Official Journal of the
Italian Society of Otorhinolaryngology - Head and Neck Surgery

Organo Ufficiale della
Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale

Argomenti di
ACTA
Otorhinolaryngologica Italica

www.actaitalica.it

Vol. **XIX** • No. 1
February 2025

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PACINI EDITORE MEDICINA

Volume XIX – Number 1 – February 2025

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Publisher
Pacini Editore Srl
Via Gherardesca, 1
56121 Pisa, Italy
Tel. +39 050 313011
Fax +39 050 3130300
info@pacinieditore.it
www.pacinimedicina.it

Acta Otorhinolaryngologica Italica is cited in Index Medicus, MEDLINE, PubMed Central, Science Citation Index Expanded, Scopus, DOAJ, Open-J Gate, Free Medical Journals, Index Copernicus, Socolar

Journal printed with total chlorine free paper and water varnishing

PACINI EDITORE MEDICINA

www.actaitalica.it

SIO eChCF

Realizzazione editoriale e progetto grafico

PACINI EDITORE
Via A. Gherardesca 1, 56121 Pisa
www.pacinimedicina.it – info@pacinieditore.it

Traduzione inglese di Argomenti di ACTA, Vol. XVIII, No. 3, Novembre 2024
La supplementazione con vitamine del gruppo B nel trattamento delle lesioni iatrogene in chirurgia ORL
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Edizione digitale Febbraio 2025 in formato PDF standard

Supplementation with B-group vitamins in the treatment of iatrogenic injuries in ENT surgery

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SUMMARY

The most common complications of surgeries involving the parotid gland include iatrogenic damage to the facial and great auricular nerves, mainly motor for the former and sensory for the latter. The aim of this study is to investigate the possible benefit of the peri-operative use of appropriate dosages of B vitamins with respect to iatrogenic damage.

Forty subjects were enrolled and divided into two groups. The study group (n = 21) received a vitamin B supplement for 45 days (starting 15 days before surgery and continuing for the next 30 days). The control group (n = 19) received no vitamin supplement.

Collected data show that peri-operative treatment with B vitamins is able to protect the analyzed nerves, promoting their repair. The effect of B vitamins is significant in maintaining sensitivity in the skin area corresponding to the great auricular nerve. Additionally, a protective effect on the facial nerve has been observed.

Key words: iatrogenic injuries, neuroprotective action, B vitamins

Introduction

Parotid surgery involves different approaches depending on the site (superficial vs. deep), size, possible multifocality and the type of neoformation to be removed.

The most common type of surgery is **superficial or exofacial parotidectomy**, involving the removal of the whole parenchyma of the gland, located superficially to the facial nerve. For malignant neoplasms, neoformations of other nature located in the deep lobe or in rare cases of multifocality, **total parotidectomy** is performed. This involves the removal of the deep parenchyma after careful dissection and dislocation of the facial nerve. **Near-total parotidectomy** is a variant of the above. Here, a small portion of the gland anatomically distant from the lesion to be removed is spared in order to avoid excessive risks to the nerve. Finally, in selected cases of single, small-sized, superficially located, benign lesions at FNAB (*Fine Needle Aspiration Biopsy*), **parotid enucleoresection** can be performed. This option involves the removal of the nodule alone, without touching the superficial and deep gland parenchyma.

However, this surgery involves a similar incision, more limited in case of enucleoresection. **The most common complications include iatrogenic damage of certain nervous structures, namely the facial nerve (FN) and the great auricular nerve (GAN).**

The **facial nerve** (FN: VII pair of cranial nerves) mainly provides the motor functions for the motility of the mimic muscles of the face. Its secondary functions include the control of lacrimation and, in part, of salivation. The FN and the *chorda tympani* transport the taste sensation of the anterior 2/3 of the tongue to the central nervous system.
In its extra-cranial portion, the FN emerges from the stylomastoid foramen of the temporal bone and divides into two main branches at the level of the parotid gland, the temporo-facial and the cervical-facial branches, which further branch out before exiting the gland.
The most typical symptom of FN damage is a motor deficit which, according to the House-Brackmann (H-B) [1] classification, can have six grades depending on nerve functionality and, consequently, on the motility of mimic muscles.
The **great auricular nerve** (GAN) is a sensory nerve of the skin located on the outer face of the sternocleidomastoid (SCM) muscle and originating from the ansa cervicalis media of the cervical plexus, made of fibers coming from C2 and C3. It divides into two branches: an anterior branch, directed to the parotid gland into which it penetrates, sometimes with further branches, and a posterior branch, directed to the cutaneous region of the auricle.
In parotid surgery, the parotid branch is sacrificed, whereas the posterior branch is usually spared in order to reduce the sensory deficit of the skin areas, particularly of the auricle, mastoid and angular-mandibular regions.
The development of adjuvant strategies is currently acknowledged as highly indicated to increase the potential of neuro-regeneration and is an extremely attractive field of research. In this scenario, B vitamins may play an important role due to their neurotrophic activity. **B-group vitamins maintain the viability of neurons in several ways**. Firstly, they consistently protect nerves against adverse environmental influences. In particular, **vitamin B1 works as a direct antioxidant, vitamin B6 balances nerve metabolism and vitamin B12 maintains the myelin sheath. When nerve injuries occur, vitamins B1, B6 and B12 are essential in supporting subsequent regeneration. During the process of injured nerve repair, vitamin B1 facilitates the utilization of carbohydrates for energy production, while vitamin B6 is essential for the synthesis of neurotransmitters and for inhibiting the release of neurotoxic glutamate, and vitamin B12 promotes nerve cell survival and is directly involved in the remyelination process**. Conversely, a lack of these vitamins promotes permanent nerve degeneration and pain, eventually leading to peripheral neuropathy [2].
The aim of this clinical data collection is to investigate the possible benefit of peri-operative use of B vitamins with respect to iatrogenic damage (motor on the FN and sensory on the GAN) compared with an untreated control group.

Materials and methods

Study design and participants

A single-center prospective case-control observational study was performed to assess the efficacy of B vitamins supplementation in patients undergoing parotid surgery. More specifically, depending on the situation of each single patient, the following surgical interventions were performed: enucleoresection, superficial parotidectomy and total/near-total parotidectomy. Patients, who were free of any pre-operative nervous deficit, were observed and examined at specific time points: in the early post-operative period (baseline = days 1 to 3 post-surgery), at 30 days, 90 days and 180 days post-surgery. The study and the related follow-up covered a period comprised between January 2021 and November 2023.
The aim of the research was to investigate whether B-complex vitamins are able to improve the process of nerve repair following surgical procedures affecting them. The study group received a dietary supplement of B vitamins (one tablet per day) for 15 days before surgery and for 30 days afterwards. The use of the multivitamin product did not change the treatment with any drugs already taken or prescribed peri-operatively.
The food supplement used is marketed in Italy under the name B-Vital® totale 500 film-coated tablets

Table I. House-Brackmann (H-B) classification.

Grade	Deficit	Characteristics
I	None	Normal function of the facial muscles in all areas
II	Slight	Very slight deficits, visible only on close inspection. Possible very slight synkinesis
III	Moderate	Obvious but not disfiguring asymmetry between the two sides. Obvious but not severe synkinesis, contractures and/or hemifacial spasms
IV	Moderately severe	Obvious weakness and/or disfiguring asymmetry
V	Severe	Only barely perceptible movement
VI	Complete paralysis	No movement

(Pharma Line S.r.l., Milan, commercially available since 2019, food supplement register number 118552).

Outcomes

The primary objective of this study is to determine the efficacy of B vitamins (taken for 45 days) in preventing or limiting FN and GAN alterations with assessments performed at different time points (follow-up), compared to untreated subjects (control group). Secondarily, we considered useful to investigate the relationship between the type of intervention performed and the scores obtained by the patients in the different assessments carried out on the two nerves involved. In all analyses performed, a 5% significance level was considered.

The FN's function was evaluated using the H-B scale. This is an ordinal scale consisting of six different grades. Grade I indicates normal efficiency; deficits are progressively described from Grade II, in which only muscle weakness is present, to Grade IV, representing the total absence of any mimic movements of the affected side (Tab. I) [1].

For the GAN, sensitivity was assessed on different skin areas according to the scheme proposed by Ryan et al. [3], identifying the presence of hypoesthesia or anesthesia on each. This evaluation was carried out using an esthesiometer. In order to standardize the procedure, all areas were stimulated with a 2 gr and 4 gr filament, ensuring that the tip would touch the skin surface with a modest flexion of the filament itself. Patients (with their eyes closed) were asked to describe their tactile perception of the stimulus (Fig. 1). On that basis, three scores were assigned for each stimulated area:

1. **normal** sensitivity (score = 0), if patients reported tactile perception with just the 2 gr stimulus;
2. **hypoesthesia** (score = 1), if perception was only present with the 4 gr stimulus, but not with the 2 gr stimulus;
3. **anesthesia** (score = 2), if no tactile sensation was present, not even with the 4 gr stimulus.

Three different types of scores where then developed: GAN Hypoesthesia, GAN Anesthesia and GAN Total.

- The GAN Hypoesthesia (**GAN Hypo**) provides the number of areas presenting with hypoesthesia;
- The GAN Anesthesia (**GAN Ane**) results from the number of areas presenting with anesthesia, i.e., areas not responding to any stimulation;
- The **GAN Total** is a composite measure in which the score is calculated by summing up the areas of hypoesthesia, whose value is 1, and those of anesthesia, whose value is 2.

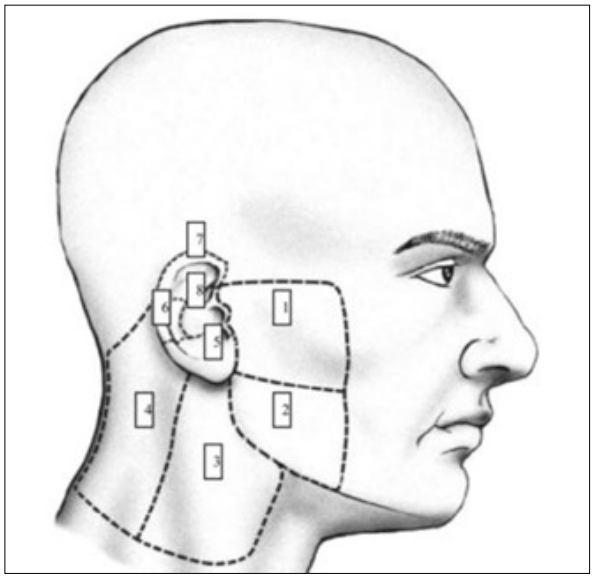

Figure 1. The 8 areas evaluated with the esthesiometer (mod. from Ryan, Fee, 2009) [3].

The GAN Total thus represents an overall assessment of the sensory deficit and can take on values ranging from 0 (all normal) to 16 (anesthesia of all 8 areas), while the GAN Hypo and GAN Ane range from 0 to 8.

For each scale (H-B and GAN) obtained from each patient, a comparison was made at specific time points: baseline (day 1 to 3 post-operatively) and at 30 days, 90 days and 180 days post-surgery. The timeline described above and in Figure 2 were supplemented by a further assessment of the H-B score, for which a pre-operative measurement was also carried out (approximately 20 to 30 days before surgery) with the aim of confirming the initial absence of any motor deficits.

Forty adult patients (21 in the study group and 19 in the control group) participated in the study. Subjects with motor deficits of the FN or sensory deficits of the GAN already present prior to surgery, known neuropathies, psychiatric disorders, cognitive deficits capable of affecting data collection, pregnant women and patients with major complications during surgery were excluded. Enrolled subjects signed an appropriate informed consent form for the processing of their personal data.

The socio-demographic characteristics of the study participants are reported in Table II.

Statistical analysis

The data of the 40 patients were analyzed using the

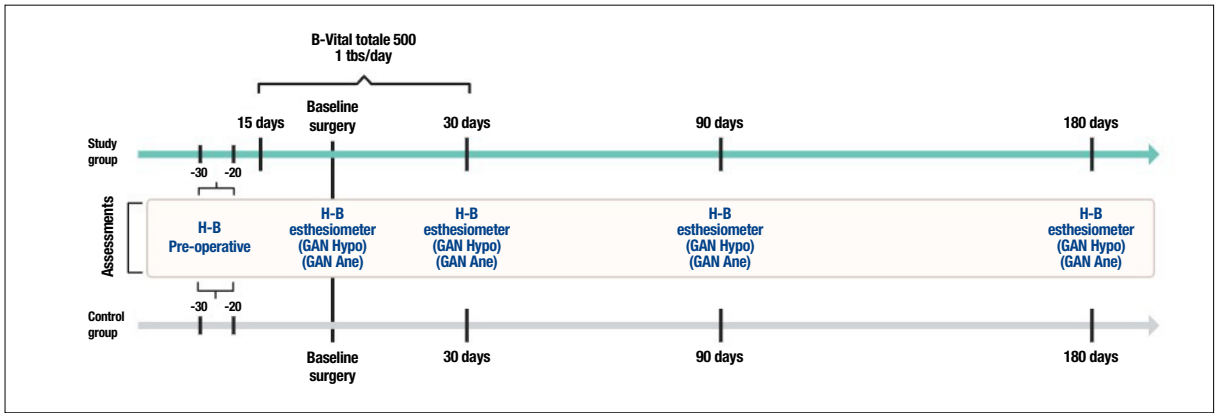

Figure 2. Study design.

Table II. Socio-demographic characteristics of patients and types of surgery performed.

Characteristics	Value
Age (years)	62 ± (18.05)
Group	
Study	21 (52.5%)
Control	19 (47.5%)
Tumor	8 (20%)
Surgery	
Enucleoresection	4 (10%)
Superficial parotidectomy	16 (40%)
Parotidectomy: total	20 (50%)
or near-total	
Side	
Left	23 (57.5%)
Right	17 (42.5%)

Notes. The values reported in brackets are the relative frequencies by class. For age, standard deviation is reported instead.

statistical software Stata14. Several aspects were investigated, including a comparison between the study and the control group; we checked whether the type of intervention produced a different effect on the score at baseline; we assessed whether there were any significant improvements over time and whether being in a specific group and the type of surgical intervention performed played a role in patients' recovery.

In order to achieve these objectives, four types of analysis were performed. Firstly, a non-parametric Mann-Whitney test was employed to assess the existence of a significant difference – in terms of score – between the two groups of data due to the use of the supplement. Subsequently, the Kruskal-Wallis test was only applied on the baseline period (i.e., the post-surgery period) to assess whether there were any significant differences between the scores attributed to each of the three types of surgery performed. Then, the Wilcoxon matched-pairs signed-rank test allowed an overall assessment of the improvement in patients' recovery times by performing a "before and after" comparison on the same subjects [4]. In this case, parallel analyses were carried out between the two groups with the aim of assessing at what time point there had been an actual improvement between one period and another, taking into account that, in addition to the difference in supplement intake, other factors may have contributed to this improvement, such as, for example, the different type of intervention that patients underwent. Finally, ordinal logistic regression (Ologit) [5] allowed us to identify the characteristics of the subjects who had the greatest benefits over time, comparing the results of the scores for the H-B scale, the GAN Hypo and the GAN Ane. In short, the aim was to show at what time points belonging to a certain group (study or control) and the type of intervention carried out significantly impacted the score, in terms of a cause-effect relationship. Table III shows the coding of the variables used to perform the Ologit analyses. The same coding was also used for the other analyses performed in this study, except for the GAN Total scores.

Results

Graphs were drawn from the study scores to describe the trend in post-operative recovery over time. The mean scores according to the H-B scale (Fig. 3), the GAN Total score, (calculated as previously explained) (Fig. 4), and according to the mean scores of the GAN areas of hypoesthesia (Fig. 5) and anesthesia (Fig. 6) were considered.

The Mann-Whitney test showed that the two groups (treated and control) had significantly different scores (at different significance levels) for the H-B score and for the number of areas of hypoesthesia (from day 90 onwards) (Tab. IV).
The Kruskal-Wallis test was applied to the scores collected post-operatively (at baseline) to evaluate the possible impact of the different surgical interventions. The analysis showed no significant differences at baseline for any of the assessments performed (Tab. V).
When comparing the results between the two groups in parallel using the Wilcoxon test (Tab. VI), it can be seen that a significant recovery was observed past day 90 post-surgery in the patients in the study group with the onset of anesthesia; on the contrary, this recovery was not observed in the control group.
Regarding the Ologit results, the statistically significant relationships concern the H-B and GAN Hypo scores. For the sake of brevity, only the coefficients useful for assessing the relationship between the scores and the variables considered as regressors were reported in Table VII.

Table III. Numerical coding of variables used for Ologit analyses

Variable name	Type	Code	Description
H-B	Ordinal	1,2,3,4,5,6	6 = Complete paralysis 5 = Severe 4 = Moderately severe 3 = Moderate 2 = Slight 1 = None
GAN Hypo	Ordinal	0,1,2,3,4	4 = Four areas of hypoesthesia 3 = Three areas of hypoesthesia 2 = Two areas of hypoesthesia 1 = One area of hypoesthesia 0 = No areas of hypoesthesia
GAN Ane	Ordinal	0,1,2,3,4	4 = Four areas of anesthesia 3 = Three areas of anesthesia 2 = Two areas of anesthesia 1 = One area of anesthesia 0 = No areas of anesthesia
Surgery	Ordinal	1,2,3	3 = Total parotidectomy 2 = Superficial parotidectomy 1 = Enucleoresection
Group	Nominal Binary	0.1	0 = Control; 1 = Study

Notes. The coding of the areas of hypoesthesia and anesthesia ranges from 0 to 4 because there were no cases of study patients with more areas (effective minimum score = 0; effective maximum score = 4).

Discussion

The Mann-Whitney test (Tab. IV) shows that the two groups (study and control) have significantly different values for the H-B scores in all time points investigated, from baseline to day 180, as well as for the number of areas of hypoesthesia of the GAN (in this case, from day 90 onwards). **Therefore, we can say that the use of supplementation** – in the 15 days before and 30 days after surgery – **plays a significant protective role for the FN and exerts a significant recovery action for the areas of hypoesthesia**, which is not as evident for those of GAN anesthesia.
This important result seems to suggest that vitamins B group treatment acts in the very short term to promote the recovery of the FN and GAN nerve function following iatrogenic damage and even in a preventive manner in the case of the FN. This can be seen by analyzing the H-B scores of the two groups immediately after surgery (Fig. 3). In this graph, the mean H-B scores are very different between the two groups already at baseline, although there are no statistically significant differences in the distribution of the different types of surgery (enucleoresection: 2 interventions in the control group and 2 in the study group; superficial parotidectomy: 6 in the control group and 9 in the study group; total/near-total parotidectomy: 11 interventions in the control group and 10 in the study group).

In fact, the Kruskal-Wallis test did not detect any significant difference in the two groups as regards the type of surgery performed, as all p-values are above the threshold of statistical significance ($p < 0.05$) (Tab. V). This allows us to conclude that the post-operative condition related to nerve function is the same for all patients who participated in the study, regardless of the type of surgery performed and the group to which they belong.
Just after surgery, the study group (pre-treated with vitamins B) has a mean value of 1.67 (= mild deficits of the FN according to the H-B scale), while the control group has a noticeable higher value: 3.16 (= moderate deficits). **This means that preventive treatment with B vitamins was able to protect the FN, limiting iatrogenic damage and best preserving its motor function.**
With the Wilcoxon test (Tab. VI), it can be seen that the time point of greatest recovery for all patients assessed was 90 days post-surgery.
Regarding the Ologit results, the statistically significant relationships concern the H-B and GAN Hypo scores. More specifically, for the H-B evaluation on

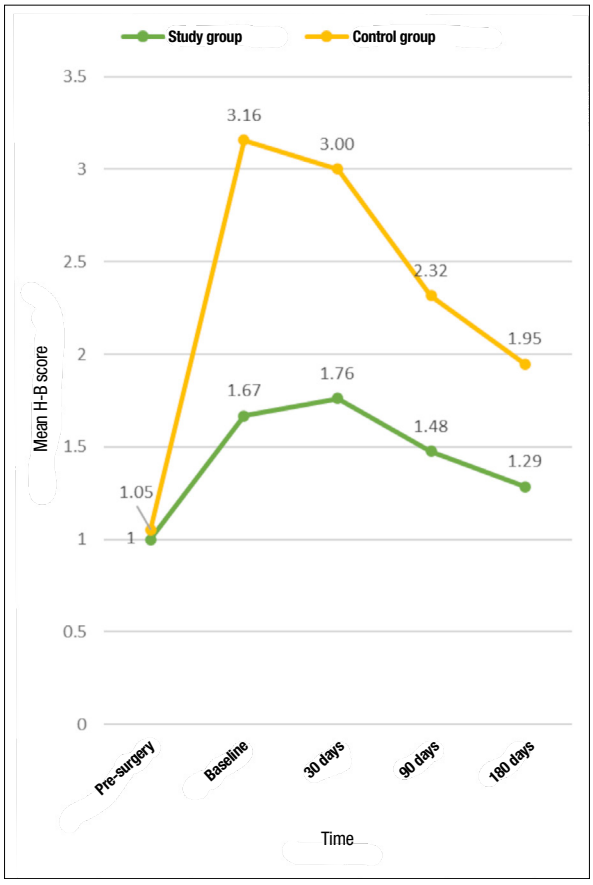

Figure 3. Distribution of mean scores for the H-B scale over time.

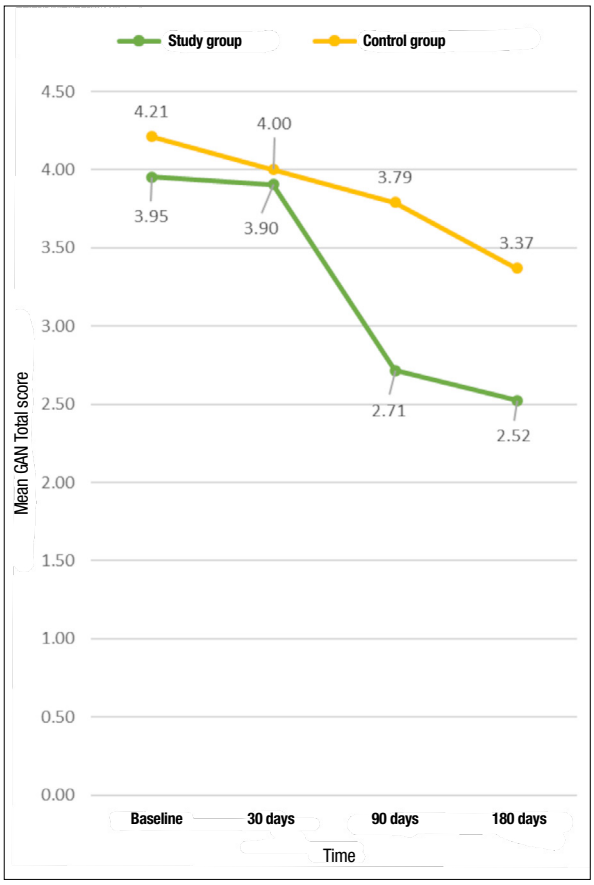

Figure 4. Distribution of mean scores for the GAN Total over time (global assessment of sensory deficit).

the FN, the subjects who did not take the supplement had more difficulties recovering than those who took it from 15 days before their surgery. This further confirms the beneficial action of B vitamins in protecting against iatrogenic damage to the nerves. As regards surgery, scores were only affected by the invasiveness of the procedure in the period comprised between the baseline and 30 days post-surgery.

Concerning the GAN Hypo, the patients who took the supplement (whose effects are observed from day 90 onwards) and who underwent a less invasive procedure show less areas of hypoesthesia (a common finding for all time points considered).

This is in partial agreement with our surgical experience: while the risk of iatrogenic injury of the FN is influenced by the type of surgery (definitely higher in total and near-total parotidectomy than in partial surgeries), the injuries of the GAN do not vary considerably in this respect, as the skin incision and the exposure of the gland are essentially the same.

Finally, given that the anatomical integrity of the GAN was maintained in its extra-parenchymal posterior branches, the non-significance of the relationships between the GAN Ane score and supplement intake highlights that B vitamins work well in the context of milder iatrogenic damage, but not for severe damage, even when the nerve is anatomically intact.

Interpretation of the data collected

The repair processes that are activated following iatrogenic injury to the peripheral nervous system presuppose a precise coordination of interactions between different cells, in particular between Schwann cells (SCs) and macrophages. The inflammatory and reparative roles of macrophages have proven to be essential, as it has been proven that impaired macrophage functioning after peripheral nerve injury impairs the neuro-regeneration process, associated with long-term impairment of neuronal function [6].

Macrophages show remarkable plasticity and are highly heterogeneous. Depending on their activation state and functions, they are classified into two opposite phenotypes: pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2) [7]. M1 macrophages have been recognized as the pri-

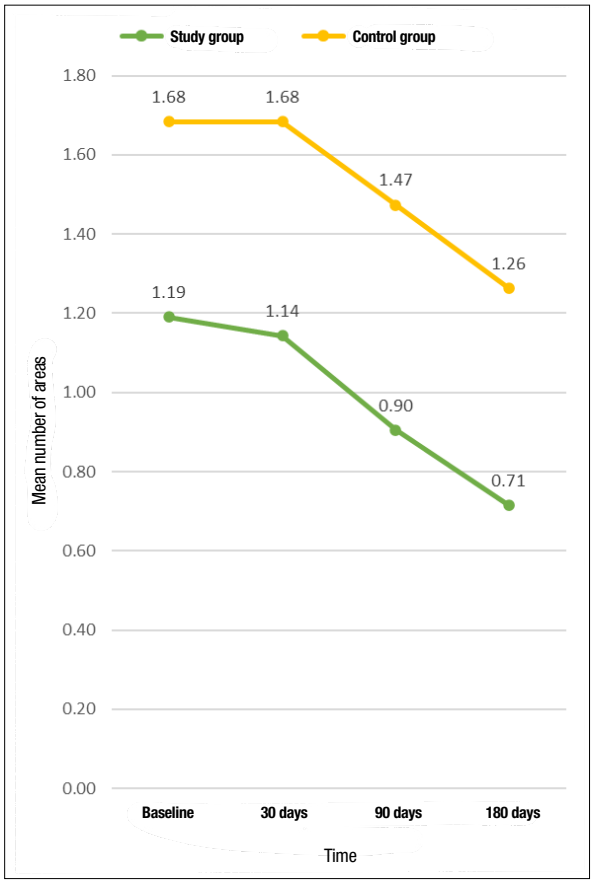

Figure 5. Distribution of mean scores for the GAN Hypoesthesia over time (number of areas of hypoesthesia).

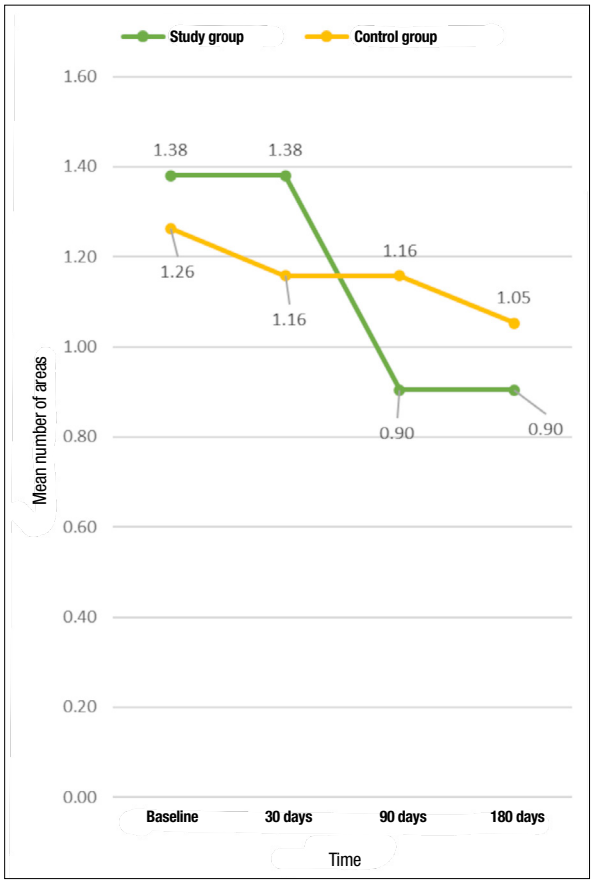

Figure 6. Distribution of mean scores for the GAN Anesthesia over time (number of areas of anesthesia).

mary phagocytes at the site of peripheral nerve injury, while M2 macrophages take over later in neuro-repair processes, the timely activation of which becomes vital to overcome the neurotoxicity of the M1 phenotype [8].

SCs are considered crucial in orchestrating the functional modes of the macrophage phenotypes. Initially, the SCs release cytokines that boost the macrophage activity and recruit other monocytes in the injured site [9]. Subsequently, the interactions between the SCs and tissue macrophages restore the myelinating phenotype of the SCs, which plays a key role in axonal regeneration [10].

B vitamins act as necessary co-enzymes in many enzymatic reactions, critically affecting vital cell functions such as energy production, protein synthesis, methylation, nucleic acid synthesis, etc. Several studies in animal models have revealed the therapeutic potential of B-complex vitamins in the functional recovery of damaged peripheral nerves [11-13].

In particular, it was shown that **the administration of these vitamins can improve the process of nerve regeneration after an injury** [12]. Recent evidenc-

Table IV. Mann-Whitney test.

Score	Time	z test	p-value
H-B	Baseline	2.91	**0.00**
	30 days	2.97	**0.00**
	90 days	2.17	**0.03**
	180 days	1.98	**0.05**
GAN Total	Baseline	0.73	0.47
	30 days	0.63	0.53
	90 days	1.27	0.20
	180 days	1.12	0.26
GAN Hypo	Baseline	1.67	0.09
	30 days	1.81	0.07
	90 days	2.29	**0.02**
	180 days	2.14	**0.03**
GAN Ane	Baseline	-0.12	0.91
	30 days	-0.42	0.68
	90 days	0.51	0.61
	180 days	0.25	0.80

Notes. The critical z-values for 2-tailed tests with 5% significance levels (α) is 1,96.

es suggests that several mechanisms are involved: **B vitamins seem to promote the transition of macrophages from the pro-inflammatory M1 to the anti-inflammatory/repair M2 phenotype and contribute to the resolution of neuroinflammation** [13].
In a recent study of nerves isolated from animals with femoral nerve injury, treated with B-complex vitamins, a decrease in the number of M1 macrophages was observed, together with preserved SC morphology and myelinization in the injured nerve. These results led the authors of the study to hypothesize that treatment with B-group vitamins can reduce the extent of degeneration of injured axons and facilitate their repair [14].
Several studies in the literature attest that the status of B-complex vitamins is often insufficient in the general population. Frank, marginal and functional deficiencies or conditions of increased demand are in fact common, and these can compromise the numerous biochemical reactions in which these vitamins are involved, thus also impairing the repair of nerves that have suffered injury [15].
Iatrogenic damage certainly represents a condition of increased need for vitamins and, considering the results obtained in this study, it can be hypothesized that peri-operative treatment with B vitamins is a valuable aid in protecting the nerves and promoting their repair. This is because the treatment, started 15 days before surgery and continued for another 30 days, makes the vitamins readily available at the time the surgery is performed and the iatrogenic damage is caused. This damage must be repaired by the body within a defined timeframe, with a precise coordination of the interactions occurring between SCs and the macrophages. These complex interactions may be facilitated by the availability of B-vitamins and by their contribution to the resolution of neuro-inflammation.

Table V. Kruskal-Wallis test on comparisons for type of surgery post-operatively (baseline).

Score	$\chi 2$	p-value
H-B	3.608	0.165
GAN Total	2.420	0.298
GAN Hypo	3.039	0.219
GAN Ane	0.686	0.710

Notes: the critical $\chi 2$ values for 2-tailed tests with a 5% significance level (α) is 7.738.

Table VI. Wilcoxon test on comparisons of scores considering the post-operative period (baseline) as the reference period.

		Study group (n = 21)		Control group (n = 19)	
Score	Time	z test	p-value	z test	p-value
H-B	30 days	0.31	0.760	0.86	0.388
	90 days	1.42	0.156	3.27	**0.001**
	180 days	2.15	**0.032**	3.62	**0.000**
GAN Total	30 days	1.00	0.317	1.41	0.157
	90 days	3.26	**0.001**	2.30	**0.022**
	180 days	3.51	**0.001**	2.96	**0.003**
GAN Hypo	30 days	1.00	0.317	n.a.	n.a.
	90 days	2.45	**0.014**	1.74	0.082
	180 days	3.16	**0.002**	2.64	**0.008**
GAN Ane	30 days	n.a.	n.a.	1.41	0.157
	90 days	2.82	**0.005**	0.94	0.347
	180 days	2.82	**0.005**	1.73	0.084

Notes. The values for the GAN Ane at 30 days and GAN Hypo at 30 days in the control group are "n.a." because their scores between the baseline and these two specific cases are the same and, therefore, there is no difference.

Conclusions

Although this is a small case study requiring further research, based on the data collected, it can be stated that B vitamins, taken in the peri-operative period, have a significant neuroprotective function, accelerating the functional recovery of any iatrogenic (motor of the FN and sensory of the GAN) damage. The effect of B vitamins is significant, as long as the damage the patient has suffered to the GAN is not too extensive. A protective action of B vitamins taken before surgery was also observed for the FN.

Declaration of interests

The Authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ilaria Carnevali, Stefania Colombo and Daria Sicari are employees of Pharma Line S.r.l. and have contributed to the writing of the paper without actively participating in the data collection. The remaining Authors declare that the study was conducted in the absence of any commercial or financial relationships which may be considered as potential competing interests.

Funding

Funding for the conduct of the study: none.
Pharma Line S.r.l. bore the publication costs.

Data availability

Data will be available upon request.

Table VII. Ordinal logistic regression (Ologit).

		Group			Surgery		
Score	**Time**	**Coefficient**	**z**	**p-value**	**Coefficient**	**z**	**p-value**
H-B	Baseline	-1.96	-2.93	**0.003**	0.86	1.79	0.073
	30 days	-2.22	-3.00	**0.003**	1.57	2.86	**0.004**
	90 days	-1.46	-2.14	**0.032**	0.77	1.44	0.151
	180 days	-1.48	-2.01	**0.044**	0.97	1.61	0.106
GAN Hypo	Baseline	-1.13	-1.69	0.09	1.00	1.98	**0.047**
	30 days	-1.27	-1.91	0.056	1.27	2.46	**0.014**
	90 days	-1.80	-2.51	**0.012**	1.74	3.01	**0.003**
	180 days	-1.52	-2.25	**0.024**	1.67	3.00	**0.003**
GAN Ane	Baseline	0.06	0.10	0.919	0.38	0.82	0.415
	30 days	0.21	0.35	0.725	0.40	0.87	0.385
	90 days	-0.33	-0.53	0.596	0.07	0.16	0.872
	180 days	-0.17	-0.27	0.785	0.14	0.31	0.76

Notes. The critical z-values for 2-tailed tests with 5% significance levels (α) is 1.96.

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