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Effect of the use of combination uridine triphosphate, cytidine monophosphate, and hydroxycobalamin on the recovery of neurosensory disturbance after bilateral sagittal split osteotomy: a randomized, double-blind trial

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Abstract. The change in neurosensory lesions that develop after bilateral sagittal split osteotomy (BSSO) was explored, and the influence of the application of combination uridine triphosphate (UTP), cytidine monophosphate (CMP), and hydroxycobalamin (vitamin B12) on patient outcomes was assessed. This was a randomized, controlled, double-blind trial. The study sample comprised 12 patients, each evaluated on both sides (thus 24 sides). All patients fulfilled defined selection criteria. Changes in the lesions were measured both subjectively and objectively. The sample was divided into two patient groups: an experimental group receiving medication and a control group receiving placebo. The statistical analysis was performed using SPSS software. Lesions in both groups improved and no statistically significant difference between the groups was observed at any time. 'Severe' injuries in the experimental group were more likely to exhibit a significant improvement after 6 months. Based on the results of the present study, it is concluded that the combination UTP, CMP, and hydroxycobalamin did not influence recovery from neurosensory disorders.

Key words: orthognathic surgery; mandibular-nerve; nervous system trauma; therapeutics.

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The osteotomies required during orthognathic surgery are performed near to the sensory nerves. Transient changes in skin sensitivity may develop, attributable to soft tissue swelling and inflammation, or direct or indirect nerve injury, depending on the nerve distribution. The rate and extent of facial sensation recovery are affected by several factors, among which are the type of surgery, the number of procedures performed, and patient age.[1]

Drugs exhibiting neurotrophic characteristics and mimicking neuronal growth factors would be valuable to treat nerve damage; neuronal growth factors synthesized during embryogenesis guide nerve growth towards target organs.[2]

Wattig et al.[3] reported that drugs stimulating neural regeneration would be very useful to treat both minor and severe nerve injuries, and also problems developing after nerve suturing. Such drugs would foster a faster recovery, shorten the time to reinnervation, and minimize secondary injuries caused by denervation of effector areas. In recent years, intensive research has been devoted to this end. Drugs including vitamin B complex (associated or not with corticosteroids), multivitamin preparations, and gangliosides and nucleotides have been investigated as stimulators of peripheral nerve regeneration.

The nucleotide cytidine-5-monophosphate (CMP) improves muscle strength and general neuronal functionality. CMP is a metabolite of the nervous system, serving as a coenzyme of enzymes involved in phospholipid and glycolipid synthesis. Such lipids, which are essential for normal nervous system functionality, undergo continuous cycles of breakdown and synthesis. CMP, which stimulates glycolipid synthetic activity, complemented by the action of uridine 5′-triphosphate (UTP), is an enzyme cofactor that is essential for the maintenance and regeneration of nervous system structures, especially that of the myelin sheath. Recent work in rats has shown that a lack of CMP triggers axonal swelling and neuronal degeneration.[4]

The compound made up of UTP, CMP, and hydroxycobalamin (UTP/CMP/hydroxycobalamin) contains sodium salts of pyrimidine ribonucleotides derived from CMP and UTP contained in RNAs degraded by pancreatic ribonuclease. In vitro studies have shown that the uridine and cytidine are incorporated into RNA early after neuronal injury. In animal tests, the UTP/CMP/hydroxycobalamin compound accelerated axonal maturation and improved the sensory and motor conduction velocities of individual fibres.[5]

In addition, neuronal regeneration is associated with many metabolic, functional, and structural changes in both the neuronal cell body and peripheral nerve fibres. Such changes affect lipid synthesis and use. Protein and carbohydrate levels are also influenced by associated hormones, reflecting the need for the increased synthesis of materials required for axonal transport, growth, and restoration of nerve fibres.[6] In this context, it has been shown that the administration of materials at high concentrations promotes fibre regeneration in normal neuronal tissue. Thus, the administration of UTP and CMP (together with hydroxycobalamin (vitamin B12)) may play a useful role: not only are UTP and CMP constituents of DNA and RNA, but these materials also play important roles in the biosynthesis of phospholipids and glycolipids.[4]

Hence, drug therapies that enhance nerve regeneration are required. However a literature search did not identify any studies that have attempted to develop such an approach for the treatment of disturbances caused by bilateral sagittal split osteotomy (BSSO). Thus, the aim of the present study was to quantitatively monitor lesional changes after such surgery and to explore whether the combination UTP/CMP/hydroxycobalamin aides the recovery from neurosensory changes. The hypothesis was that the medication studied would facilitate the recovery of sensation in patients with nerve damage caused by the surgical procedure.

Patients and methods

This was a prospective and cross-sectional study. Patients treated in the department of maxillofacial surgery and traumatology of the university hospital in Pernambuco, Brazil, were recruited. All patients had facial skeletal deformities requiring jaw surgery involving the use of the BSSO technique, and all met the inclusion/exclusion criteria shown in Table 1. The study sample comprised 12 patients recruited between March and June 2013, who thus formed a non-probabilistic sample of convenience. The project scheme was submitted to and approved by the Ethics Committee of the Brazil Platform. All patients were told of the aim of the work and signed an informed consent form.

Patients were divided randomly (using the 'Random.org' programme) into an experimental group of six patients who received medication and a placebo control group of six patients. The dosage of medication was one ampoule intramuscularly daily for 3 days, followed by one capsule orally three times daily for 60 days, as suggested by the manufacturer for patients with trauma – compressive peripheral neural disorders. The six controls received placebos containing 5 mg starch. Data obtained for the 12 sides of the six patients in group 1 (experimental) were compared to those obtained for the 12 sides of the six patients in group 2 (controls).

This was a double-blind study; the researcher responsible for patient assessment was blinded to the choice of the intervention or control treatment.

All surgical procedures were performed by a single surgeon experienced in the relevant techniques, aided by residents and student surgeons. All patients had similar conditions, and the surgical technique was standardized following the principles of Epker et al.[7]

Table 1. Inclusion and exclusion criteria.

Criteria	Selection of sample
Inclusion criteria	• Age 18–35 years • A facial skeletal deformity requiring mandibular surgery using BSSO of the mandibular ramus; range of motion less than 7 mm • No craniofacial syndrome • No history of jaw trauma or nerve injury • No history of mandibular orthognathic surgery • No history of a mental disorder • Agreed to participate after reading the Statement of Informed Consent • Absence of nerve deficits on objective pre-surgical testing
Exclusion criteria	• No neurosensory deficit upon immediate post-surgical testing • Loss to follow-up • Contraindications identified by the manufacturer of the medication: acute (not chronic) ischaemic stroke • Any proliferative disorder • Use of an antiviral agent or citicoline (posing a risk of a drug interaction) • Pregnancy

BSSO, bilateral sagittal split osteotomy.