area (Fig. 2a).

EG Loose connective tissue replacing the damaged muscle tissue showed numerous blood vessels with abscesses in some fragments. This tissue was still disorganized and had been penetrated by some remainders of atrophic muscle fibers in degeneration processes. There were areas of hyaline on the surface (Fig. 2b).

CO_2 An extensive ulcerated area, covered by hyaline material, was seen, with re-epithelization in the ulcerated area. In one of the fragments we observed severe epithelial atypia, showing a cellular pleomorphism and loss of the relation nucleus/cytoplasm, cellular hyperchromatism,

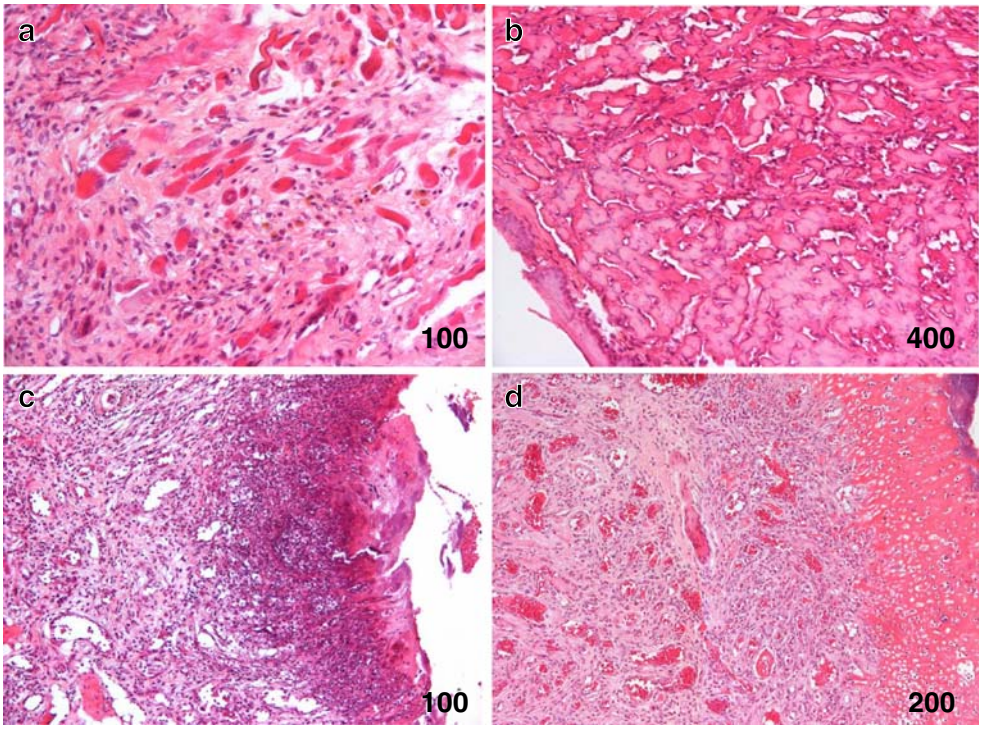

Fig. 1 After of 7 days. **a** Scalpel group, **b** electrocautery group, **c** CO_2 group, and **d** Nd:YAG group. Hematoxylin–eosin

intra-epithelial keratinization, duplicated basic layer and loss of epithelial stratification. An extensive area of loose connective tissue was verified, well cellularized and well organized, with a diffuse infiltrate of mononuclear inflammatory cells. Beyond that, there were new muscle fibers, distributed randomly, and degeneration of the remaining muscle bundles (Fig. 2c).

Nd:YAG There was substitution of muscle in superficial and deep layers, up to the middle of the fragment, by loose connective tissue. There were diffusing infiltrates of mononuclear inflammatory cells, and new muscle fibers distributed randomly adjacent to the damaged region; some muscle fiber degeneration remained (Fig. 2d).

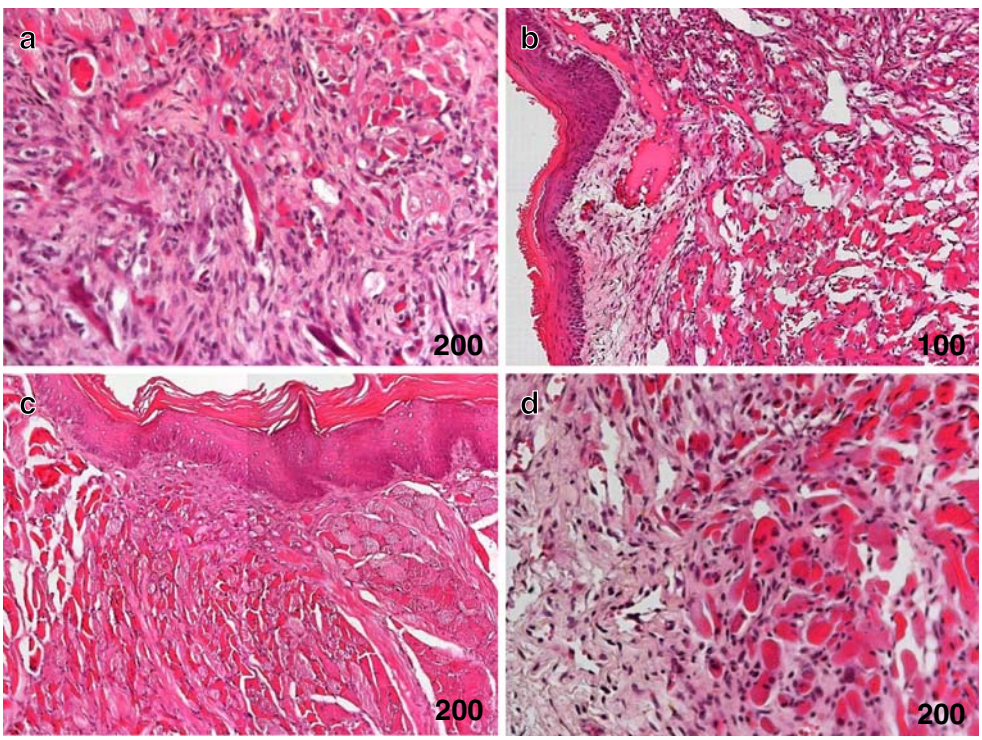

Fig. 2 After 14 days. **a** Scalpel group, **b** electrocautery group, **c** CO_2 group, and **d** Nd:YAG group. Hematoxylin–eosin

After 21 days

The re-epithelization was complete in the treated areas in the four groups.

SG Skeletal muscle fibers in a new formation were in the exeresis region, permeated with loose connective tissue distributed irregularly and in bundles. Collagen fibers were present, in irregular arrangement, and there were moderate infiltrates of mononuclear inflammatory cells (Fig. 3a).

EG There were some atrophic muscle bundles and numerous newly formed skeletal muscle fibers, randomly distributed and permeated with loose connective tissue with intense tecidual disorganization. The connective tissue presented low cellularity and vascularization, as well as discrete and diffuse infiltrates of mononuclear inflammatory cells (Fig. 3b).

CO_2 We observed numerous skeletal muscle fibers, permeated with well-cellularized connective tissue. The fibers were atrophic and with uniform aspects, restocking the connective tissue. In relation to the muscle tissue, the connective tissue was predominant and was disorganized on the surface of the fragment. Several mononuclear inflammatory cells were detected in the treated region (Fig. 3c).

Nd:YAG Some isolated newly formed muscle fibers, permeated with well-cellularized connective tissue, were seen. The muscle bundles exhibited an organized arrangement (Fig. 3d).

After 28 days

SG The muscle bundles presented numerous and more organized and scarce fibrous connective tissue among the muscle fibers (Fig. 4a).

EG We observed atrophic muscle bundles and some skeletal muscle fibers disposed in isolated groups and among the connective tissue rich in collagen fibers. There was a predominance of connective tissue over muscle fibers, and there was a discrete infiltrate of mononuclear inflammatory cells (Fig. 4b).

CO_2 There was a predominance of well-cellularized connective tissue, interspersed with isolated skeletal muscle fibers and some bundles. In addition, some muscle fibers presented structural alterations, such as central nuclei and hypertrophy. Moderate infiltrates of mononuclear inflammatory cells were present and, in some histological views, showed the remains of hyaline material in degradation processes (Fig. 4c).

Nd:YAG We observed a predominance of isolated muscle fibers among connective tissue rich in collagen fibers (Fig. 4d).

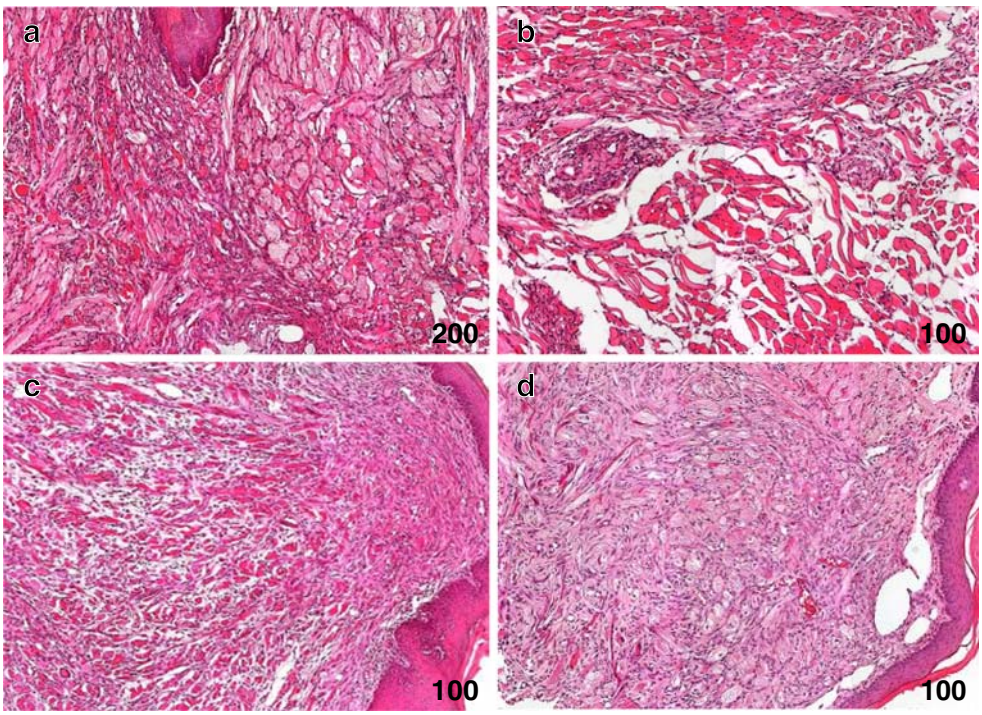

Fig. 3 After 21 days. **a** Scalpel group, **b** electrocautery group, **c** CO_2 group, and **d** Nd:YAG group. Hematoxylin–eosin

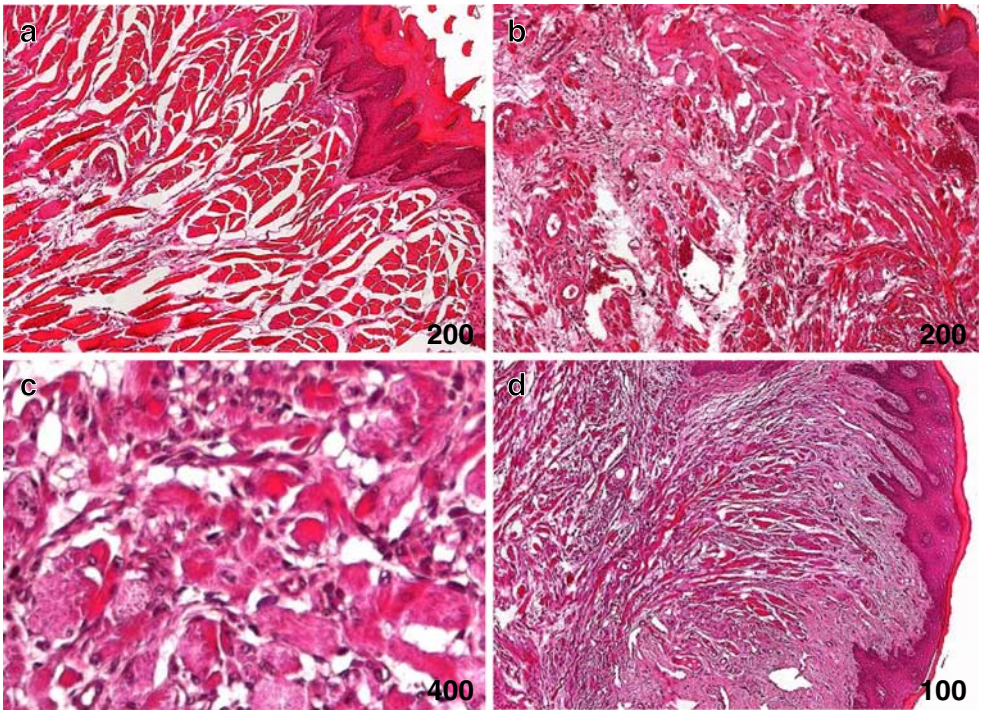

Fig. 4 After 28 days **a** Scalpel group, **b** electrocautery group, **c** CO_2 group, and **d** Nd:YAG group. Hematoxylin–eosin

In all the groups there was re-establishment of the papilla, predominantly the filiform papilla, on the dorsal surface of the tongue.

Histomorphometric analysis

We performed histomorphometric analysis to quantity the density of skeletal muscle fibers in the areas treated by scalpel, electrocautery, CO_2 and Nd:YAG. The results indicated a significant difference in the density of skeletal muscle fibers in the 14-day period only in SG, in comparison with the other experimental groups (Fig. 5).

The SG showed statistically significant differences between the 7 and 14 day, 7 and 21 day and 7 and 28 day periods. In the EG statistical differences were observed between the 7 and 21 day, 7 and 28 day and 14 and 21 day periods. In the CO_2 there was a verified statistical difference between the 7 and 21 day, 7 and 28 day and 14 and 28 day periods. The Nd:YAG showed statistically significant differences only between the 7 and 21 day periods (Fig. 6).

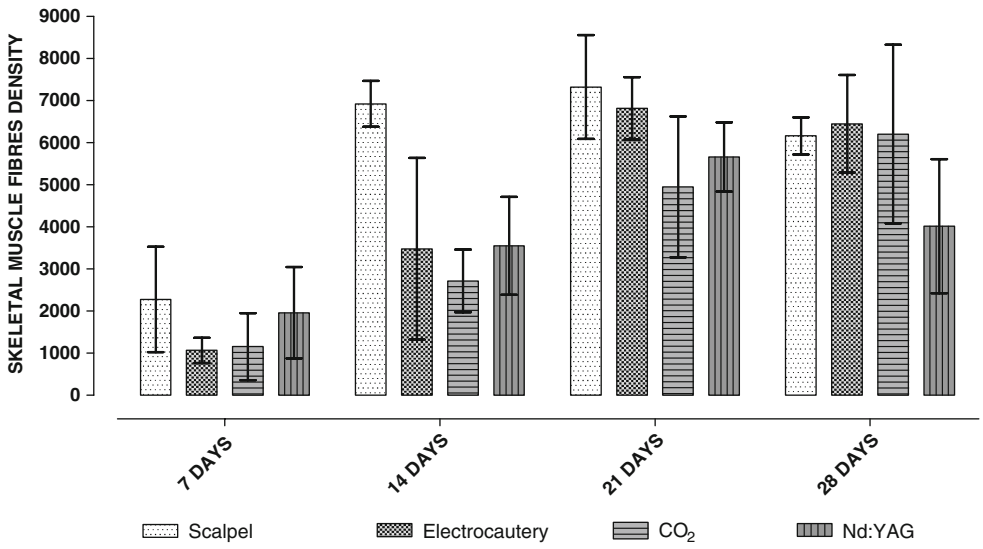

Fig. 5 Graphic representation of the density of skeletal muscle fibers (μm^2) in the region underlying the treated area in hamster tongues. Comparison between the groups. *Error bars* represent standard deviation of the average

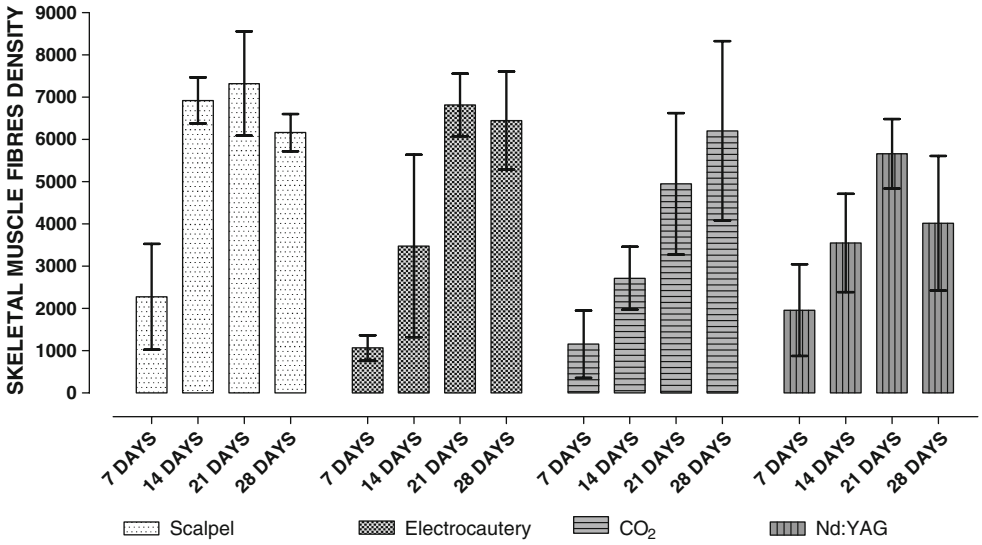

Fig. 6 Graphic representation of the density of skeletal muscle fibers (μm^2) in the region underlying the treated area in hamster tongues. Comparison between the periods. *Error bars* represent standard deviation of the average

Discussion

During the tecidual repair process of the ulcerated wound induced by the 5% aqueous solution of mono-ethanolamine oleate, we observed that the physiopathologic mechanism could be classified into three phases: necrotic (7 days), substitution (14 days) and reparatory (28 days). The necrotic phase constituted extensive areas of necrotic tissue on the surface of the treated wound and was associated with bacterial colonies as well as edema. In the underlying layer, there was an intense infiltrate of polymorphonuclear inflammatory cells, with granulation tissue and damaged skeletal muscle fibers among this granulation tissue.

In this research we verified that the 5% aqueous solution of mono-ethanolamine oleate had disseminated into the muscle layers of the tongue, provoking extensive areas of necrosis. This occurred due to the association between the high toxicity of this drug and the mechanical action during the drug's administration. Masaki et al. [14] considered a 5% aqueous solution of mono-ethanolamine oleate to be a sclerosant substance, able to dissolve the cell membranes and intercellular adhesions, increasing the permeability of the endothelial membrane, conditioning the wound to subsequent cellular and tecidual necrosis; the latter was seen in the histomorphologic analysis.

In the 7-day period the extent of the necrosis in the scalpel group was less than that in the others groups. The histomorphologic analysis showed minor tecidual damage, since the tissue had not been subjected to the deleterious effects of thermocoagulation and carbonization from the laser irradiation or burn from the electrocautery. Some authors have reported that the scalpel did not cause any thermal damage to the wound but permitted overflow of blood and lymph, causing a more accentuated inflammatory reaction that resulted in more edema and the formation of scars [15, 16]. Furthermore, from the tecidual damage provoked by the laser radiation and electrocautery, other authors have established a delay in the repair mechanism [3, 17–20]. This was also confirmed by the results of the histomorphologic analysis in our research.

At 7 days and 14 days, we observed in the laser radiation groups extensive bloody areas covered by a thick layer of amorphous material with hyaline aspects. According to the studies by Thuaksuban and Nuntanaranont [21], Sinha and Gallagher [11], and Horch and Deppe [22], the presence of this hyaline material is a result of the denaturation of the proteins and helps the tissue to contract. Other authors have reported that this hyaline layer of denatured collagen, observed on the irradiated surface at the beginning of the repair, acts as a biological waterproof dressing, reducing the irritation of the tissue and, consequently, reducing the intensity of the inflammation process and acting like a biomechanical barrier against microorganisms and hemorrhages [3, 4, 15, 22, 23]. Re-epithelization was observed in the majority of the animals in all the groups to the 14th postoperative day and had been completed by the 21st day. This phenomenon was not well shown in the 7-day period after lesion removal, due to the extent of the necrotic tissue associated with the bacterial colonies and due to the effects of the toxicity of the inductive drug. Research by Kardos et al. [24], Fortune and colleagues [25], and Romanos and co-workers [3] revealed granulation tissue and migration of epithelial cells 7 days after incision by CO_2 laser radiation. On the other hand, Sinha and Gallagher [11] observed re-epithelization to the end of the 28-day period. This variation of re-epithelization time ratifies the hypothesis that the degree of damage to the tissue can have an influence on the occurrence of this phenomenon.

A tecidual alteration not found in the literature was the severe epithelial atypia that was shown only in one animal in the CO_2 group in the 14-day period. This might have

occurred due to a late tecidual reaction to the effects of the toxicity of the drug after this kind of laser irradiation.

The residual muscular fibers in a process of degeneration or with structural alterations located below the neo formed connective tissue possibly due to intense absorption of energy of the electrocautery as well as by the two kinds of lasers.

Regarding the distribution and organization of skeletal muscle fibers, the scalpel group showed high expressiveness in comparison with the other groups in the 7-, 14- and 21-day periods. There was a progressive increase in the density of the muscle fibers in all the groups in the periods investigated. However, the histomorphometric analysis identified a significant statistical difference in the density of the skeletal muscle fibers created only in the 14-day period in the SG when compared with the EG ($P<0.01$), CO_2 ($P<0.001$) and Nd:YAG ($P<0.01$). Based on the results of this study, it is possible that this might have been due to the high tecidual damage that occurred during the initial periods of the treatment, which was potentialized by the undesirable effects of the electrocautery and both kinds of lasers. That verification, regarding the tecidual damage, also was histologically verified by Fisher et al. [15], Fortune et al. [25], and Friesen et al. [19].

Conclusion

In this study the histomorphologic analysis showed that the skeletal muscle fibers were best organized and the dynamics of the healing process were more rapid in the scalpel group. However, between the laser radiation groups, the organization of tissue observed in the Nd:YAG laser group was excellent and also from the vascularization point of view in the CO_2 laser group. The histomorphometric analysis showed progress in the density of the skeletal muscle fibers during the healing process in all the groups; however, it increased significantly in the scalpel group in comparison with the other groups during the 14-day period.

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