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Use of Ethyl 2-cyanoacrylate in Skin Synthesis in Horses - Evaluation of Efficacy and Biocompatibility

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ABSTRACT

***Background*:** Considering the difficulties in wound healing in horses, the possibility of using a biocompatible adhesive for wound suturing presents itself as an asset for equine surgery. The tissue adhesive, which is composed of ethyl-2-cyanoacrylate, offered advantages when used in human wounds, such as the absence of discomfort, reduction of surgical and healing time, a physical barrier against environmental infectious agents, resistance to exudates, and reduction of dehiscence. The objective of this study was to evaluate the efficacy and biocompatibility of ethyl-2-cyanoacrylate as a skin adhesive in equine surgical wounds and to compare it with the use of sutures in the healing process.

***Materials, Methods & Results*:** A total of 8 horses in 2 experimental stages, neck and croup, were used and divided into 2 groups at each stage. On both sides of the neck, 7-cm-long skin incisions were made, which were sutured with nylon thread (SG; suture group; left side of neck) or glued with ethyl-2-cyanoacrylate (AG; tissue adhesive group; right side of neck). The same procedure was performed on both sides of the croup of these animals, the left side being SG and the right side, AG. Macroscopic assessments of the surgical wounds of both groups were performed on days 1 (D1), 3 (D3), 7 (D7), 10 (D10), and 12 (D12) after surgery with standardized photographs regarding spacing and position. Animals with 70% to 100% dehiscence of the wound, i.e., with a length of more than 4.9 cm, were considered as total dehiscence and excluded from the evaluations. Aspects such as touch sensitivity, tissue consistency, volume increase and temperature, healing process, and signs of biomaterial rejection were observed. On the twelfth day after surgery (D12), a fragment of healed skin was harvested for microscopic evaluation. Tissue adhesive was considered a faster and easier method compared to SG, with advantages such as barrier function against microorganisms and the fact that it does not need to be removed. However, the major disadvantage was the high rate of dehiscence. Histopathological analysis showed a greater inflammatory infiltrate at SG, suggesting a reaction to the presence of the adhesive, in addition to being a more aggressive method of synthesis.

***Discussion*:** Ethyl 2-cyanoacrylate proved to be easy and quick to apply, with the time required for synthesis being significantly shorter compared with suturing, and caused no discomfort during the transoperative period. However, it was difficult to apply in cases of heavy bleeding because the product polymerized rapidly on contact with blood, which promoted good hemostasis but led to unsatisfactory synthesis of the wound, which may have contributed to its subsequent dehiscence. There was a significant difference between the studied groups in the presence of dehiscence, as the SG had no dehiscence compared with 50% of dehiscence in the AG as a whole (n = 16), with 37.5% considered total dehiscence and 12.5% partial wound dehiscence. One possible explanation is the high tensile force in the region, possibly due to excessive movement of the wound site, combined with the wound size of 7 cm, which is probably too large for the use of tissue adhesive alone, without deep relaxing sutures. In the present study, skin samples taken on day 12 from each group were examined. The results show that there was a greater amount of inflammatory cells in the SG than in the AG. The presence of the nylon thread as a foreign body and the greater aggressiveness in performing the suture may contribute to prolonging the inflammatory phases of the tissue repair process, as was found in this group. It was also possible to observe a greater amount of tissue reaction around the area of the AG scar, i.e. perivascular and periglandular (sebaceous and sweat glands), indicating contact dermatitis due to the presence of tissue glue.

Keywords: healing, horses, wounds, surgical adhesive, cyanoacrylates.

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INTRODUCTION

Surgical procedures are common in equine medicine routine. Healing by first intention occurs in noncontaminated wounds by approximating the edges of the lesion with sutures, which contributes to healing and shortens the time of the inflammatory phase and collagen remodeling [10,11].

Cyanoacrylate-based adhesives, including ethyl- 2-cyanoacrylate, are available as an alternative to conventional sutures, aiming at a nontraumatic, fast, and simple treatment that is painless, resulting in better wound esthetics, with hemostatic and bacteriostatic effect [8]. Clinical and experimental studies have shown several advantages in their use, including reasonable biocompatibility, wide availability, and low cost. However, previous studies have shown that adverse reactions may occur with the use of ethyl 2-cyanoacrylate. Most of the work addressing the biocompatibility of ethyl 2-cyanoacrylate has been performed in rats or humans, with no record of its use in equine surgery [2,4,15,16].

Considering the wound healing difficulties in horses, such as reaction to foreign bodies and excessive granulation tissue, associated with absence of pain, reduction of surgical and healing time, physical barrier to infectious agents and resistance to the action of exudates, the possibility of using a biocompatible adhesive in the synthesis of equine wounds presents itself as an enriching tool [6,9,17]. The aim of this study was to evaluate the efficacy and biocompatibility of ethyl-2-cyanoacrylate as a skin adhesive in equine wounds.

MATERIALS AND METHODS

Experimental animals and procedure

A total of 8 horses, male and female, aged 7 ± 3 years, with an average weight of 350 kg ($\sigma = 55.5$), of mixed breed, healthy and without the presence of scars or wounds on the neck and croup were selected for the surgical procedures. The experiment was divided into 2 stages so that the surgical procedures were performed on the 8 animals at 2 different time points. Stage 1 (S1) consisted of inducing surgical wounds in the neck region, and stage 2 (S2) in the croup region, both of which were considered day zero (D0) of the evaluation of the wounds of the respective regions. Both groups were divided into a tissue adhesive group (AG) and a suture group (SG).

After sedation with intravenous detomidine[1] [Detomidin® - 10 µg/kg], and anesthetic blockade with 2% lidocaine[2] [Lidovet®], a vertical skin incision of 7 cm was made on each side of the neck board, left and right of each horse, with the left side being the suture group (SG) and the right side being the tissue adhesive group (AG). In SG group, the skin was sutured with nº1 polyamide[3] (nylon) thread in simple separate stitches, totaling 7 stitches. In AG, EPIGLU®[4] (ethyl-2-cyanoacrylate) surgical adhesive was used in three layers, using about 0.25 mL of adhesive per animal. To apply the adhesive (Figure 1), the wound was pulled according to the manufacturer's instructions, so that the edges were adjacent, and glued with an initial fixation layer and 2 new layers to finish, waiting 2 min between each layer. Before applying the tissue adhesive, the wound was compressed with gauze for 3 min to promote hemostasis. Suturing and adhesive application occurred simultaneously, and the time required to synthesize each wound was recorded. In phase 2, the same protocols were used, except that a vertical skin incision of 7 cm was made on each side of the croup.

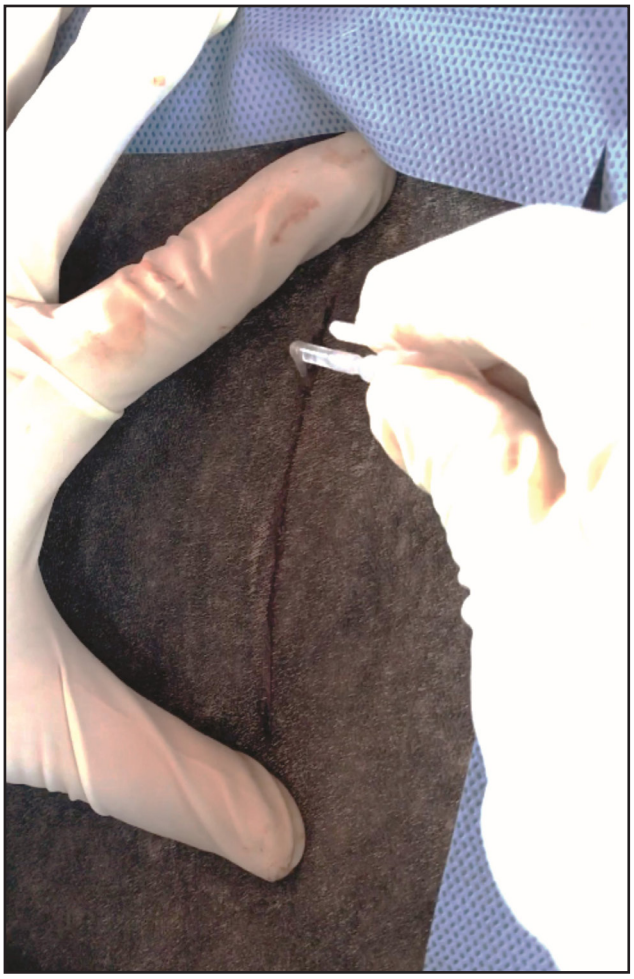

Figure 1. Application of EPIGLU® in the equine skin.

After both surgical procedures, horses were treated with flunixin meglumine[5] [Flumax® - 1.1 mg/kg every 24 h for 3 days] and repellent was used around the surgical wounds. At SG, sutures were removed 10 days after surgery. In the adhesive group AG, self-detachment of the adhesive was expected, which usually occurs between 5 and 10 days after application according to the instructions of the manufacturer of the surgical adhesive.

Macroscopic evaluation

The wounds were observed after the surgical procedure from the macroscopic aspect, evaluating the local presence of pain, increase in volume, temperature rise, and extravasation of secretion at the site. In addition, the coaptation of the edges, the formation of crusts and the presence of granulation tissue were evaluated.

Palpation was used to assess local touch sensitivity, which was graded as absent (0), mild (1), moderate (2), and severe (3), and local tissue consistency, which was graded as normal (0), fluctuating (1), edematous (2), or firm (3). The presence of secretion, presence of granulation tissue, increase in local volume, and formation of crusts were graded according to the following classification: absent (0), mild (1), moderate (2), and severe (3). The local temperature of the region was determined with a digital infrared thermometer, comparing the temperature measured in the central region of the wound with the temperature of the intact skin region at the upper left edge, in the trichotomized region. A significant temperature increase was defined as wounds that had a temperature deviation greater than or equal to 0.3°C compared with intact skin. Edge coaptation was rated as poor (0), moderate (1), good (2), and excellent (3). Animals in which the adhesive detached to some degree or that had rupture of the suture, with wound opening, and continuity solution was present after completion of the surgical procedure were classified as dehiscence. It was classified as follows: no dehiscence (0), dehiscence of up to 33% of the wound (1), dehiscence of 34% to 69% (2), or dehiscence of 70% to 100% of the wound (3). In the tissue adhesive group (GA), the detachment time of the adhesive was evaluated.

Animals were evaluated on days 1 (D1), 3 (D3), 7 (D7), 10 (D10), and 12 (D12) postoperatively with standardized photographs on distance and position. On day 12 (D12) of the experiment, the cosmetics of the resulting scar were evaluated. The evaluations were always performed by the same researcher. Animals with 70% to 100% dehiscence of the wound, i.e., with a length of more than 4.9 cm, were considered to have total dehiscence and were excluded from the evaluations.

Histological evaluation

Twelve days after each surgical procedure, samples of healed skin were obtained for histologic evaluation. Biopsy of the scar tissue fragment was performed with a size of 1 x 1 x 1 cm over the central region of the incision line. The tissue was placed in 10% formalin and sent to a specialized laboratory. Microscopic evaluation was performed by histological analysis of specific healing indicators, by assessing the integrity of the epithelium, the organization of the connective tissue, the presence of hemorrhage, fibroplasia, epithelial hyperplasia, hyperkeratosis, neovascularization, and the types of cells present. The presence of necrosis, inflammatory processes (neutrophils, lymphocytes, and eosinophils), giant cells, vascular neoformation, fibroblasts, and collagen deposition were evaluated.

Statistical analysis

All data were subjected to the Shapiro-Wilk test for residual normality test. Homoscedasticity of model residuals was tested with Levene's test. If the assumptions were sufficiently met (homogeneity of variances, normal distribution, residual with normal distribution), the Anova was performed, followed by the Tukey HSD test for multiple comparisons. If the assumptions were not met, the Kruskall-Wallis comparison was used, followed by a post-hoc multiple least squares comparison of means with Sidak adjustment. The interaction between factors was performed with the linear model Y ~ Treatment + Animal + Days, where Y represents the dependent variable to be explained, such as touch sensitivity, tissue consistency, granulation tissue, temperature fluctuations, volume increase, crust formation, presence of secretion, coaptation of margins, and dehiscence. A significance level of 5% was used. All plots were generated with the ggplot package [19] using R software[6].

RESULTS

The time required to coapt with the adhesive and to perform the suture in both stages is shown in Figure 2. It was found that the synthesis time with nylon was significantly longer compared to the surgical adhesive in 100% of the results obtained ($P < 0.05$).

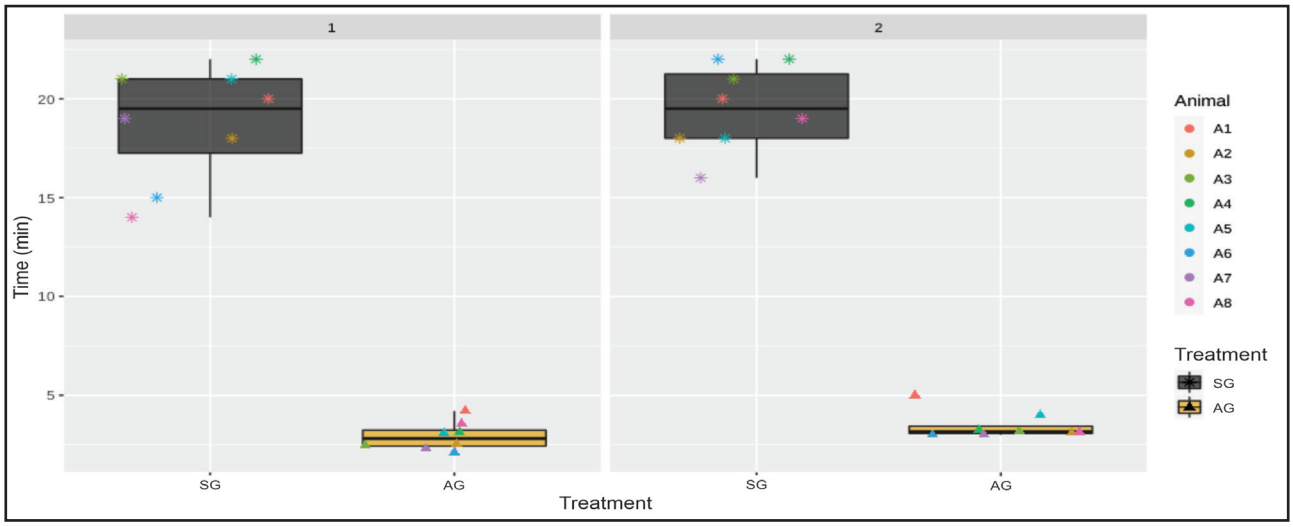

Figure 2. Diagram comparing the times required for synthesis with suture and tissue adhesive at different stages.

The ethyl-2-cyanoacrylate-based tissue adhesive[4] (Epiglu®) was practical to use and formed a flexible, strong, and impermeable layer over the wound, with satisfactory results at the end of application (Figure 3). In some cases, there were difficulties in applying the adhesive when there was persistent bleeding, resulting in unsatisfactory synthesis.

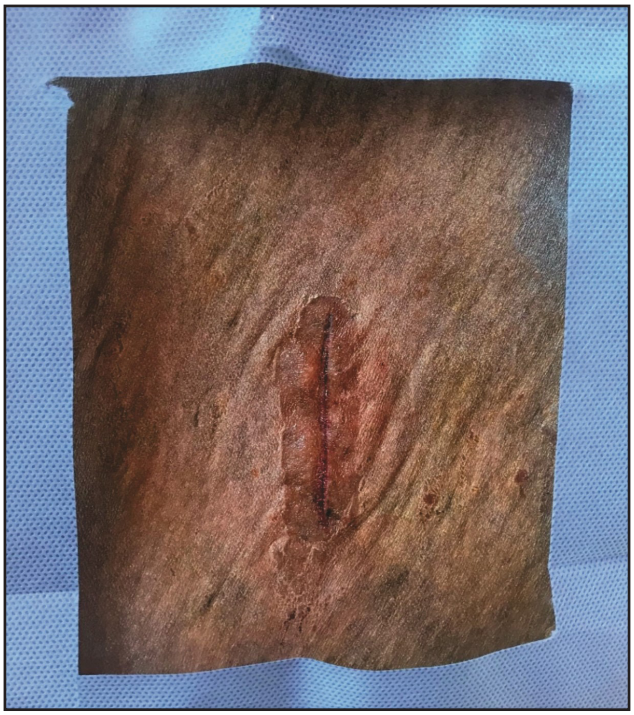

Figure 3. Satisfactory result immediately after the application of the tissue adhesive on the day of the surgical procedure in stage 1.

In macroscopic analysis, there were no significant differences in touch sensitivity, temperature increase, presence of secretion, formation of crusts and granulation tissue between the studied groups.

In stage 1 of the evaluation, no significant differences ($P > 0.05$) in tissue consistency were observed between SG and AG within each evaluation day (D1, D3, D7, D10, and D12), but significant differences ($P < 0.05$) were observed between the groups on all evaluation days in stage 2. In stage 2 there was also significant difference in volume increase, with the SG presenting volume increase for a longer time than AG.

Regarding coaptation of the margins, there was a significant difference between the groups only in stage 1 ($P < 0.05$), with worse coaptation of the margins in AG compared with SG, whereas in stage 2 there was hardly any difference between the results.

In the suture group (SG), tissue dehiscence did not occur at any of the stages. In the tissue adhesive group (AG), complete tissue adhesive dehiscence occurred between the first and third day after surgery (D1 to D3) in 3 animals at each stage (Figure 4). That is, considering the 2 stages of AG (n = 16), 6 animals (37.5%) had complete wound dehiscence. In addition, 2 animals (12.5%) had partial dehiscence at AG, making a total of 8 animals (50%) in this group with some degree of dehiscence.

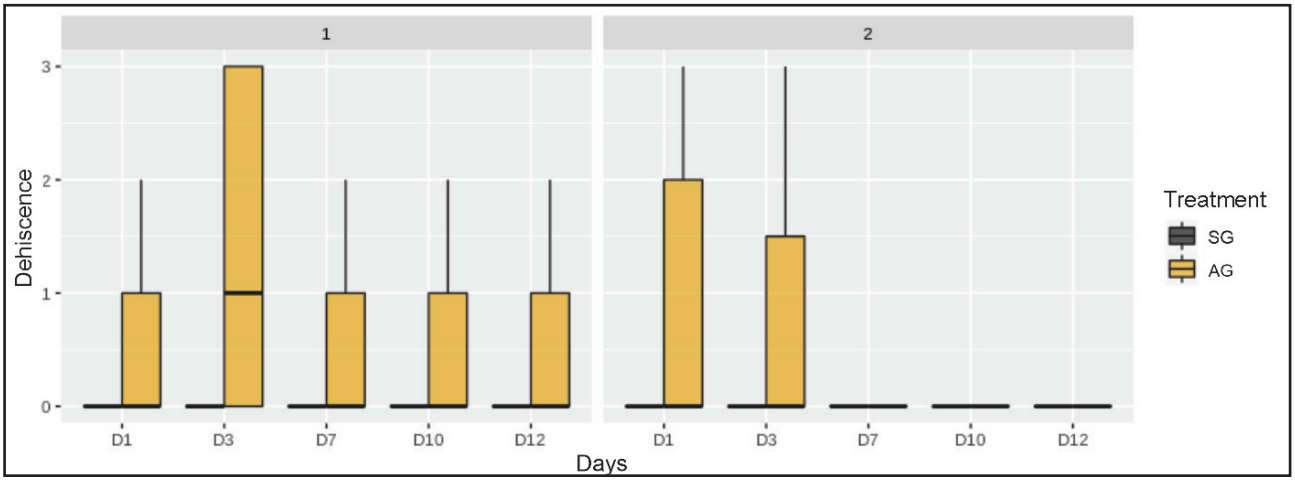

Figure 4. Diagram showing the relationship between the type of treatment (suture group - SG or adhesive group - AG) and the presence of tissue dehiscence at each stage (stage 1 - neck and stage 2 - croup) on the different evaluation days (D1, D3, D7, D10, and D12.

Microscopic analyzes were performed in animals that did not show complete dehiscence using biopsies taken on the 12th day (D12) after surgery. At each stage (1 and 2), samples were taken from 5 animals in each group for histopathologic examination.

At stage 1, complete epithelialization was observed when slides from both groups were evaluated. Three animals (60 %) from AG (n = 5) had areas of fibroplasia ranging from discreet areas with arranged fibroblast bundles present only in the superficial dermis to areas of more extensive fibrosis extending from the superficial dermis to the deep dermis with small numbers of macrophages and eosinophils present (Figure 5). Four animals (80 %) from SG (n = 5) had mild to moderate areas of fibroplasia. Of these, 3 (60 %) were in the superficial dermis and 1 (20 %) was in the deep dermis. Of the 3 animals that had an area of fibroplasia in the superficial dermis, only one had disorganized fibroblasts. Four animals from SG showed an inflammatory infiltrate of macrophages, neutrophils, eosinophils, and lymphocytes. In these animals, a mononuclear (macrophages) or mixed (macrophages, lymphocytes, neutrophils, and eosinophils) inflammatory infiltrate was also observed in the periglandular and perivascular regions adjacent to the scar in mild to moderate amounts (Figure 6).

At stage 2, complete epithelialization of the skin was observed in all animals in both groups, except for 1 animal from SG (n = 5), which had initial epithelialization at the wound edges. Three animals (60 %) from AG (n = 5) had areas of fibroplasia ranging from discrete and only in the superficial dermis with bundles of arranged fibroblasts to areas of more extensive fibrosis extending from the superficial dermis to the deep dermis and containing a small number of macrophages and eosinophils. The area of fibroplasia was narrower in the superficial dermis and wider in the deep dermis. In addition, arranged fibroblasts were present in the superficial dermis, whereas they were disorganized in the deep dermis. Neovascularization in the scar (area of fibroplasia) was mild to moderate, and few collagen fibers were present. One animal (20%) from the SG group had a large area of fibroplasia (connective tissue) that contained fibrin and a marked inflammatory infiltrate of macrophages, lymphocytes, eosinophils, and neutrophils that extended from the superficial dermis to the deep dermis (Figure 7). Healing in this animal was delayed compared to the others. In contrast to SG from stage 1, no inflammatory infiltrate was observed adjacent to the scar (perivascular and periglandular) in SG from stage 2.

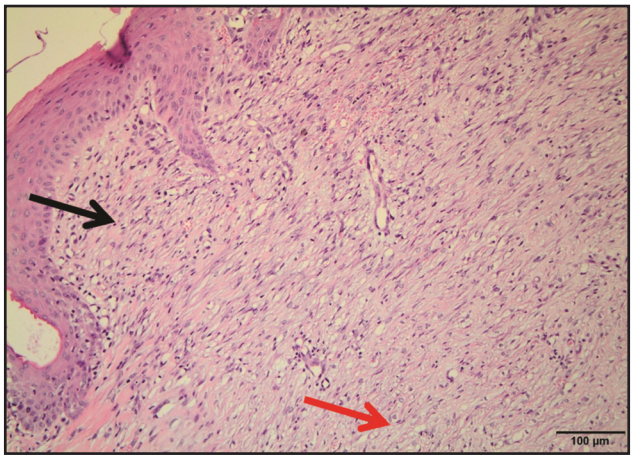

Figure 5. Microscopic image of equine skin from the tissue adhesive group of stage1, showing fibroplasia extending from the superficial dermis to the deep dermis and containing a small amount of collagen, multiple blood vessels, and rare macrophages. Fibroblasts with a more ordered architecture in the superficial dermis (black arrow) and a more disorganized one in the deep dermis (red arrow). [HE; 200x].

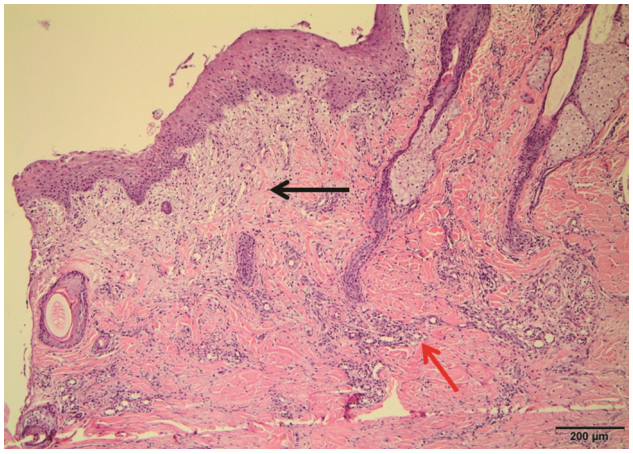

Figure 6. Microscopic image of the skin of a horse from the suture group of stage 1, showing connective tissue in the superficial dermis, focal, moderate, disorganized, with rare macrophages (black arrow). A periglandular mononuclear infiltrate is seen in the red arrow. [HE; 100x].

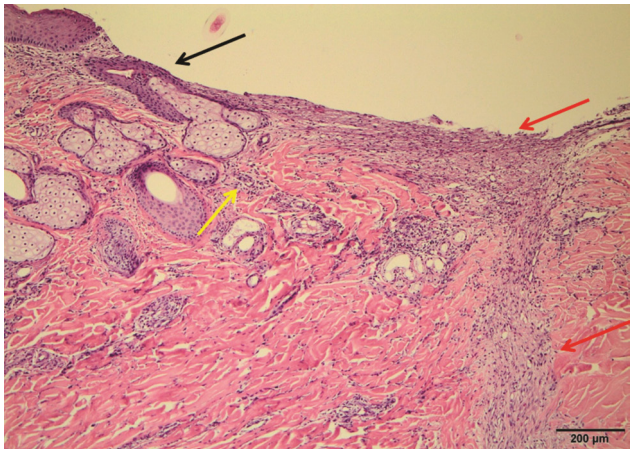

Figure 7. Microscopic image of the skin of a horse from the suture group of stage 2, showing an ulcer with incipient reepithelialization at the edges (black arrow), consisting of an area of connective tissue with low relief, without covering crust, extending into the deep dermis (red arrows). Surrounding the sebaceous and sweat glands is an infiltrate of macrophages, neutrophils, and eosinophils in low amounts near the wound (yellow arrow). [HE; 100x].

DISCUSSION

The advantages of using surgical adhesives for wound synthesis, such as ethyl- 2-cyanoacrylate, compared with conventional sutures have been widely reported [1,5,7,14,18]. However, some studies have shown disadvantages in the use of ethyl 2-cyanoacrylate due to the occurrence of adverse reactions such as increased inflammatory activity, cytotoxicity, tissue necrosis, and contact dermatitis. In addition, the existing literature evaluates the biocompatibility of ethyl- 2-cyanoacrylate based on studies in rats or humans, with no record of its use in equine surgery [2-4,14-16]. In the present work, the biocompatibility of ethyl- 2-cyanoacrylate in the synthesis of equine wounds was investigated using macroscopic and microscopic aspects and compared with suturing of skin.

Ethyl-2-cyanoacrylate proved to be compliant in terms of ease and speed of application, with the time required for synthesis with tissue adhesive being significantly shorter compared to suturing for all results obtained in the experiment. In addition, it did not cause discomfort in animals during intraoperative synthesis without the need to apply a local anesthetic (lidocaine). However, it was difficult to apply the tissue adhesive in heavily bleeding animals because the product polymerized rapidly upon contact with blood, which promoted good hemostasis but resulted in unsatisfactory synthesis of the wound, which may have contributed to its subsequent dehiscence.

Dehiscence is a constant problem in the use of cyanoacrylate-based adhesives. In the present study, a significant difference was observed between the studied groups in terms of the presence of dehiscence, as the SG showed no dehiscence compared with the observation of 50% dehiscence in the AG as a whole (n = 16), with 37.5% considered total dehiscence and 12.5% partial dehiscence of the wound. One possible explanation is the high traction force applied to the region, possibly due to excessive movement of the wound site, combined with the wound size of 7 cm, which is presumably large for the use of tissue adhesive alone, without deep relaxing sutures. The use of subdermal sutures in conjunction with ethyl- 2-cyanoacrylate has been reported in the literature as an alternative for sites with large tension, with satisfactory results [2,16]. However, the need to perform deep sutures to reduce local tension limits the practicality of using the adhesive.

Other assumptions for the dehiscence results presented are related to the possibility of bites to scratch the wound site, resulting in mechanical removal of the tissue adhesive. The alleged bite marks were also found in the SG, including secretion and loosening of the suture site.

A review study of cyanoacrylate-based adhesives [1] cited that ethyl cyanoacrylate histologically promoted initial tissue repair of less aggressiveness in rats compared with sutures, which would be an addi-

tional factor of aggression at the wound site and explain the prolonged volume increase in the SG compared with the AG. In AG, the animals that suffered some degree of wound dehiscence showed volume increase.

In the evaluation of tissue consistency, the SG showed more results with firm consistency compared with the AG, which had normal tissue consistency in most results, justified by the presence of the suture, which acted like a foreign body at the site and led to more inflammation and fibrosis formation and collagen deposition, as observed in the histopathological results.

The assessment of biocompatibility based on microscopic aspects described in the literature aims to evaluate the inflammatory process by the presence of neutrophils and lymphocytes, vascular neoformation, the presence of giant cells, fibroblasts, deposits of collagen, and eosinophils [2,12]. In the present study, skin samples taken on day 12 from each group were examined to analyze epithelial integrity, fibroplasia and connective tissue organization, presence of hemorrhage, neovascularization, presence of inflammatory infiltrates (neutrophils, lymphocytes, macrophages, and eosinophils), presence of fibroblasts, and collagen deposition. From the results, a greater amount of inflammatory cells was observed in the SG than in the AG. As discussed and presented in other studies [12,13], the presence of the nylon thread as a foreign body and the greater aggressiveness in performing the suture may contribute to prolong the inflammatory phases of the tissue repair process, as it was observed in this group. It was also possible to observe a greater amount of tissue reaction around the area of the AG scar, i.e. perivascular and periglandular (sebaceous and sweat glands), indicating contact dermatitis due to the presence of tissue adhesive.

According to the manufacturer's instructions, self-release of the adhesive can be expected in 5 to 10 days. In the present study, gradual detachment of the adhesive was observed, which showed cracks and peeled off in small pieces over time. In several animals, parts of the adhesive were still present on day 12 and in some, almost all the adhesive was still present at the end of the study period.

CONCLUSION

In conclusion, the ethyl-2-cyanoacrylate adhesive showed good biocompatibility with equine skin, although it did not give good results in all horses when applied without relaxing sutures, because of excessive tension, resulting in a great number of dehiscence, with the conventional suture group being more efficient in coapting edges. In terms of practicality, the adhesive proved to be easier and faster to apply than the suture. It also acts as a physical barrier to microorganisms, does not need to be removed postoperatively, and is a less aggressive method of synthesis resulting in a lower postoperative inflammatory response.

MANUFACTURERS

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***Ethical approval*.** All procedures, treatments and care of the animals were approved by the Ethics Committee for the Use of Animals of the Faculdade de Zootecnia e Engenharia de Alimentos of the University of São Paulo - FZEA/USP (CEUA/FZEA) in the meeting of 02/07/2020 (Protocol No. 6602200320).

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

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