

The Use of Stem Cells in the Surgical Treatment of Cleft Palate

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Abstract

Mesenchymal stem cells, pluripotent and differentiable cells found naturally within bone marrow, adipose tissue, the blood of the umbilical cord, and dental pulp have the capability to transform the field of oral surgery. With the capability to differentiate into different types of tissue, stem cells are currently being studied as an alternative to autologous bone grafting for treatment of cleft palate in young children. The long-standing treatment of autologous bone-grafting, while very effective, has many risks associated with it such as graft rejection, post-operative morbidity, and long recovery time. The harvesting and transplantation of stem cells using bio-compatible scaffolding that will differentiate and form new bone tissue is the future of valvuloplasty protocol in the field of oral surgery. This paper will investigate the way in which this treatment will be performed, the advantages and risks of stem cell therapy, the future applications, as well as the issue of global accessibility to innovative treatment such as this.

Keywords

Stem Cells; Therapy; Cleft Palate

Background

Affecting about 1 in every 1,700 babies in the United States, cleft palate consistently remains one of the most common birth defects in the country (along with congenital heart defects, spina bifida, and Down Syndrome) and present unique and multidisciplinary challenges for dentists, plastic surgeons, pediatricians, and oral surgeons [1]. Cleft palate is defined as an opening or split in the upper roof or palate of the mouth, separating the oral and nasal cavities, sometimes in conjunction with cleft lip. This fusion of tissue normally occurs in the second or third month of pregnancy and improper fusion could be due to a variety of environmental, as well as genetic, factors [2]. Cleft palate can lead to complications for the patient such as difficulty breathing, poor feeding ability, nasal-forward speaking voice, poor tooth development, and ear infections. Therefore, it is important to treat individuals born with cleft palate from an early age so as to not hinder their speech and eating development, preferably during the mixed dentition phase to avoid tooth decay caused by the cleft palate [3]. It is also favorable to begin treatment at a young age due to the long duration of multi-step treatment that must be conducted to safely and effectively engineer the palate. Despite cleft palate being so commonly observed by surgeons and physicians, no standard protocol or method of treatment has been developed [4]. It is still highly variable among surgeons. However, the large majority of cleft palate patients are treated by performance of autologous bone grafting. This autologous bone (bone donated from a different location of the recipient's body) is typically relocated from the iliac crest of the hip bone to the palate of the patient to close the gap in the roof of the mouth and fuse it into one singular component, thereby relieving the patient of breathing and feeding difficulties. A variety of procedures such as alveoloplasties, gingivoperiosteoplasties, and cheiloplasties are used to correct palatal clefts with the least amount of damage and shortest recovery period (Figure 1).

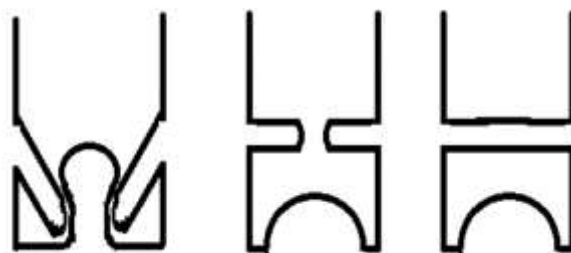


Figure 1: Palatogenesis: the development of the palatal shelves during fetal development. Occurring between weeks 8-12, the palatal shelves begin by growing in a downward direction before turning upward and fusing together to separate the nasal and oral cavities. This fusion does not properly occur for children with cleft palate [4].

A new technique to repair clefts in the palate involves implementation of stem-cell regenerative procedures into the existing cleft palate surgical treatment to reduce procedural risks, as well as the healing time for patients after cleft palate surgical treatment. The main types of mesenchymal stem cells currently being used in engineered palates are stem cells derived from the umbilical cord blood, adipocytes, dental pulp, and bone marrow. This paper will focus on stem cells from both bone marrow and umbilical cord blood. Both types of stem cells are currently being utilized in treatment. While stem

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cell treatment is still regarded as a rather controversial treatment option given the risks of stem cell transplantation and the lack of long-term clinical research, the potential for stem cell regenerative treatment in the field of oral surgery is great (Figure 2).

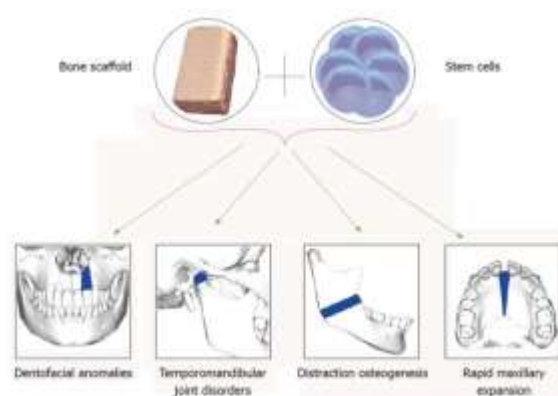


Figure 2: Application and Placement of stem cells in conjunction with bone scaffolds for orofacial deformities or disease. The placement of the stem cell transplantation for cleft palate can be seen on the far right, however there are many other applications and capabilities for these stem cells in oral surgery [5].

Alveoloplasty Surgical Protocol Using Stem Cells

An alveoloplasty surgical procedure is one in which the size or shape of the alveolar bone is altered or manipulated. For treatment of cleft palate, a primary alveoloplasty procedure is typically performed prior to the patient turning two years of age. Any alveoloplasty procedure performed after that time would be considered a secondary alveoloplasty [3]. Alveoloplasty procedures have been performed on patients to treat cleft palate for over 170 years, with the most common method being Boyne's Method. Boyne's Method involves an autologous bone graft from either the iliac crest or, in the case of larger grafts, ribs of the patient. The bone graft is harvested in the desired shape and size, and then transferred to the site to correct the alveolar process. However, the use of autologous bone grafting can lead to complications and health risks, such as infection, prolonged drainage and pain, sensory loss, long-time hospitalization, and high cost [6]. Especially in pediatric patients, this invasive procedure requires a large availability of bone for harvesting. This is rather limited in young patients. [7]. Stem cells from autologous bone marrow or from store umbilical cord blood can be used as an alternative method to autologous bone grafting as an effort to avoid the aforementioned risks. With the ability to regenerate various tissues, the method of transferring stem cells from bone marrow, dental pulp, or umbilical cord blood to the cleft palate via scaffolds could prove to provide a safer and more pleasant procedure for the patient. The purpose of a scaffold is to act as a sort of framework at the site stem cells transplantation, as well as allow the new tissue to be vascularized, integrate with the existing tissue, and survive as it is being generated [8]. It is important to note that these scaffolds must be biocompatible, as well as have a rate of absorption comparable to the bone growth rate to avoid immune-rejection or transplant-site morbidity [7]. Synthetic bone grafting also relies on its osteoconductive and osteoinductive capabilities. The ability of the stem cells to move across the scaffold to attach, migrate, and grow to regenerate the bone tissue is known as osteoconduction [9]. Osteoinduction is the process

in which the bone-forming stem cells stimulate osteogenesis (formation of bone) through recruitment of cells [10]. Both are crucial in the success of the regenerated tissue after being transplanted to the palate.

Despite the novelty of this method of oral surgical cleft palate rehabilitation, these cells in conjunction with a suitable scaffold show great promise in their capability to regenerate bone tissue. This surgical protocol has also proven to reduce the overall time of treatment, “decrease the inflammatory process”, and improve the appearance of visible scarring visible on the patient [11]. The largest obstacle for this method is its cost-effectiveness. Currently, it is generally more expensive to transfer multipotent stem cells in conjunction with a scaffold than to perform an autologous bone graft [12], however the cost has decreased over time and is predicted to keep decreasing as more regenerative techniques are established.

Umbilical vs. Bone Marrow Mesenchymal Stem Cells

Stem cells are a fundamental part of human biology and act as a starting point for all organs and tissues of the body. These stem cells can either exist only during human development (known as embryonic stem cells) or can develop later in fetal development and remain in the body for life, such as the case for mesenchymal stem cells found in bone marrow [13]. In the treatment of cleft palate, the two main sources of stem cells are bone marrow and the umbilical cord. Both are considered human mesenchymal stem cells. Mesenchymal stem cells (MSC's) are present in all tissue types and have the ability to differentiate into a wide variety of body tissues, including cardiac muscle, cartilage, and, in the case of cleft palate, bone. With easy accessibility and isolation, MSC's have been identified as prime candidates for autologous and allogenic transplants over other types of stem cells such as embryonic stem cells. While most of clinical research that has been conducted uses MSC's sourced from bone marrow, recent use involving stem cells sourced from the umbilical cord could prove to widen the application of stem cells globally in a clinical sense.

Bone marrow is a very complex body tissue system, consisting of many different specialized cells with unique functions. A network of connective tissue known as the marrow stroma includes of undifferentiated cells that do not perform hematopoietic functions and have the capability to form a range of different phenotypes. The mesenchymal stem cells make up a very small percentage of the nucleated cells in this bone marrow stromal network. The cells within the stroma have been defined as mesenchymal stem cells because of their ability to proliferate and differentiate. Bone marrow mesenchymal cells, while widely accessible and available, do have their limitations regarding “the high degree of viral exposure” that they face, the slowing of proliferation capabilities as the individual ages, and the invasive, painful means to obtain bone marrow samples. Therefore, the ability to source stem cells from a different location could have clinical benefits [14] (Figure 3).

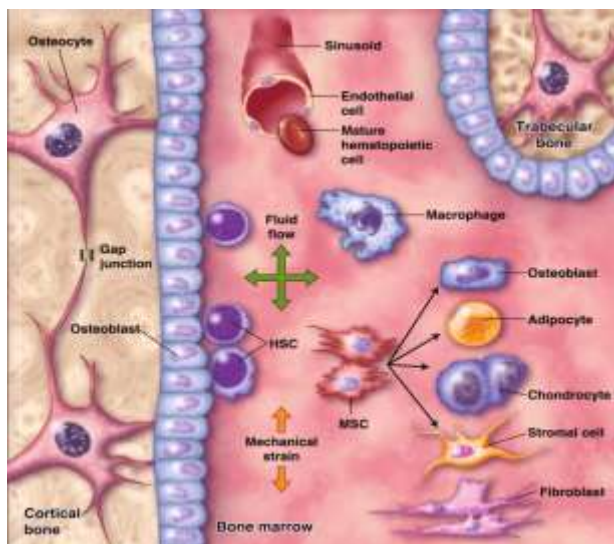


Figure 3: Anatomy of bone marrow, showing the stromal complex within the bone marrow containing mesenchymal stem cells. These stem cells have a great capability to differentiate into osteoblasts, adipocytes, chondrocytes, as well as other cell types [15].

The anatomy of the human umbilical cord includes two arteries and one vein surrounded by a mucoid connective tissue called “Wharton’s jelly”. After birth, the blood within the umbilical cord “contains a rich source of hematopoietic stem and progenitor cells” and can be obtained in a painless and ethical manner for the both the mother and child. Primitive stromal cell can be obtained from Wharton’s jelly and differentiated [14]. Sourcing stem cells from the blood of the umbilical cord has grown increasingly more popular due to the low-cost and ethical means of harvesting. Unlike embryonic stem cells, no damage is done to the child when the umbilical cord blood is banked or used later for stem cell harvesting [16].

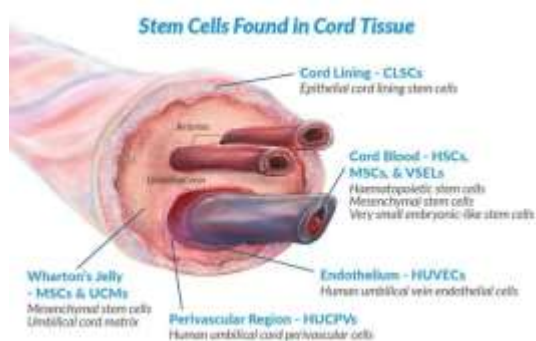


Figure 4: Anatomy of the human umbilical cord, with mesenchymal stem cells found within the Wharton’s Jelly cord matrix and surrounding by the umbilical cord epithelial lining [17].

One of the greatest clinical advantages to umbilical cord stem cells is the ability to store the cells for use at a later time. This is made possible with the rise in umbilical cord blood banking. After birth, mothers are given the choice to have their child’s umbilical cord preserved and stored for potential later use.

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Studies have found that umbilical cord stem cells that have been frozen and preserved for over a decade still provide regenerative properties. This is different than bone marrow MSC's that must be collected just prior to being transplanted. Stem cells derived from the umbilical cord are also less likely to cause Graft vs. Host Disease because cord blood is "more primitive than bone marrow." Another reason why umbilical cord blood could be preferred for stem cell autologous transplantation is because of the sheer availability. Experts have found that there is a much greater abundance of stem cells within the blood umbilical cord as compared to within bone marrow. When coupled with the fact that bone marrow extraction is a much more difficult and demanding procedure, many favor the umbilical cord as their stem cell source. While there is an abundance of research that promotes the advantages of umbilical stem cells over bone marrow, the likelihood of graft rejection from bone marrow cells remains much lower than for umbilical cord cells [18]. However, graft rejection is much more common when the donor of the stem cells is a different individual than the recipient. Since cleft palate protocol is usually autologous transplantation, this does not normally apply in terms of cleft palate surgical treatment.

Current Concerns & Obstacles Regarding Stem Cell Treatment

With many advantages provided by the use of stem cells in engineered palates come unique obstacles and concerns for the safety, ethics, and long-term success of their use. The main risks correlated to the use of stem cells transplantation include tumorigenesis (tumor formation), immune rejection, post-procedural infection, high cost, and ethical concerns.

Tumor Formation

Stem cells and cancer cells share commonalities including long life span, ability to replicate for long periods of time, and resistance to cell death. These similarities give them the ability to be candidates for tumorigenic transformation [19]. While rather rare, the risk of tumor formation following transplantation of undifferentiated embryonic stem cells is still present. Tumor formation after stem cell transplantation is dependent on cell type, location of transplantation, and the cell's potency and proliferative capabilities. Undifferentiated embryonic cells have a high affinity to divide rapidly and uncontrollably, making them unfit for transplantation. Pre-differentiation of these cells by way of genetically modified stem cell lines [20] and sorting of cells to limit the number of pluripotent cells during cell promotion can help to decrease this risk (Figure 5).

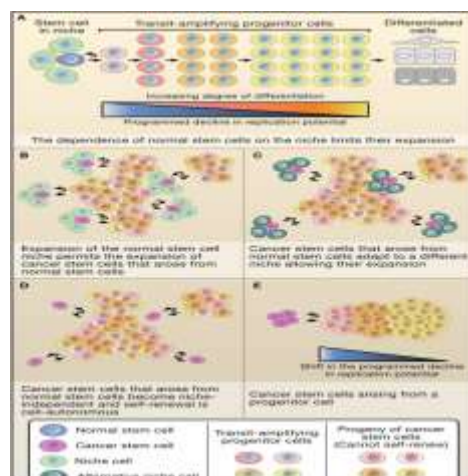


Figure 5: Possible Origin of Cancer cells from normally functioning stem cells. Due to the long life-span of stem cells, this leads to the opportunity for more mutations to occur, the niche for cancer cells to expand, and their growth to become uncontrollable [21].

Immune rejection

The administration of stem cells from sources like bone marrow and umbilical cord blood can potentially have modulating effects on the immune system and, as a result, induce a response. Despite mesenchymal stem cells showing a low potential for modulation of the immune system, these cells may become more immunogenic following differentiation. A lot of factors can affect this immunogenicity and it remains rather unpredictable. Rejection of a graft can have adverse effects for the patient, including loss-of-function and diseases such as Graft-versus-Host Disease (GvHD). GvHD is much more common in stem cell transplantation procedures that are non-autologous (stem cell donor and recipient are not the same). Often in the case of cleft palate surgical procedure, the transplantation performed is autologous. However, despite being much less common, immune rejection following autologous transplantation is not impossible. Immunosuppressant drugs can be administered to the patient to minimize risk of adverse immune response [19].

Post-Operative infection

As with any surgery, the risk of infection following the procedure is present. Particularly, two to three weeks following autologous stem cell transplantation during the period of “neutropenia” when new bone tissue leukocytes are formed, the risk of bacterial infection is rather high. The immune system may also be compromised following treatment, leaving the patient even more susceptible to bacterial, fungal, or viral infections. Prophylactic antibiotics are given to the patient as preventative protocol [22].

Economic Implications

Perhaps the largest tangible drawback to stem cell research and treatment is the high cost of materials, training, and treatment. The field of stem cells research and treatment is highly specialized and still has yet to be adopted by many physicians, patients, and health insurance companies. With many harsh restrictions from hospitals, insurance companies, and the FDA, it remains a very costly treatment option that is not accessible to many within the United States, as well as globally. There is also not always a

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direct correlation between cost of stem cell treatment and adequacy of training to perform these procedures, so an abundance of caution must be taken before committing to such a costly treatment. Another major obstacle is the lack of government incentives to utilize stem cells, leaving much of the financial burden on recipients. As healthcare continues to evolve and more of the public seeks alternative treatment for conditions such as cleft palate, it is likely that the cost will sufficiently decrease or be covered by insurance [23]. The timeline remains unknown and is dependent upon further research and clinical studies.

Ethical concerns

As with any treatment using novel materials, the ethical use of stem cells should be of the highest regard. As the stem cell field broadens and becomes more widely practiced, the concern of clarity in the terminology and usage of “stem cell” should be clearly addressed. It is imperative that physicians, patients, and the greater public have the capacity to distinguish between “experimental stem cell intervention and proven stem cell therapies” [24] such as autologous transplantation as in the case of cleft palate. Due to the controversial manner of obtaining embryonic stem cells through destruction of the embryo, many are skeptical of the need for their use and if the benefits outweigh the downfalls in an ethical and health-safety sense [25]. The best way to ease concern and further improve public opinion of stem cell treatment is through education. Explaining the benefits as well as the risks of treatment, while also not establishing over-expectations is crucial. The future of stem cells treatment is bright, as long as caution is expressed in the same abundance as optimism [24].

Stem cells and global health

As stem cell regenerative treatment and surgical protocol gains popularity in the United States and more patients in the US and much of the western world access these alternative treatments, a discussion of global health and the availability of these treatments to developing countries in a manner that is safe, accessible, and ethical should be proposed. Will patients in developing countries be able to receive treatment without great financial burden and who will be administering safe treatment? As countries like China, Brazil, and India invest into the research of stem cells despite a lack of sufficient healthcare infrastructure, the conversation of making stem cell treatment accessible is important. Despite countries such as China and India being among the most populated in the world, the lack of infrastructure and funding are a major issue and the development of stem cell therapy in developing countries such as these should be implemented in parallel to improvement in access to essential medicine and medical treatments [26]. Some of the biggest challenges to global stem cell treatment integration are issues with equitable access to individuals living outside of major cities, cultural apprehension, a need for ethical testing and approval that can be performed domestically, lack of trained personnel, lack of clarity in stem cell terminology, and the overall high risk of investment into stem cell therapies [27]. Therefore, an open dialogue between health professionals in affluent and developing countries is absolutely essential. While research and clinical trials being performed in the United States and then communicated to other nations is important, it would be more beneficial for this research and development to be occurring by these developing countries independently. Domestic advancement “tailors innovation based on the local context in order to make treatments more affordable and contributes toward the economic development of those countries.” [28]. The best way for scientific and medical innovation to reach

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everyone is by all nations being able to conduct research and allocate funds in the way that best benefits their culture, economy, and patients. Fostering high-quality education and training to local physicians, increasing public awareness of alternative protocols, and establishing regulatory framework regarding stem cells optimizes the number of individuals globally that could receive safe and ethical care [28].

Future applications of stem cells in oral surgery context

The widespread application of stem cells in the field of dentistry and oral surgery is possible and achievable. As more research is conducted and more is understood about the capabilities of these cells, it is very likely that they will be fully incorporated into the surgical treatments and procedures of patients for many maxillofacial diseases and deformities. However, there must be more studies done on human patients. Currently, most of the research data has been collected from use on animal subjects. This leaves the knowledge of effects on humans very minimal. There is also a necessary need for proper infrastructure development for both stem cell therapy technology and training [29].

In the near future, it is possible that stem cells will be widely incorporated into many oral surgical procedures such as gingivoperiostoplasty and cheiloplasty procedures, as a means to prevent the need for secondary alveoplasties [30]. Stem cells also create the opportunity for the dental profession to become more biologically-driven. This will be seen through the use of “biologically viable” scaffolding to reconstruct orofacial bone, the regeneration of the tooth and dental pulp, and the increased popularity in stem cell banking for future dental utilization [31]. Through the reinvention of how dentists treat patients and their choices to use more natural, biological sources for repair and regeneration, we will hopefully see a decrease in the need for artificial materials and a rise in the sourcing of naturally occurring stem cells for their amazing regenerative capabilities. A more wide-spread use of stem cells could also lead to patients receive oral/dental treatment facing shorter recovery times, less discomfort, and lower risk of infection.

Conclusion

The practice of regenerative medicine and the use of stem cell therapy is one that is very promising to many fields of health, especially oral surgery. As more children are diagnosed with cleft palate and other orofacial deformities and diseases, the desire to undergo alternative treatment becomes more attractive. While there is still plenty of room for more understanding regarding the applications and full potential of human mesenchymal cells in regard to autologous transplantation, it appears to be a viable and safe option to provide patients with the relief and aesthetic corrections that they desire. The obstacles that stem cells therapy faces in terms of ethical reputation, global accessibility, funding from health-care insurance, and need for a streamlined protocol will need to be addressed in order for a biologically-driven approach such as this to be fully incorporated in dentistry. Stem cells are incredibly complex cells with the ability to bring new techniques, ideas, and perspectives to the field and patients could see greater accessibility to these therapies in the near future.

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