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The use of stem cells in cleft lip surgery

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ABSTRACT:

The use of stem cells therapy in oral and maxillofacial surgery is a developing field, which includes management of osseous defects, distraction osteogenesis, implants, TMJ reconstruction, and cleft palate cases. Clinical reports regarding the utilization of stem cells in clef lip surgery are lacking. Since the efficacy of stem cells as tissue inductor in cleft lip and their role in wound healing are not well documented, we aimed at reporting a case where stem cells were used as coadyuvant in cleft lip surgery. The efficacy of these cells as tissue inductor and their role in wound healing are discussed.

KEYWORDS*: stem cells, cleft lip, millard.*

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INTRODUCTION:

The use of stem cells (SCs) in oral and maxillofacial surgery is a developing, yet interesting field that has opened new horizons for us surgeons. Management of osseous defects, distraction osteogenesis, implants, TMJ reconstruction and cleft palate cases are counted among the surgical procedures that have been treated in conjunction with SCs and that have been reported in both human and animal models,[1-7] thus giving clinicians new treatment options for their patients.

A cell, in order to be considered stem, must have the ability to self-replicate and be able to differentiate into at least two different cell types.[8-9] They are classified into three main categories: Embryonic stem cells (ESCs), adult stem cells (ASCs) and induced pluripotent stem cells. A stem cell should have two basic characteristics: renewal and potency. While the first term refers to the capacity of the cell to undergo many cycles of cell division keeping its undifferentiated stage, the later has to do with the cell's capacity of diferentiation.[10]

ASCs have been identified and isolated from adult tissues such as bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, adipose tissue and dental pulp. The use of ASCs for therapeutic purposes includes a wide range of pathologies where replacement and repair of tissues and organs are required to restore form and function. Therefore, stem cells, growth factors and scaffolds are indispensable when applying this technology to humans or animals.[10]

On the other hand, cleft lip and palate (CLP) is a congenital defect that causes functional, esthetic, social and psychological disturbances. It is considered one of the most common congenital malformations, ranging from 0.5 to 2 cases per 1000 live births.[11] According to its location, a cleft in the lip may be unilateral or bilateral and, according to the extent, it can be complete or incomplete. Regardless of the location and severity of the cleft, this congenital condition generates an obvious facial deformity that the surgeon must overcome in order to achieve excellent cosmetic and functional results.[12]

Although many papers have been published reporting the use of SCs in oral and maxillofacial surgery procedures, reports regarding the utilization of these cells in

clef lip surgery are lacking. Since the efficacy of stem cells as tissue inductor in cleft lip and their role in wound healing are not well documented, we aimed at reporting a case where SCs were used as coadjuvant in cleft lip surgery. The efficacy of SCs as tissue inductor and their role in wound healing are discussed.

CASE REPORT

A young couple from Barranquilla, Colombia with neither personal nor familiar history of cleft lip or other congenital condition visited the gynecologist for prenatal control of their first child. While performing an echography with tridimensional reconstruction he documented a complete, unilateral cleft lip on the fetus (Fig 1). The defect was limited to the left lip, with the fetus having an otherwise normal growth and development. The facultative advised the couple on treatment options, proposed harvesting stem cells upon birth from umbilical cord and referred the couple to the Oral and Maxillofacial Surgery Division at *Clínica Someca* in Barranquilla.

The patient was born on March 17, 2012 with immediate harvesting of cord blood stem cells. Once in the laboratory, the sample was centrifuged, trypsinized, propagated under ideal conditions in a master cell bank, Stem *Medicina Regenerativa* (Bogotá, Colombia) and stored from March 24 to August 17, 2012 at -196°C (sample ID 044668). Two weeks after delivery the couple returned to *Clínica Someca* for comprehensive physical examination of the newborn, whom presented with an unilateral, complete cleft lip with no involvement of the alveolar crest. No other physical characteristic called the attention of the examiner. The surgical approach for the correction of the deformity in conjunction with stem cells were explained to the parents, who understood that while the former is a predictable treatment plan, the latter is a developing technology. The use of SCs for this patient was approved by *Clínica Someca* Committee on Ethics.

On August 17, 2012 at the patient's parent's request, Stem *Medicina Regenerativa* (Bogotá, Colombia) provided the surgical team with a vial of SCs that contained

20% of the stored sample. At the time of surgery patient was 5 months old with the following lab results: RBC RBC $4.38x10^6$/ul, Hematocrit 36.70%, Hemoglobin 12.30g/dl. Coagulation times and glycaemia were within normal limits. At 7:00 am and under general anesthesia, the surgery started with the obtaining of platelet rich plasma and growth factors (PRPGF). It continued with the marking of anatomical structures with a sterile surgical pen. Incisions were made according to the technique described by Millard.[13] After reorienting and repositioning the anatomical structures and before suturing, a mixture of 10cc of PRPGF and 10cc of stem cells was injected into the incised orbicularis oris muscle. The wound was closed with No. 5-0 nylon and a final injection of 5cc of the mixture in the subcutaneous cellular tissue adjacent to the cleft lip.

After surgery the patient was put in an antibiotic and analgesic scheme for five days. The patient was admitted for overnight monitoring and discharged home the next day (Fig 2). Parents were instructed not to feed the patient with a bottle, using instead a syringe fitted with a wide-gauge catheter for 1 week. Follow up protocol included the next day before leaving the clinic, which showed some swelling on the surgical site. It continued once a week for a month, where we noticed the formation of a mucocele-like lesion on the upper left lip along the suture line. A six-month follow up shows acceptable results with a barely noticeable scar.

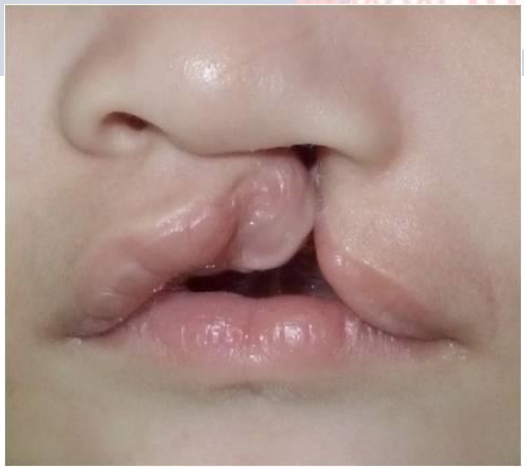

Figure 1. Clinical appearance of the newborn confirms cleft lip.

Figure 2. Marking anatomical structures with a sterile surgical pen.

Figure 3. Injecting a mixture of 10cc of PRPGF and 10cc of stem cells into the incised orbicularis oris muscle.

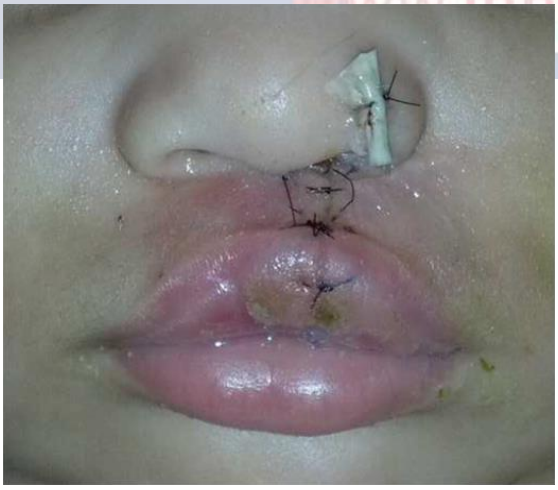

Figure 4. Immediate POP.

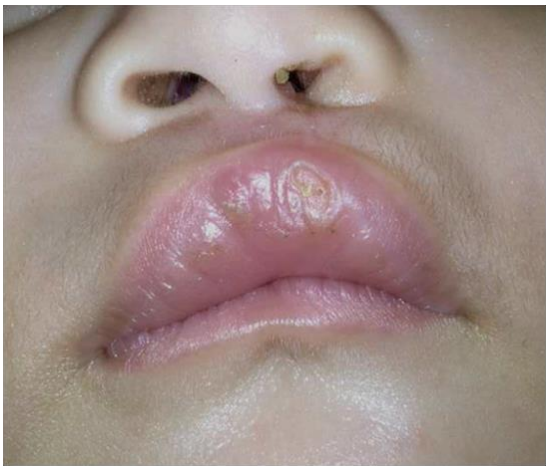

Figure 5. Actual results showing a barely noticeable scar with an optimal function of the upper lip and acceptable aesthetic outcome.

DISCUSSION:

Cleft lip surgery is a complex procedure regardless of who the surgeon is or which approach is used to correct the defect. However, when following the surgery's basic principles it usually yields to both functionally and aesthetically satisfying results.[12] Since the procedure itself is a challenging task, we can now benefit from technology by using SCs as coadyuvant in the healing process. In fact, recently Tamari[14] et al suggested that mesenchymal stem cells contain growth factors that are able to accelerate wound healing.

Growth factors (GFs) are proteins that bind to cells receptors and induce cellular proliferation and differentiation. They are used to control SCs activity and to induce regeneration of damaged tissues. The most commonly used GFs are: A) Bone morphogenic protein (BMP), which induces osteoblastic differentiation and bone mineralization, B) Platelet-derived growth factor (PDGF), which promotes proliferation of connective tissue and muscle, C) Fibroblastic growth factor (FGF), which promotes cellular proliferation, D) Transforming growth factor beta (TGF-B), used for tissue reparation, and E) Epidermal growth factor (EGF), which promotes mesenchymal and epithelial cell proliferation.[3]

The use of SCs and the ideal scaffold for the cleft lip patient is barely known. Up to date research has concentrated primarily on the use of SCs and scaffolds for the

reconstruction of the alveolar crest in order to replace the more morbid iliac crest bone marrow transplant procedure. The reason for using SCs on these patients is to decrease the mobility of the donor site and postoperative disturbances.[6] To the best of our knowledge, the use of SCs as coadyuvant in cleft lip surgery is not reported anywhere in the scientific literature. The purpose of this article was to report the case of a cleft lip patient in which we used SCs as coadyuvant in surgery. The patient's lip healed uneventfully, only having minor inflammation around the surgical site, which lasted few days and disappearing shortly after that. No infection or exaggerated swelling developed.

Although SCs have been used for other oral and maxillofacial pathologies, this report is probably the first one where SCs are used to enhance the aesthetic and functional results offered by surgery alone. We strongly believe that long-term prospective follow-up studies of patients in which SCs are used in conjunction with cleft lip surgery will help us elucidate whether or not patients with this anomaly can truly benefit from the use of SCs. Our clinical observations extend the limited knowledge regarding the potential use of SCs for cleft lip repair and regeneration.

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