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Thermographic and histopathological study of the effects of plasma jet therapy upon dermis repair in rat

Estudo termográfico e histopatológico dos efeitos da terapia com jato de plasma na reparação na pele em rato

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Abstract
Background: Biomodulatory therapies have been used to improve the healing pattern and assist in tissue repair. The plasma jet is a therapy that has been currently indicated for dermatological use and aesthetic purposes. This study aimed to evaluate the effects of plasma jet on the repair of skin wounds in rats through thermographic imaging and histopathological analysis. **Methodology :** 20 Wistar rats were divided into a control group (CG) and plasma jet group (PJG). A cutaneous surgical wound was performed on the back of the animals, and thermographic recording was performed at different periods. Only the PJG was submitted to plasma jet therapy immediately after the surgery and in the following two days. Half of the animals in each group were sacrificed on the fifth day, after the surgical procedure, and another half on the tenth day. A tissue sample from the animals was removed and processed for histological analysis. **Results:** Thermograms showed greater variation in the thermal coefficient in the PJG, especially on the fifth day (p>0.05). These results confirm the histological findings in this period that exhibited greater collagen biosynthesis in the dermis (p<0.05). **Conclusio**n: Plasma jet treatment promoted an improvement in the collagen fibers pattern, and the use of Infrared Thermography was useful for monitoring tissue repair.
Keywords: Biomodulatory therapy; histological analysis; plasma jet; skin repair; thermography.

Resumo
Introdução: *Terapias biomodulatórias têm sido utilizadas para melhorar o padrão de cicatrização e auxiliar no reparo tecidual. O jato de plasma é uma terapia que vem sendo indicada atualmente para uso dermatológico e para fins estéticos. O objetivo deste estudo foi avaliar os efeitos do jato de plasma no reparo de feridas cutâneas em ratos por meio de imagens termográficas e análise histopatológica.* **Metodologia:** *20 ratos Wistar foram divididos em grupo controle (GC) e grupo jato de plasma (GJP). Foi realizada ferida cirúrgica cutânea no dorso dos animais e registro termográfico em diferentes períodos. Apenas o GJP foi submetido à terapia com jato de plasma, imediatamente após a cirurgia e nos dois dias seguintes. Metade dos animais de cada grupo foi sacrificada no quinto dia, após o procedimento cirúrgico, e a outra metade no décimo dia. Uma amostra de tecido dos animais foi retirada e processada para análise histológica.* **Resultados:** *Os termogramas apresentaram maior variação no coeficiente térmico no PJG principalmente no quinto dia (p>0,05). Esses resultados confirmam os achados histológicos nesse período que apresentaram maior biossíntese de colágeno na derme (p<0,05).* **Conclusão:** *O tratamento com jato de plasma foi capaz de promover melhora no padrão das fibras colágenas e o uso da Termografia Infravermelha foi útil para monitorar a reparação tecidual.*
Palavras-chave: *Análise histológica; jato de plasma; reparação tecidual; terapia biomoduladora; termografia.*

INTRODUCTION

Health care includes the management of biomodulatory therapies. Such therapies can apply analgesic and anti-inflammatory effects and contribute to tissue repair improvement in different types of wounds[1]. In this context, several therapeutic modalities have been mentioned in the literature. For instance, Laser Photobiomodulation (LP), also known as Low-Level Laser Therapy (LLLT), is capable of eliminating microorganisms and generating an increase in the biosynthesis of ATP and collagen fibers in addition to inducing the proliferation of lymphocytes and fibroblasts[2,3]. Another therapy that triggers a similar effect

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is ozone therapy, which has documented bactericidal and immunomodulatory action[4,5]. In recent years, another type of gas has also been used as a biomodulatory therapy in order to stimulate wound healing - the plasma jet.

In physics, plasma is considered the fourth state of matter and stands out from others for having a high energy content[6]. When ionized, it reaches the superficial layer of the skin and produces a type of thermal damage that stimulates the biosynthesis of collagen and elastin while restructuring the organisation pattern of existing fibers[7]. Although its most common indication is still focused on aesthetic purposes, some studies have demonstrated its potential for biomodulator action, a fact that suggests the use of this tool for other therapeutic purposes such as tissue repair[8].

Significant hemodynamic changes occur during tissue repair as vasodilation, increased vascular permeability and neoangiogenesis[9], and these alterations can induce temperature increase. Thermal variation may be related to circulatory factors and undergo changes due to variations in blood flow and volume[10]. Thus, it becomes possible to show the thermal distribution in the tissue and check if there is an increase in temperature on its surface to be evaluated due to heat dissipation in different pathophysiological contexts, similar to what happens in tissue repair[11]. Infrared thermography is a non-invasive, non-contact and painless tool that does not provide information on the morphological characteristics but on the functional, thermal and vascular alterations, which, as a rule, result from the inflammatory process that unfolds in the evaluated tissue and are characterised by areas of hyperradiation[12].

In the literature, there is a lack of studies documenting the relationship between thermal coefficient variation and histopathological variables of repair at different stages of wound healing, especially when the tissue is submitted to plasma jet therapy. Therefore, the goal of the present study was to evaluate the effects of plasma jet upon skin temperature through infrared thermography and verify, through histomorphometric analysis, its influence on the variables of cutaneous wound healing like inflammatory infiltrate, vascular density and neocollagenesis.

MATERIAL AND METHODS

This experimental study was forwarded to the Commission for Ethics in the Use of Animals (CEUA), and a favourable judgment was obtained. A sample calculation was performed to determine the n required for this study[13,14]. Samples included 20 male Wistar rats weighing between 200-250 grams. The animals were randomly allocated into two groups of 10 rats each, which were sacrificed on the fifth and tenth days after the start of the experiment. These days were selected since it is possible to observe the proliferative phase of wound repair on both. In each of these periods, five rats from each experimental group were sacrificed. Group 1 corresponded to the Control Group (CG) and did not receive any type of treatment; Group 2, named Plasma Jet Group (PJG), underwent the action of this biomodulatory therapy (Chart 1).

The animals were weighed and anesthetised, and after verifying the loss of flexion reflex removal of the paw, dorsal trichotomy was performed. A circular incision was made in the dorsal region with the aid of a circular metallic scalpel, without coupling it with another device, punch (Biopsy Punch, Stiefel, Germany) with diameter of 6 mm to obtain full-thickness wound, which was performed by a single calibrated operator, in the same manner as described by Marchionni et al.[15] (2010) and Reis et al.[16] (2008) (Figure 1).

Figure 1- *Clinical aspect of the surgical wound on the back of the rat.*

Source: Authors

The PJG rats were submitted to biomodulatory therapy with a plasma jet, performed daily for three consecutive days, beginning from the day corresponding to the cutaneous surgery. The equipment used was the Jett Plasma Lift (Celebrim, Importation and Distribution LTDA, Sao Paulo, Brazil). A flat applicator was used for the application, with a diameter of 3mm and non-thermal action. This was moved over the conductive gel and applied to the edge of the wound, performing electrical stimulation by direct current, with an intensity of 5/8 and an application time of 1 minute and 30 seconds (Figure 2). Animals in the control group were subjected to the same process by applying the conductive tip on the wounds' edge but with the equipment turned off, without plasma emission in the lesion area.

Figure 2 – *Plasma Jet Lift equipment and application tips (red arrow)*

Source: Authors.

Figure 3- *Application of plasma jet biomodulatory therapy to the rat wound.*

Source: Authors.

An infrared camera (FLIR E-Series, Sweden) was used to assess the local circulatory pattern. The following protocol was adopted: the anesthetised rats were placed in an orthostatic position on a fixed object 0.5 m from the ground and acclimatised for a period of 10 minutes before data collection. The distance between the camera and the animals was 0.5 m. The environment's temperature was controlled around 20°C ± 1°C.

On the first day, the rats were photographed at the following times: 10 minutes after trichotomy; immediately after surgery and immediately after therapy (except the control group). On the fifth and tenth days, the rats in each group were anaesthetised again and photographed with the thermographic camera 10 minutes after anaesthesia. The normality and abnormality criteria adopted were based on the study by Haddad et al.[17] (2014), which established the pattern of clinical abnormality according to temperature variation (Table 1). Thus, it can be determined whether there was a significant change in temperature for each period in the studied area by calculating the average and standard deviation in each experimental group.

Table 1 – *Clinical abnormalities according to temperature variation according to Haddad et al.[17] (2014).*

Thermal variation	**Standard of normality**
< 0.24° C	*Normal*
> 0.30° C	*Suggesting to abnormalities*
> 0.60° C	*Strongly suggesting*
1.0° C	*Significant abnormality*

Research date source

After deep sedation, the animals were placed in groups in the carbon dioxide (CO^2) chamber. After death was confirmed, a portion of tissue from the back of the rats comprising the surgical wound was removed. Then, the tissue was processed for staining with hematoxylin-eosin and picrosirius red. Images capturing of tissue sections submitted to the described staining was performed using the Motic Images Advanced 3.0® software (Motic China Group CO. LTD).

The level of tissue inflammation was measured and adapted from the study by Alvarenga et al.[18] (2020). A semi-quantitative study of the sections was carried out, which included the analysis of the variables polymorphic and monomorphonuclear inflammatory infiltrate, the intensity of the inflammatory reaction and vascular density, in which the criteria of absent (0), discrete (+), moderate (++) and intense were adopted. (+++). The definition of the histological evaluation criteria was based on the following aspects: when the variable was present in a percentage equal to or greater than 50% in the analysed section, the degree was considered intense; for 25 to 50% of cells in tissue, moderate grade; and less than or equal to 25%, discrete.

Collagen biosynthesis was evaluated according to the criteria established by Alvarenga et al.[18] (2020), whose collagen fibers were classified using three scores: 1. thin, delicate, loosely organised collagen fibers seen throughout the wound area; 2. thin, delicate, loosely arranged collagen fibers in some areas and thicker, coarser ones in other areas of the wound; and 3. thick, coarse, densely organised collagen fibers seen throughout the whole wound area.

The analysis was performed using R software version 4.2.1. Descriptive analysis (absolute/relative frequency, median, and quartiles) was performed to identify the general and specific characteristics of the studied sample. The Shapiro-Wilk test and analysis of symmetry and kurtosis verified the normality of the data distribution.

The chi-square test or Fisher's exact test was used to identify associations between qualitative variables. On the other hand, the Mann-Whitney test was performed among the variables according to the groups of interest. For this study, the significance level established was 5%.

RESULTS

Table 2 illustrates the temperature values of the animals at different experiment times. It was observed that the mean basal temperature of all rats was 33,2º C. After trichotomy, there was an increase in the mean local temperature to 34.3º C in the 20 animals that belonged to the two study groups (ΔT= +1 .1°C; $p<0.05$). Just after the surgical procedure, there was a significant decrease in temperature in the wound area of all rats, with an average of 32.8º C (ΔT= -1.5º C; $p<0.05$).

Once it was determined that the average temperature to be adopted as a basis for evaluating plasma jet therapy corresponded to the average calculated after skin surgery, it was found that immediately after using the plasma jet, the average local temperature in the wound area in treated animals it dropped to 30.2º C (ΔT= -2.6º C; $p<0.05$); (Table 2).

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Table 2 – *Average temperature of experimental groups in different study times.*

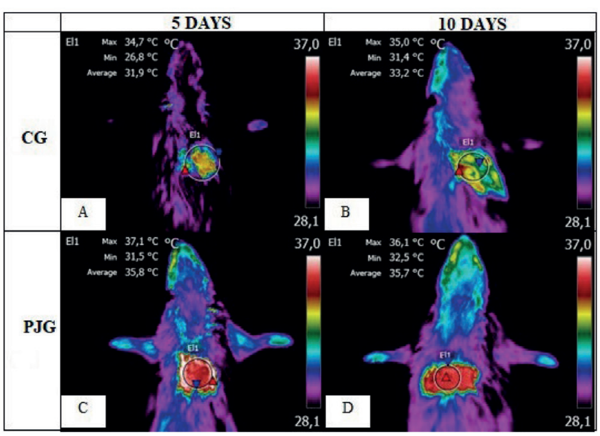
Experimental groups	Average temperature in °C/standard deviation				
	After -trichotomy	*After surgery*	*After 1ª session of therapy*	*5 days*	*10 days*
Control group (CG)	$34.3^{A}\pm0.5$	$32.8^{B}\pm0.5$	$32.8^{BC}\pm0.5$	$32.6^{BCE}\pm1.1$	$33.8^{G}\pm1.3$
Plasma jet group (PJG)	$34.3^{A}\pm0.6$	$32.8^{B}\pm0.7$	$30.2^{D}\pm0.9$	$34.6^{AF}\pm0.6$	$33.9^{G}\pm2.2$

Statistically significant difference (p<0.05) when capital letter is different.

Research date source

Regarding the PJG, the average temperature in the wound area at the end of the fifth day was 34.6° C, performing a temperature increase of around +1.8° C (ΔT= +1.8o C; p <0.05), while in the control group, the mean local temperature was 32.6° (ΔT= -0.2o C; p>0.05). During this period, it was observed a statistically significant difference between the groups with thermal variation of the order of +2° C (p<0.05); (Figures 4); (Table 2).

Figure 4 – *Thermograms of animals in the CG and the PJG, on the fifth and tenth day, showing the maximum, average and minimum temperature in the skin wound area, five days.*

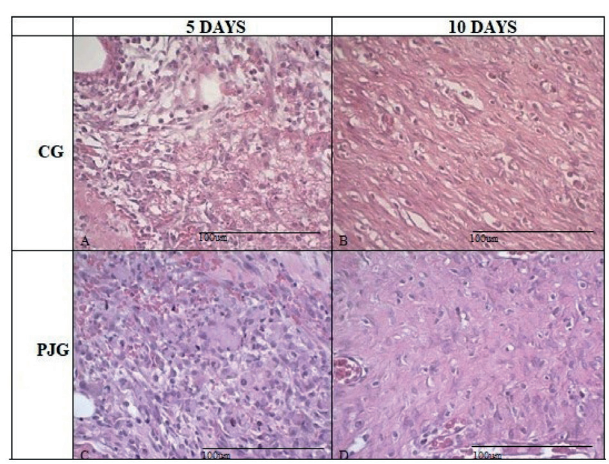


Source: Authors

Around the tenth day, both in the control group and the group treated with a plasma jet, the average temperature was 33.8°C. The variation of the thermal coefficient was ascending in the control group (ΔT= +1.2° C; p< 0.05) and negative for the group treated with a plasma jet, with a decrease in temperature (ΔT= -0.8° C; p<0.05). About the thermal coefficient variation was not statistically significant between groups (p>0.05); (Figures 4); (Table 2).

Considering intergroup analysis, in the period of 5 days, the tissue sections stained with hematoxylin-eosin showed the presence of monomorphonuclear inflammatory infiltrate, which is characteristic of diffuse chronic inflammation with the intensity that varied from moderate to intense, in both experimental groups, with no significant difference between these (p>0.05). A high number of neoformed blood vessels were seen in both groups with no statistically significant difference (p>0.05). Also, in the sections stained with picrosirius red, regarding the control group, it was observed a pattern of disorganisation of newly formed collagen fibers in the areas corresponding to the edges of the standardised skin wound, just below the epithelial tissue in formation. On the other hand, in the plasma jet group, the collagen fibers were presented in an organised way, thicker and thicker in some areas of the wound (p=0.008). In the period of 10 days, both groups presented characteristics compatible with more advanced stages of the healing process, with mild inflammation and a larger area of denser and more organised collagen fibers (p>0.05); (Figure 5) (Table 3).

Figure 5 - *Morphological analysis of experimental groups. Photomicrographs of histological sections (HE) of the regions of the standardised skin wounds, which illustrate the histomorphological characteristics in the groups with 5 and 10 days. It is noticed that on the fifth day, the CG and JPG groups showed similar aspects with the presence of monomorphonuclear inflammatory infiltrate, characteristic of chronic diffuse inflammation with intensity ranging from moderate to intense and numerous blood vessels (arrows). In the period of 10 days, both groups presented characteristics compatible with more advanced stages of the healing process, with mild inflammation and a larger area of fibroplasia.*



Source: Authors

Table 3 – *Comparison between groups where CG means Control Group and PJG means Plasma Jet Group.*

Variables	Grading	5 days		10 days	
		GC	GJP	GC	GJP
		n(%)	n(%)	n(%)	n(%)
Type of inflammation	Acute	-	-	-	-
	Acute Diffuse	1 (20)	-	-	-
	Chronic	4 (80)	5 (100)	-	1 (20)
	Absent	-	-	5 (100)	4 (80)
Fisher's exact test	**p-value**		1.0		1.0
Intensity level of inflammation	Absent	-	-	5 (100)	5 (100)
	Discrete	2 (40)	1 (20)	-	-
	Moderate	3 (60)	4 (80)	-	-
	Intense	-	-	-	-
Fisher's exact test	**p-value**		1.0		-
Vascular density	Absent	4 (80)	1 (20)	3 (60)	-
	Discrete	1 (20)	4 (80)	2 (40)	5 (100)
	Moderate	-	-	-	-
	Intense	-	-	-	-
Fisher's exact test	**p-value**		0.206		0.167
Collagen	(1)	5 (100)	-	-	-
	(2)	-	4 (80)	4 (80)	4 (80)
	(3)	-	1 (20)	1 (20)	1 (20)
Fisher's exact test	**p-value**		0.008*		1.000

**p<0.05*

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In the intragroup analysis, the CG presented a predominantly chronic inflammatory process on the fifth day, while on the tenth day, it showed resolution of the chronic inflammation (p=0.008). Regarding the intensity of inflammation, there was an intense degree of inflammation on the fifth day, but on the 10th day, this inflammation was predominantly mild (p=0.008). There were no statistically significant findings regarding the formation of new vessels (p>0.005).

Relating to the Plasma Jet Group (PJG), on the fifth day, all animals had chronic inflammation with a more intense degree compared to the tenth day (p=0.008), which already showed a mild degree of inflammation in all animals and resolution of chronic inflammation (p>0.05). Regarding vascularisation, there were no statistically significant differences between the studied periods (p>0.05) (Figure 6) (Table 4).

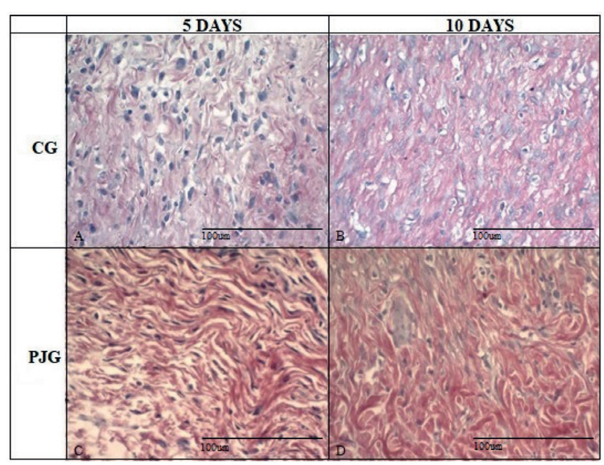

Figure 6 - *Morphological analysis of experimental groups. Photomicrographs of histological sections (picrosirius red) of the regions of the standardised skin wounds, which illustrate the histomorphological characteristics in the groups with 5 and 10 days. Regard that on the fifth day, the CG group showed a pattern of disorganisation of newly formed collagen fibers in the areas corresponding to the edges of the wound just below the epithelial tissue in formation, while in the GJP the collagen fibers were organised form, thicker and thicker in some areas of the wound. At 10 ten days, the organisational pattern of collagen fibers was quite similar in both*

Source: Authors

Table 4 – *Time comparison intragroup where CG and PJG.*

Variables	Result	CG		PJG	
		5 days	10 days	5 days	10 days
		n(%)	n(%)	n(%)	n(%)
Type of inflammation	Absent	-	-	-	-
	Acute Diffuse	1 (20)	-	-	-
	Chronic	4 (80)	-	5 (100)	1 (20)
	Absent	-	5 (100)	-	4 (80)
	p-value	0.008*		0.48	
Intensity level of inflammation	Absent	-	5 (100)	-	5 (100)
	Discrete	2 (40)	-	1 (20)	-
	Moderate	3 (60)	-	4 (80)	-
	Intense	-	-	-	-
	p-value	0.008*		0.008*	
Vascular Density	Absent	4 (80)	3 (60)	1 (20)	-
	Discrete	1 (20)	2 (40)	4 (80)	5 (100)
	Moderate	-	-	-	-
	Intense	-	-	-	-
	p-value	1.0		1.0	
Collagen	(+1)	5 (100)	-	-	-
	(+2)	-	4 (80)	4 (80)	4 (80)
	(+3)	-	1 (20)	1 (20)	1 (20)
	p-value	0.008*		1.0	

**p<0.05*

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DISCUSSION

This study described the thermal coefficient variation and concomitant tissue changes during two different periods of tissue repair. The findings suggest that the use of thermograms might be useful to follow up the microcirculatory pattern and the increase of metabolic activity in the tissue in a quali and quantitative way.

Infrared thermography has been cited as a diagnostic tool that enables the measurement of the temperature emitted by the body, and it also allows the identification of the temperature variability of each evaluated tissue[19]. In the present study, the coefficient of thermal variation (ΔT) oscillated positively due to the initial inflammatory response. It is known that the biochemical and vascular changes resulting from the injury trigger the biosynthesis of chemical mediators that activate the cells involved in tissue repair[20]. After performing the skin surgery, the ΔT was significantly lower in all studied animals. This negative variation could have probably been determined by the transient ischemia resulting from the pressure exerted by the circular scalpel at the time of the injury.

It was possible to notice that there was a significant decrease in temperature in the wound area just after plasma jet application. A plausible hypothesis to be considered would be that the action of the plasma jet influenced the local microcirculation pattern, which may suggest a possible immediate anti-inflammatory effect. Fridman et al.[21] (2007) described the anti-inflammatory action of plasma jet and suggested that it might partially be attributed to its potential for antibacterial action. In a more recent study in the literature, it was reported that the plasma jet was able to promote acceleration in blood coagulation and transmigration of leukocytes, as well as regulation of transmembrane proteins[22].

It was also noted that, on the fifth day of the postoperative period, a significant increase in temperature was observed in the group of animals submitted to plasma jet treatment. Histomorphometric analysis indicated a greater presence of blood vessels and more advanced collagen biosynthesis in this study group. These findings could explain the thermal variation in the tissue during this period since the temperature rise seems to suggest an increase in metabolic activity in the microenvironment of aggression. Such results corroborate those described by Kubinova et al.[23] (2017), which documented that the non-thermal plasma jet contributed to the occurrence of beneficial effects in wound healing. According to these authors, in addition to playing a key role in the injured tissue regarding its antimicrobial potential during the inflammatory phase, the non-thermal plasma jet was able to regulate cell migration and proliferation, as well as angiogenesis. They also demonstrated that around 72 hours after using this therapy, there was a decrease in *the intensity of tissue inflammatory infiltrate and the beginning of collagen biosynthesis in the provisional matrix represented by the granulation tissue.*

When comparing the CG with the PJG on the fifth day of the postoperative period, it was possible to verify that both groups also exhibited a transition to the proliferative phase, especially regarding collagen formation. PJG showed dense and organised collagen fibers in 80% of the animals, whereas CG presented delicate and thin collagen fibers in 100% (p=0.008). These findings suggest that the proliferative phase and fibroblasts activity were biomodulated by plasma jet action in the group submitted to this therapy and were like those described by Kubinova et al.[23] (2017). These authors observed a rise of collagen biosynthesis in the group treated with non-thermal plasma on the 7th day of repair, although this result was not statistically significant.

From the clinical point of view, the late phase of tissue repair in cutaneous tissue of rats ends up in the wound's closing around the second week after induction of tissue injury. Our study observed a tendency to return to homeostasis on the tenth day since the temperature decreased and presented very similar values in both experimental groups. Histological findings were compatible with those of thermograms as both groups presented very similar results, with no statistically significant differences.

It should be mentioned that the present study has some limitations since the punctual analysis of only two periods of wound repair could have been broadened, especially regarding the first days of the postoperative period. The authors also suggest the development of studies that assess the bactericidal potential of the plasma jet to correlate it with the temperature variation assessed through infrared thermography and the use of different times of plasma jet therapy.

CONCLUSION

Plasma jet was able to generate a significant thermal variation on the skin in relation to the control experimental group, especially on the fifth day. Histological analysis showed a significant improvement in the pattern of collagen fibers of the animals submitted to the use of plasma jet. Plasma jet is a promising adjuvant tool capable of helping in controlling inflammation and improving wound healing. Besides, the authors suggest that thermograms could be useful to assess the local temperature and relate it to the histological profile of the wound.

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AUTHORS' CONTRIBUTIONS

C.B.S.C. participated in the literature survey and discussion of the research project. P.B.S., M.A.C. and A.M.T.M. elaborated on the project's initial conception and participated in its methodological development. A.R.A.P.M. performed the critical review of the project. J.B.T.L.M. guided all phases of the research.

CONFLICTS OF INTEREST

No financial, legal, or political conflicts involving third parties (government, private companies and foundations, etc.) have been declared for any aspect of the submitted study (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

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