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Clinical evaluation of the perception of post-trauma paresthesia in the mandible, using a biomimetic material: A preliminary study in humans

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A R T I C L E I N F O

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A B S T R A C T

There is a great effort from numerous research groups in the development of materials and therapeutic strategies for the functional recovery of patients who have suffered peripheral nerve injuries (PNI). In an article ***in vivo***, the formation of a nerve bridge was observed, reconnecting the distal and proximal stumps, in the sciatic nerve of rats, indicating the effective participation of the biomaterial in the recovery of peripheral nerve injuries. For the current pilot study, 15 cases of multiple fractures of the mandible, with involvement of the inferior alveolar nerve (IAN) were selected and studied: JC (control cases) $n = 6$ with conventional treatment, and JT (treated cases) $n = 9$, with the use of biomimetic biomaterial. The evaluation of the return to sensitivity was measured through a self-assessment, where the patients assigned scores from 0 to 10, where zero (0) represented the complete absence of sensitivity and ten (10) the normality of the perception of local sensitivity. Patients were evaluated from the preoperative period to the 360th day. The statistical results obtained by the t-Student, Shapiro-Wilk normality and non-parametric One-Way ANOVA tests indicated statistically significant differences ($\mathbf{p} < 0.005$; 0.005 e 0.5 respectively), between the two treatments, which were reflected in the clinical results observed, we also calculate the size of the effect represented by ϵ^2, calculated by Cohen's **d**. The results indicate a great difference between the treatments performed, $\epsilon^2 = 1.00$. In the 6 cases followed up in the JC group, four remained with a significant deficit until the end of the evaluations and two indicated the remission of the lack of sensitivity in this period. In the JT group, in 28 days, all cases indicated complete remission of the lack of sensitivity with healing concentration. In one of the cases where there was a complete rupture of the mental nerve, the (score-10) was observed in 60 days. The observed results indicate the existence of a statistical significance between the groups and an important relationship when using the biomimetic biomaterial during the recovery of the

Abbreviations: Growth Factors, (GF); Schwann Cells, (SC); Inferior Alveolar Nerve, (IAN); Peripheral Nerve Injuries, (NIP); Kilo Gray, (k-Gy).

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perception of sensitivity in polytraumatized patients, compatible with the results observed in laboratory animals, which may indicate its clinical feasibility in the reduction of sequelae in PNI.

1. Introduction

It is estimated that the incidence of traumatic injuries to peripheral nerves in Brazil is close to 500,000 cases per year. Approximately 2.8% of these patients become permanently disabled because of these injuries [1,2]. In the United States of America (USA) about twenty million people suffer injuries to the peripheral nerves, derived from traumatic injuries, resulting in approximately US$ 150 billion in annual expenses [3]. Finding strategies to mitigate such financial and especially social costs resulting from injuries to peripheral nerves is the objective of several research groups that use different strategies, varying from the use of neurotrophic drugs, growth factors, stem cells, hollow conduits, or the combination of these strategies, with the aim of mitigating the financial costs and especially the social ones [4–6]. However, this huge effort to develop therapeutic strategies so far has not been able to produce an effective treatment for patients who have suffered peripheral nerve damage [7].

Regenerative medicine is an emerging field of biotechnology that combines various aspects of natural sciences, including cellular and molecular biology, materials science, bioengineering, chemistry and biochemistry, among others, in order to regenerate, repair or replace injured tissues [4]. One of these emerging fields is called "biomimetics", which is an area of regenerative science that aims to study biological structures and their functions, mimicking them and creating alternative strategies for developing simple solutions to complex problems [8–10]. The selected strategy was to locally provide microelements capable of interacting with the intra and extracellular environment, thus promoting a favorable environment, capable of promoting the repair of the injured target tissue, reducing local oxidative stress, providing favorable conditions for cellular respiration and promoting growth of the injured target tissue. Although unorthodox, this strategy has shown good results in preliminary studies carried out in laboratory animals [11–13].

The golden standard for peripheral nerve repair (axonotmesis and neurotmesis) currently is the microsurgery, called: epineural, perineural and fascicular, but they do not ensure functional recovery and reduce the production of neurotrophic factors, which can lead to nerve bundle degeneration [14]. Other alternatives have been used, such as nerve grafts, which are divided into autogenous and allografts. In the case of autologous grafts, there is a clear complication that is the morbidity of the donor region, in addition to the formation of neuromas and the choice of the donor region [15]. Regarding allogeneic grafts that are taken from cadavers, therefore without the occurrence of morbidity, they require the patient's immunosuppression, which can cause secondary infections and the formation of tumors. An alternative to this problem is acellular allograft, but its results are still doubtful, especially when used in long nerves. The addition of growth factors can improve outcomes in this type of situation [16,17].

There are also fibrin glues, which allow primary repair without the use of sutures. Its biggest disadvantage is the possibility of transmission of infections, fibrosis, toxicity and necrosis [18,19]. Another alternative for nerve repair are conduits, which are hollow structures associated or not with neurotrophic factors, which provide support and a favorable microenvironment for nerve growth [20], but they are still under experimental evaluation [18,20–23]. The basic limitations of this therapy are the slow nerve regeneration process and insufficient nerve filling in cases of large spaces [7].

The complexity of nerve regeneration involves a range of elements that interact with each other and are fundamental in this process. Among them are the growth factors (GF) of great interest to the scientific community, for their role as an important cell modulator [24–39]. The degenerating peripheral nerve itself also provides important growth factors, as the Schwann cells (SC). These proteins are basically a set of three families of molecules and their respective receptors, responsible for maintaining the growth and survival of axons and motor and sensory neurons after tissue damage [40]. However, these same growth factors are also responsible for important pathologies such as tumor formation [41,42].

The objective of this preliminary translational study carried out in humans was to evaluate the behavior of sensory perception of patients who suffered mandible fractures with inferior alveolar nerve involvement (IAN), using biomimetic material and comparing it to conventional treatment. Our preliminary results indicated a synergism with the results observed in animals [12,13], which in a short period of time could become an important tool for peripheral nerve injuries (NIP).

2. Materials and methods

Fifteen hemi-mandibles were selected in ten patients (total **n** = 15), nine were treated with the biomimetic material, treated group (JT) **n** = 9 and six received a conventional treatment, control group **n** = 6. All patients included in this research suffered cycling accidents and/or interpersonal aggression, where the fracture line was directly related to the mandibular canal or the mental foramen. Another criterion for inclusion in this research was the occurrence of a pre-existing sensory deficit, that is, all patients reported a perception of lack of sensitivity in the lower lip and chin before the surgical procedure of reduction and fixation of the mandible. Another inclusion criterion was stretching equal to or greater than 50% of the diameter of the inferior alveolar nerve (IAN) in the transoperative [43,44]. A consent form was submitted to all patients who met the pre-surgical criteria, and those whose IAN stretch was less than 50% were excluded from the study. This research was submitted and approved by the Human Ethics Committee of Ibirapuera University under number: 2.490.419.

2.1. Surgical technique

The treatment of maxillary fractures varies widely in clinical practice, however surgical reduction and fixation is the main objective. The decision on which surgical approach will be chosen, its reduction and fixation depend on multiple factors such as: trauma kinetics, location, patient's systemic conditions, surgical time, surgeon's experience, patient's age and adherence to treatment. In this work, we used the open treatment modality, where extraoral incisions of the Risdon or Transcervical type were performed, and intraoral incisions in the fornix region were performed using rigid internal fixation (RIF) through plates and screws. The anesthetic procedures followed the hospital criteria and protocols, and the intubation was nasotracheal.

2.2. Data analysis

For the evaluation of the results, the score method (self-assessment) was chosen [45–49], where the patient was asked to assign a note within a scale of zero (0) to 10, where zero (0) was considered to be the complete absence of local sensitivity and ten (10) was considered to be normal sensitivity of the affected region. The initial assessment of these patients took place in the preoperative period when a grade was assigned prior to the surgical procedure. In the immediate postoperative period (1 day after the surgical procedure), and later on the 7th, 14th, 28th, 60th, 90th, 180th, 240th and 360th days, further evaluations were performed. These assessments were preferably performed in the hospital, on the outpatient's premises, during return visits for clinical/surgical assessments, and also by telephone, in cases where there was no possibility for the patient to attend the previously scheduled appointment.

2.3. Composition of biomimetic material

The entire manufacturing process was carried out in a controlled environment, clean room, under temperature and lighting control.

The vitamin compound was prepared using the following components: β-carotene (BASF, Ludwigshafen am Rhein, Germany), α-tocoferol (BASF), complex B (F. Hoffmann-La Roche AG, Basel, Switzerland), calciferol (BASF), selenium salts (BASF), zinc salts (Merck KGaA, Darmstadt, Germany), magnesium salts (Merck KGaA), calcium salts (Merck KGaA), phosphoro salts (Merck KGaA), glutamic acid (BASF), soy lecithin (BASF), hydrolyzed collagen (BASF), glycosaminoglycan sulfate (BASF), and chondroitin sulfate (BASF). The selenium, zinc, and magnesium salts varied between 10 and 15% of the total weight of the active portion, and selenium in a proportion of 20%–30% of the relative weight of the other magnesium and zinc salts, these with proportions of 1.8% and 1.2%, respectively. β-carotene and α-tocopherol vitamins ranged from 15 to 20%, with α-tocopherol having a ratio of 64% to β-carotene. Complex B had a proportion ranging from 20 to 30% of the total weight of the active portion of the material, with vitamins B1 and B6 maintaining a proportion of 30% of the complex and glutamic acid 50% of vitamin B6. Calcium and phosphorus salts were used in the

Table-1

(Overview Results). Tabulation of the results of the JC (control group) and the treated group (JT). In this table all 15 cases that participated in the study are indicated. The evaluation times can be observed from the preoperative period to the 360th day. The evaluation of the sensory deficit was performed by a self-assessment of the patients, who assigned a score on a scale of 0–10, where 0 is the complete absence of sensitivity of the lip and chin, while 10 represents a perception of normality of the lip and chin in the affected region. It is also possible to check their means (Md), standard deviation (SD) and standard error (SE), results used to make (Fig. 1). It is also possible to verify that in the JT group there is a concentration of cure on the 28th day, which is not observed in the JC group, where the cure (score-10) was dispersed throughout the study period and in only two cases it was achieved.

Jaw	Pre-Op	Post-op	7 days	14 days	28 days	60 days	90 days	120 days	240 days	360 days
JT-1	4	0	0	3	7	10	10	10	10	10
JT-2	4	0	0	4	6	10	10	10	10	10
JT-3	7	0	0	7	10	10	10	10	10	10
JT-4	6	0	8	10	10	10	10	10	10	10
JT-5	7	0	8	10	10	10	10	10	10	10
JT-6	8	0	7	9	10	10	10	10	10	10
JT-7	8	0	0	7	8	9	10	10	10	10
JT-8	4	0	0	0	7	10	10	10	10	10
JT-9	4	0	0	6	10	10	10	10	10	10
JC-1	7	0	0	0	2	5	6	7	9	10
JC-2	6	0	0	0	0	0	0	2	5	5
JC-3	6	0	0	0	0	0	0	1	4	5
JC-4	9	0	0	0	0	2	3	4	4	5
JC-5	4	0	0	0	1	3	8	10	10	10
JC-6	6	0	0	0	0	0	2	2	3	3
SS-JT	9,00	9,00	9,00	9,00	9,00	9,00	9,00	9,00	9,00	9,00
Md-JT	5,78	0,00	2,56	6,22	8,67	9,89	10,00	10,00	10,00	10,00
SD-JT	1,79	0,00	3,84	3,38	1,66	0,33	0,00	0,00	0,00	0,00
SE-JT	0,60	0,00	1,28	1,13	0,55	0,11	0,00	0,00	0,00	0,00
SS-JC	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00	6,00
Md-JC	6,33	0,00	0,00	0,00	0,50	1,67	3,17	4,33	5,83	6,33
SD-JC	1,63	0,00	0,00	0,00	0,84	2,07	3,25	3,50	2,93	2,94
SE-JC	0,67	0,00	0,00	0,00	0,34	0,84	1,33	1,43	1,19	1,20

proportion of 30% of the total weight of the active portion and in the proportion of 54% between them. Vitamin D (calciferol) was added at the end of the process, at a ratio of at most 40 parts per million of the total weight of the material. Hydrolyzed collagen (gelatin), glycosaminoglycan sulfate and chondroitin sulfate were added in the ratio of 60, 20, and 20%, respectively.

Subsequently, the material was packaged (double packaging), the first one in an amber colored acrylic blister, and the second one in an opaque polypropylene envelope for protection from light, containing 01 g of biomaterial. Then the material was sterilized using gamma rays with an intensity of 20 kGy (EMBRARAD - Empresa Brasileira de Radiação) at room temperature.

2.4. *Statistical analysis*

The results were collected and tabulated (Table 1), between the JT and JC groups. In this table, the scores assigned by each patient were inserted, according to their own perception of sensitivity in the regions of the lower lip and chin. In addition, the different evaluation periods were also inserted: preoperative, immediate postoperative (1 day after the surgical procedure), 7 days, 14 days, 28 days, 60 days, 90 days, 120 days, 240 days and 360 days. These data were submitted to statistical tests using the open-source software JAMOVI, ***t***-Student, normality (Shapiro-Wilk) and non-parametric One-Way ANOVA (Kruskal-Wallis) and size of the effect calculated by Cohen's ***d***.

2.5. *Qualitative analysis*

We highlighted two pairs of cases that showed some similarity between the JC and JT groups, to better illustrate the behavior of differences in sensitivity return. We also highlighted a clinical case where the IAN was sectioned and whose evolution was followed up.

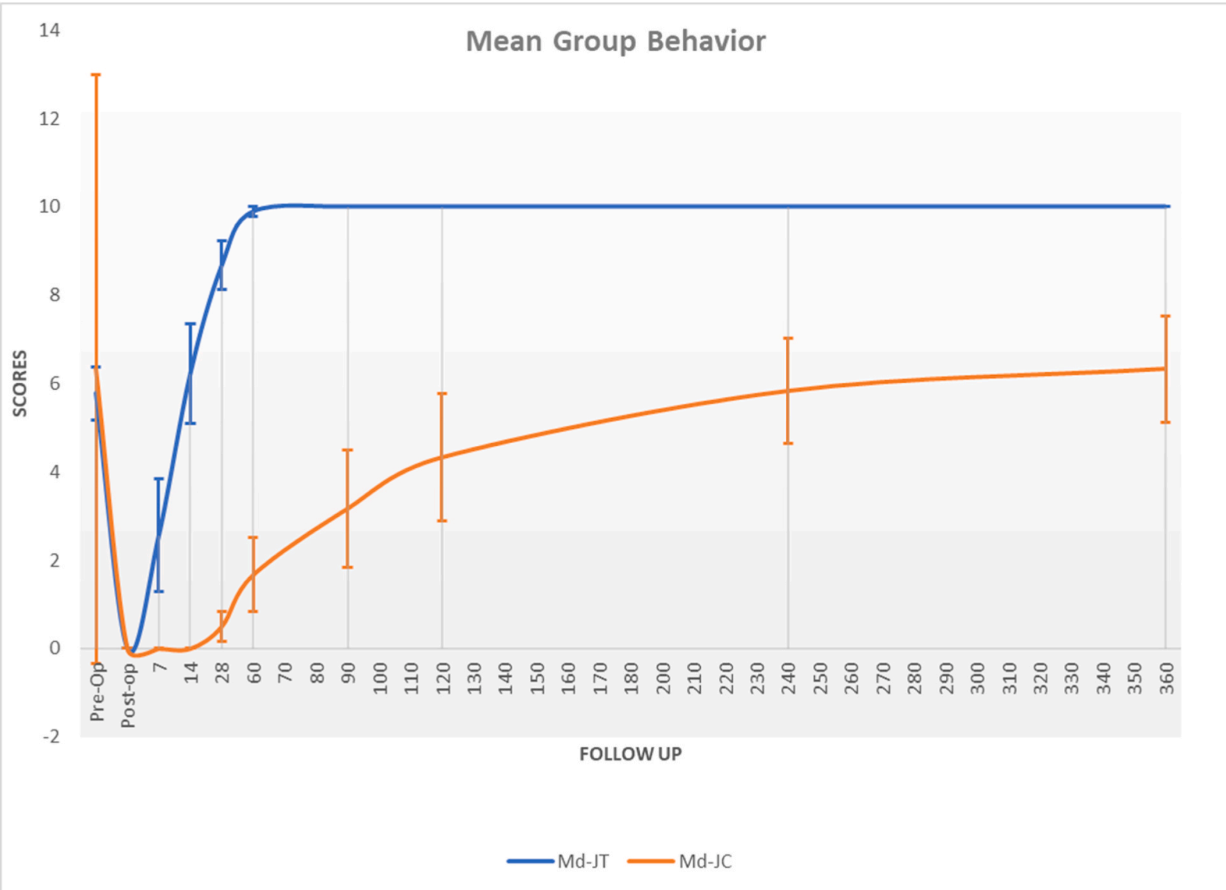

Figure-1. Indicates the mean of the sensitivity perception of the studied patients, from the preoperative period to the 360th day, observed in (Table 1). In this graphic representation, we can observe the differences in sensory perception as indicated by the patients, and their evolution over the study period, between the JC control group and the JT treated group. As shown in this graph, the evolution of the JT group was more evident than the JC group, where sensory perception occurred progressively throughout the evaluation period. In the JT group, the evolution occurred much faster, indicating a positive interference of the biomimetic material for the return to normal functioning in patients with damage to the NAI.

3. Results

The results are shown in (Table 1), where it is possible to observe that all cases indicated a sensory deficit in the preoperative period, where the mean was (5.78) for JT and (6.33) for JC, with no statistically significant difference. In the immediate postoperative period, the perception of all cases was the complete lack of sensitivity in the lower lip and chin. On the 14th and 28th postoperative days, the perception of improvement in paresthesia was more evident in the JT cases, with highest concentration of improvement on the 28th day (mean = 8.67), where 5 of 9 hemi-mandibles treated with the biomimetic material reached a score of 10, according to the patients' perception, while during the same period of 28t^{h} days, the JC hemi-mandibles showed the beginning of improvement in local sensitivity (mean = 0.50), indicating a statistically significant difference.

Also, in this (Table 1) it is possible to notice that the perception of improvement was more dispersed in the JC, starting from the 28th to the 360th days, where in 3 cases the observed sensation of sensorineural deficit remained throughout the period of this study. In contrast, the longest time of sensory deficit in JT was 90 days.

The mean of the two groups (JC and JT) at the different times studied are shown in (Fig. 1). It is possible to notice a significant improvement of the JT patients in relation to the JC patients. In this graphic figure, the JT shows a high rise at the beginning, becoming constant during the 90 days of study (score-10), with complete remission of paresthesias in this group. While in the JC, the beginning of the ascent was observed only on the 28th day, with a gradual increase throughout the study period. In this JC, there was less discomfort in relation to sensations of pruritus, hypothermia or hyperthermia when compared to the JT. However, complete cure was only observed in 2 of the 6 cases studied. It is also possible to observe that in the preoperative period all patients had some sensory deficit and in the immediate postoperative period the sensory perception of all cases studied was null, that is, all patients indicated a score of 0 for this period.

The data analysis using the t-Student (Table 2) indicated that only in the immediate postoperative period and on the 7th day the ***p***-value was >0.005, while in all other periods the ***p***-value was <0.005, indicating significant statistical differences in the other periods studied. In the Shapiro-Wilk normality test (Table 3), the ***t***-Student was used for confirmation [50]. In this test, it was possible to notice that the ***p***-value was >0.05 in the preoperative period. With these complementary results, it is possible to infer that in the preoperative, postoperative and on the 7th day there is no statistically significant difference. However, from these periods onwards, all other evaluations indicated statistically significant differences.

The Kruskal-Wallis One-Way ANOVA non-parametric test was applied due to the non-normality observed in the previous tests. Nonparametric tests are useful when the assumption of normality does not hold, and when the sample size is small [51]. As indicated in (Table 4), the ***p***-value results are <0.5 in all periods, indicating statistically significant differences between the treatments performed. In the same (Table 4), we calculated the effect size for nonparametric data represented by epsilon-squared (ϵ^2). This measure indicates the strength of the relationship between different groups or the magnitude of the difference between the variables, making possible to calculate the scope of the study. The effect size was calculated using Cohen's-***d*** and is interpreted as: small (d = 0.20–0.30), medium (d = 0.40–0.70) and large (***d*** > 0.8) [49,52]. When the coefficient found indicates 0.00 or is close to 0.00, there is little or no strength or efficacy among the treatments studied. On the opposite way, when the coefficient indicates a value close to 1.0, it is considered a perfect relationship, that is, a great strength or effectiveness between treatments. As observed in (Table 4), the epsilon-squared (ϵ^2) values show 1.00 as a result in all studied periods, indicating a great effectiveness among the treatments performed [53,54].

3.1. (Clinical) Qualitative results

As observed in the results of (Table 1), all JT patients reported at the end of this study a perception of normal sensitivity (score-10) that was observed until the 90th postoperative day, with concentration on the 28th day, being in accordance with current literature [55–58]. However, the literature also indicates that the occurrence of significant degenerative changes can occur after a stretch of 20% [43], and irreversibility is observed in a stretch of 47% [59]. In our pilot study, we considered the inclusion of patients with a strain >50% (the resulting strain promoted a stenosis ≥50% of the nerve bundle diameter).

Table-2
The T-Student test was applied to determine the existence of any statistically significant difference between the JC/JT treatments and at the period studied. For this purpose, the free open-source statistical software JAMOVI was used. Note that **p** values < 0.005 indicate the probability of statistically significant differences and 95% reliability. This can be observed in all periods studied, except for the postoperative period.

Sample T-Test				
		Statistic	df	p
Pre-Op	Student's t	13.75	14.0	<.001
Post-op	Student's t	NaN	14.0	NaN
7 days	Student's t	1.87	14.0	0.083
14 days	Student's t	3.56	14.0	0.003
28 days	Student's t	4.80	14.0	<.001
60 days	Student's t	5.87	14.0	<.001
90 days	Student's t	7.08	14.0	<.001
120 days	Student's t	8.43	14.0	<.001
240 days	Student's t	11.77	14.0	<.001
360 days	Student's t	12.91	14.0	<.001

Table-3
The Shapiro-Wilk test aims to confirm the results observed in the T-Student. Evaluating the presented distribution, we can consider whether the results diverge from normality. The **p** value must be > 0.005 for the distribution to be considered as normal. The **p** value found in the results was <0.005 in all periods studied, except in the pre and postoperative periods, indicating a violation of normality in the other periods of the experiment.

Normality Test (Shapiro-Wilk)		
	W	p
Pre-Op	0.886	0.058
Post-op	NaN	
7 days	0.511	<.001
14 days	0.809	0.005
28 days	0.805	0.004
60 days	0.726	<.001
90 days	0.705	<.001
120 days	0.660	<.001
240 days	0.632	<.001
360 days	0.604	<.001

Note. A low p-value suggests a violation of the assumption of normality.

Table-4
One-Way ANOVA (Non-parametric) is a static test used when the assumption of normality does not hold, as observed in previous tests (T-Student, Shapiro-Wilk), and when the sample size is small, as in this study. The level of significance is considered when **p** value < 0.5, rejecting the null hypothesis and indicating the existence of statistically significant differences between the periods and treatments studied, except in the postoperative period. In the same table, it was possible to calculate the size of the effect represented by ϵ^2, calculated by Cohen's **d**. The results indicate a great difference between the treatments performed, $\epsilon^2 = 1.00$ except in the postoperative period.

One-Way ANOVA (Non-parametric) Kruskal-Wallis				
	χ^2	df	p	ε^2
Pre-Op	14.0	14	0.450	1.000
Post-op	NaN	14	NaN	NaN
7 days	14.0	14	0.450	1.000
14 days	14.0	14	0.450	1.000
28 days	14.0	14	0.450	1.000
60 days	14.0	14	0.450	1.000
90 days	14.0	14	0.450	1.000
120 days	14.0	14	0.450	1.000
240 days	14.0	14	0.450	1.000
360 days	14.0	14	0.450	1.000

As for the JC cases, the perception of return to normal sensitivity was dispersed throughout the entire study period, starting on the 28th day and continuing until the 360th postoperative day. Of the 6 cases in the control group, only 2 reported normal sensory perception of the lower lip and chin (JC-1 and JC-5), the first case on the 360th day, and the second on the 120th day.

In the qualitative analysis, we will highlight two sets of JC and JT cases, and a single case where there was a complete rupture of the mental nerve and its follow-up throughout the study period.

This first set of cases (JC-1-♂/JT-3-♀) has the same origin (cycling accident). In the first case (JC-1), the fracture was observed at the base and body of the mandible, and the fracture line was related to the mandibular canal (Fig. 2/c, d). In the second case (JT-3), the fracture occurred at the base and parasymphysis, with a fracture line directly related to the mental foramen (Fig. 2/a, b). Coincidentally, in the preoperative evaluation, the patients assigned a (score-7.0) for the sensory perception deficit in the lower lip and chin region. In both cases, the fracture was unilateral (right), allowing comparison with the contralateral region (left). Postoperatively, both patients reported complete lack of sensation in the affected region (score-0). However, the positive evolution in relation to the sensory deficit was more consistent in the JT-3 case (Fig. 2/c, d), and on the 7th day the patient already reported discomfort in the region, which included a tingling sensation and occasional shocks, indicating a recovery of IAN functionality. The recovery of nerve functions was confirmed on the 14th day, where the patient reported a significant improvement assigning (score-7) to the affected region. The functional recovery of the IAN was consolidated on the 28th day, when the patient reported complete remission of the lack of sensitivity, assigning (score-10). As for the JC-1 (Fig. 2/a, b), the healing progression was slower, and the first signs of improvement were only observed on the 14th day, with a slight tingling sensation and itching in the region. Only on the 28th day the patient reported a small improvement indicating a (score-2), and this improvement in perception was continuous until, at the end of the study on the 360th day, the patient considered the local sensitivity with a (score-10) for the lower lip and chin. This difference in behavior in relation to the perception of sensitivity is shown in (Fig. 3), where it is possible to notice the differences graphically in the evolution until the cure of each JC-1/JT-3 patient.

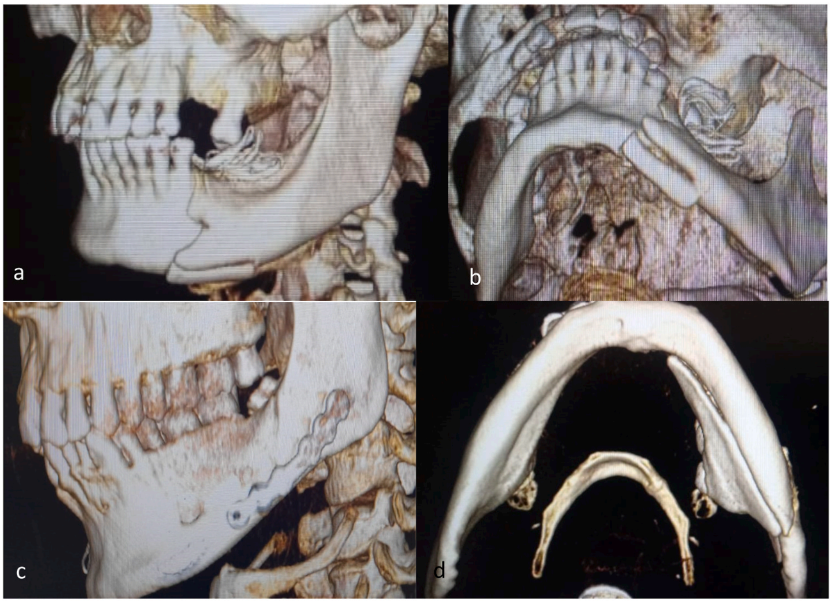

Figure-2. Tomographic images of similar traumas reaching the base and body of the mandible, where the kinetics of the trauma were the same (cycling accident). Images **a** and **b** show the treated patient and images **c** and **d** the control patient. In this studied case, it was possible to observe that the perception of complete improvement was faster in the treated patient (28 days), while in the control patient the perception occurred on the 360th postoperative day.

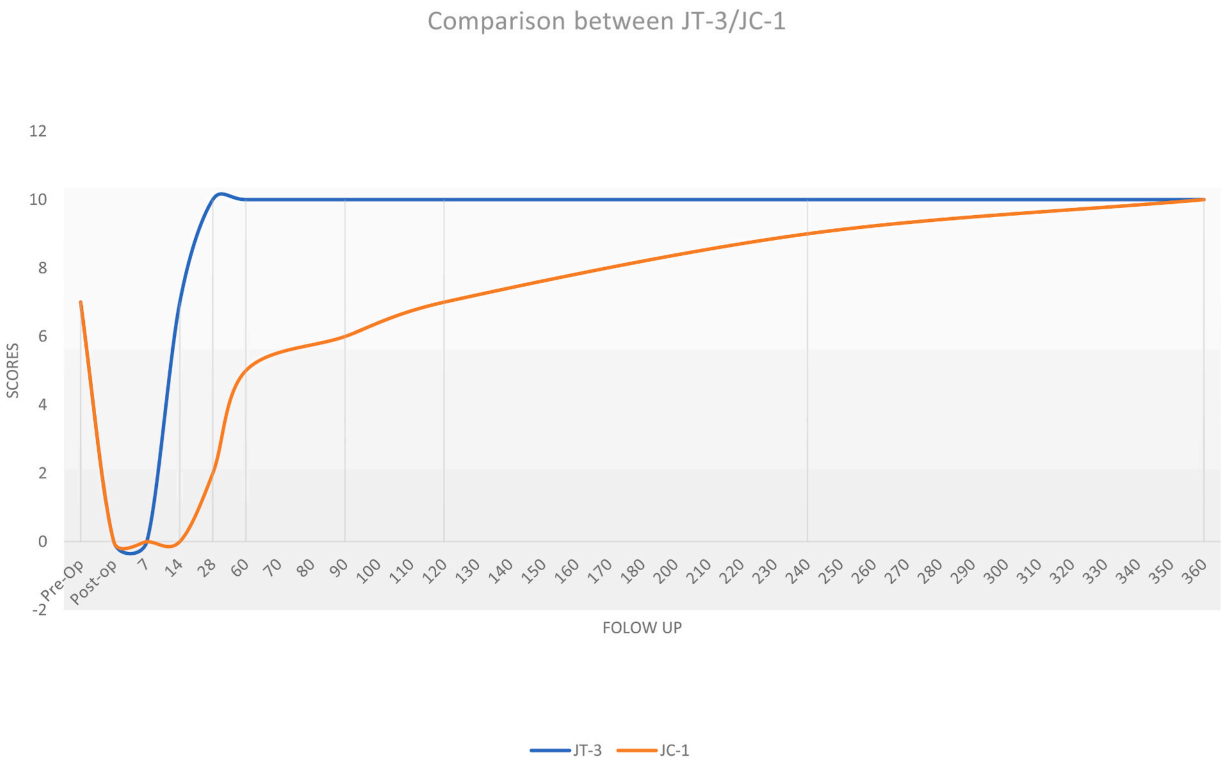

Figure-3. Represents the comparison between two similar cases (JT-3/JC-1). Note that the perception of improvement in paresthesia is the same preoperatively and postoperatively. Thus, the two patients start from a common level. However, the improvement in the perception of sensitivity occurs with greater speed in JT-3 patient, if compared to JC-1, which only indicated the complete cure of the sensitive perception (score-10) at the limit of the study period, while patient JT-3 indicated (score-10) on the 28th postoperative day.

Another possible comparison was between JC-6/JT-7, both male and approximately 32 and 27 years old respectively, with similar origins (physical aggression), and both with a displaced fracture at an angle of the mandible, with respect to the mandibular canal. In these two cases, the mandibular canal was accidently perforated by the retaining plate fixation screw as shown in (Fig. 4/a, b). In the JT-7 case, the biomimetic experimental biomaterial was inserted into the dental socket, not directly over it (NAI), due to the removal of the third and second molars. In this case, the perception of improvement in the return to sensitivity occurred 90 days after the reconstructive surgical procedure, while in the JC-6 case, the perception of improvement in the clinical condition was not observed until the end of the period of this study. The patient also reported an important sensory deficit (score 3). In (Fig. 5), the differences in the evolution of sensory perception are presented, showing a clear difference in behavior between the cases presented here (JC-6/JT-7). The fixation screws that reached the mandibular canal have not been removed so far.

In the clinical case JT-8, there was a complete rupture of the mental nerve, (Fig. 6/a, b, c). In these images, it is possible to visualize the fixed metal plate and the total rupture of the mental nerve (Fig. 6/a), its suture (b) and the presence of the biomimetic material already inserted (c). The initial threshold, that is, the perception indicated before the surgical procedure, was (score-4), indicating an important lesion to the IAN, while in the postoperative period, the patient indicated a complete lack of sensitivity in the region (score-0). On the 14th day, despite still reporting complete lack of sensitivity in the region (score-0), the patient indicated intense discomfort in the region (tingling sensation and occasional shocks). On the 28th day, the patient already reported a marked improvement, assigning a (score-8) to the affected region, and the complete remission of symptoms was observed on the 60th day, when the patient reported a (score-10) for the affected region.

4. Discussion

Peripheral nerve injuries (PNI) represent an important health problem that often lead to significant functional impairments. These permanent or transient damages result in annual costs of billions of dollars, in addition to the psychological impairments and social limitations related to these injuries [55–58]. PNI can range from compression to disruptive injuries, where the nerve bundle is completely segmented [60–62]. Functional recovery from crush injuries (axonotmesis) can occur over a period of 4–6 weeks, while in disruptive injuries (neurotmesis), functional recovery is rare [63,64].

There is a clear difference between the behavior of the two groups in this pilot work. While in the JC group the perception of return to sensitivity occurred in a dispersed and elongated way, in the JT group this perception of normality happened in a much shorter time, being concentrated on the 28th day, and all patients in this group reported the complete perception of normality, unlike JC, in which the complete perception of normality occurred on the 120th and 360th postoperative days and in only two of six cases. This difference becomes clearer when we look at (Fig. 1), where we can graphically observe the mean of the scores in relation to the study times. In this image, it is possible to verify the clear difference in behavior between the JC and JT groups, with a clear advantage for the JT group, indicating that our strategy of modulating the local repair process favored the perception of improvement in the sensitivity of the

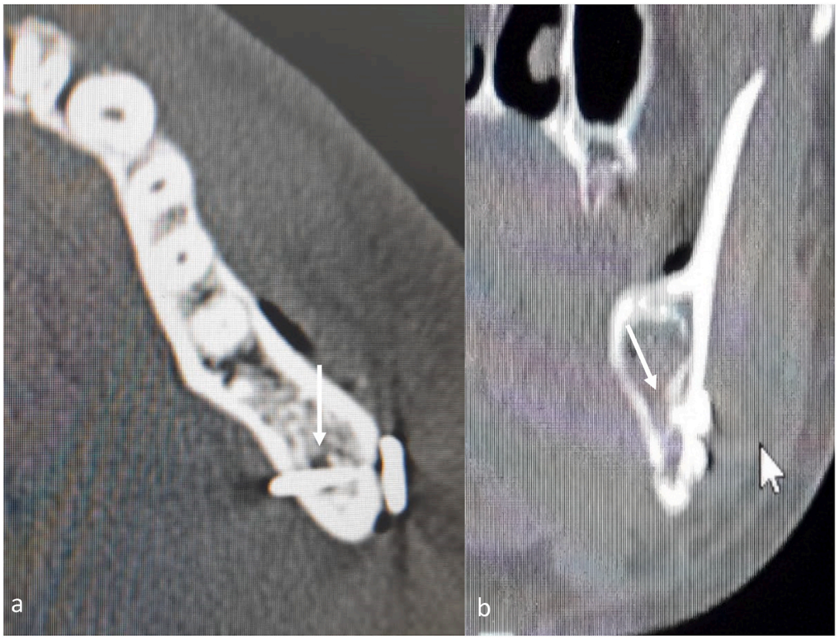

Figure-4. Images indicate an accident occurred during the surgical procedure. The plate fixation screw pierced the mandibular canal as indicated by the arrow. In JT-7 case (b), the biomimetic material was inserted into the alveolus close to the NAI, and the return of the perception of normality occurred in 90 days, while in the JC-6 control case (a), the perception of sensory deficit continued throughout the study period, with a (score-3) on the 360th day.

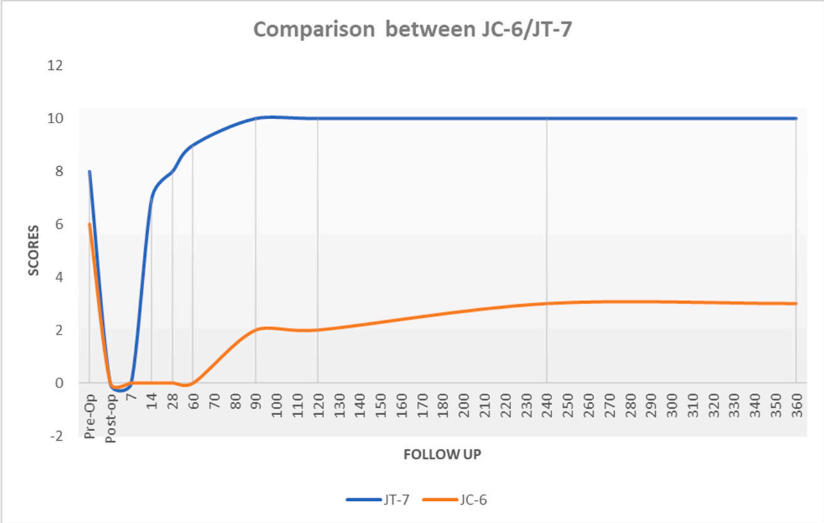

Figure-5. Graphical comparison between two similar cases, control group (JC-6) and treated group (JT-7). In both cases, there was accidental perforation of the mandibular canal by the plate fixation screw. The perception of the sensory deficit indicated by the patients in the preoperative period was (score-5) for JC-6 and (score-8) for JT-7. It is possible to notice that the cure occurred more quickly in JT-7 case 90th day, if compared to the JC-6 case, which remained with a sensory deficit even after the end of the study period (score-3).

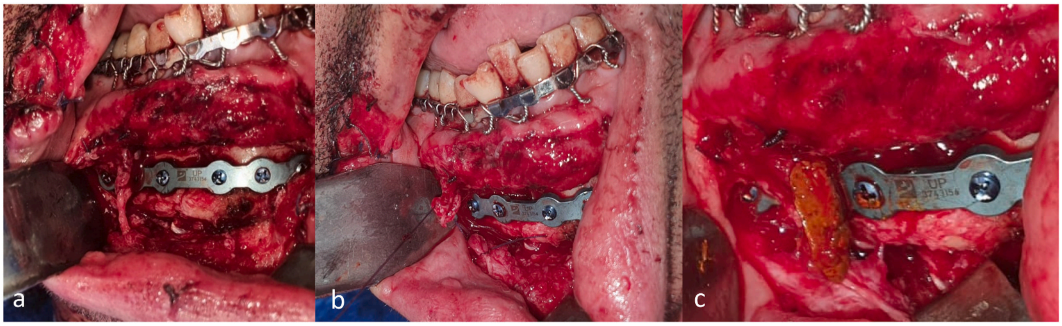

Figure-6. The sequence of clinical images of JT-8 case shows the tear in the right mental nerve in (a), its suture in (b), and the application of the biomimetic material in (c). The perception of normality occurred 60 days after surgery.

patients studied, indicating a similarity to our studies in laboratory animals [12,13].

We must clarify that our method of analysis consisted of evaluating the perception of sensitivity in the lower lip and chin through self-assessment. Although this method is an analysis model widely used in the literature [45–47], some authors also pointed out that it may incur in important methodological flaws, including possible biases in the evaluation of results [65]. We understand that this may be a methodological flaw in this preliminary work that will only be completely resolved through other studies where there is an increase in the number of patients and a more objective assessment of nerve function such as electromyography, which can be a useful tool to reach greater objectivity [66].

The results of the t-Student statistical evaluation series, the normality test (Shapiro-Wilk) and the non-parametric One-Way ANOVA (Kruskal-Wallis) in (Tabs. 02, 03 and 04) respectively, indicated deviations from normality. The results of the t-Student and Shapiro-Wilk tests together indicate a statistically significant difference already on the 14th day, observed in (Fig. 1), where it was possible to graphically notice a marked improvement in the sensory perception of the JT group when compared to the JC. This statistically significant difference was observed from the 14th day onwards, remaining until the end of this study at the 360th day. This statistically significant difference was confirmed in the non-parametric One-Way ANOVA test (Table 4), where a **p** value > 0.5 was observed in all periods studied, except for the postoperative period, which in all cases presented, had zero as the sensory perception score. In this same (Table 4), it was possible to calculate the effect size expressed by epsilon-squared (ϵ^2). This analysis makes it possible to determine the strength of the treatment between the studied groups JC and JT, that is, it allows to assess the size of the impact of the treatment performed. As indicated in (Table 4), the result of (ϵ^2) was 1.00, indicating a great statistical impact between the two treatments performed, and the relevance that the biomimetic material brought to promote the recovery of NAI functions.

This large statistical difference is illustrated by the qualitative results highlighted in this work. The first highlight are the cases (JC-1/JT-3) with fracture of the base of the mandible and trace related to the mandibular canal and mental foramen (Fig. 2/a-d). In these two cases, the sensory perception before the surgical procedure was the same (score-7), but with different evolution, while in the JC group (Fig. 2/c, d), there was a gradual progression of the perception of sensory return, starting on the 28th day and consolidating on the 360th day. In the JT group (Fig. 2/a, b), this consolidation was already observed on the 28th day (score-10) for the chin region and lower lip and is exemplified in (Fig. 3). As in these cases the fracture was unilateral, there was the possibility of a comparison of the contralateral region, thus allowing a more accurate assessment by the patients.

The comparison between the cases (JC-6/JT-7) stands out, where there was perforation of the mandibular canal by the fixation screw, indicated in (Fig. 4/a, b). In this surgical accident, the fixation screws were maintained throughout the study, characterizing a chronic compression. The literature indicates that the return of sensitivity is uncertain, taking weeks to years [67]. The results indicated an important difference in behavior in relation to the perception of sensitivity, while in the control case (JC-6), the patient began to indicate some improvement on the 90th day (score-2), but with a slow progression, ending the study period with a (score-3). In the treated group (JT-7), the evolution of sensory perception was faster, starting on the 14th day and ending on the 90th day, as shown in (Fig. 5). The literature is poor in reporting and evaluating the neurosensory damage of these accidents, but some studies related to the installation of dental implants in the posterior region of the mandible indicate a complex sensory functional recovery, which may occur in up to 2 years, or may never happen [68,69]. In addition, they also recommend removing the implant within 24 h postoperatively, to minimize the damage caused by implant insertion into the NAI. It is important to emphasize that the diameter of the drills for the installation of dental implants is thicker than the drill for fixing the plates, therefore causing greater damage to the NAI. However, the results clearly indicate a positive evolution of the patient treated with the biomimetic biomaterial, in relation to the patient with conventional treatment (Fig. 1), indicating a positive effect of this material in the recovery of nervous functions.

Another isolated but important case that we highlight was the JT-8 (Fig. 6), where there was a complete rupture of the mental nerve. Many authors indicate that full functional restoration for disruptive peripheral nerve damage is rare [63,64]. However, other authors indicate that functional restoration is possible, and it can range from 6 to 18 months [70,71]. In this specific case, we observed complete functional restoration on the 60th day, even starting from a relatively low preoperative level (score-4), indicating an important injury to the NAI. Even so, the reestablishment of sensory functions was observed in 2 months, a time considerably shorter than that described in the literature.

Despite the important limitations of this preliminary work carried out in humans, it was possible to verify the positive effects of this biomimetic material on the perception of the return to local sensitivity, in relation to the control group. This can be verified in the general results presented in (Fig. 1), where the means of the two treatments related to the study time are indicated, as well as in the statistical analyzes that indicate significant differences between these two treatments and a statistical relevance represented by the analysis of the size of the effect on ϵ^2. In addition, by highlighting the qualitative results, it was possible to clearly verify the difference in behavior between the two treatments in relation to the return to the perception of normality in the affected region.

These positive effects prompted the preparation of this article, as well as raised some questions such as: 1- What is the behavior of this material in peripheral motor nerves? 2- is it fair to assume that this composition of vitamins and mineral salts is only applicable in the mandible, or will it have the same behavior in other regions? 3- Is it possible to make some changes in its presentation, so that it can be inserted into the spine, in order to reduce the sequelae resulting from trauma in this region? As you can see through these questions, this should be just a small part of a bigger work that needs to be continued. We believe that with further studies and better development of this biomimetic material, it could become an important tool to reduce the sequelae resulting from injuries to peripheral nerves.

Author contribution statement

Salles M.B: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Horikawa F.K, Zangrando D: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Allegrini Jr, S, Yoshimoto M: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Shinohara E.H- Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at http://repositorio.unb.br.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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