Review

Use of stem cell-enriched fat grafts in facial reconstruction: have they demonstrated superiority over autologous fat grafting?

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ABSTRACT

Since the 1990s, big strides have been made in plastic and reconstructive surgery, thanks to the implementation of new techniques and resources for its execution. In cases where restoration is sought for small defects, biosurgery, involving the utilization of stem cells, biomaterials, chemical engineering, and tissue engineering, can be employed. The potential to stimulate the innate regenerative capacity of tissue and generate a persistent response over time, minimizing surgical trauma and re-interventions, lies in stem cell transplantation. However, the evidence published on this matter is very scarce, leading to divergence of opinions, suggestions, and recommendations. The aim of this review is to analyze the most recent evidence concerning the outcomes of using fat grafts enriched with stem cells in facial reconstruction, as compared to autologous fat grafts. The review of the literature demonstrates a marked trend suggesting that fat grafts enriched with stem cells may be superior to autologous grafts in facial reconstruction, with potential benefits in medium-term volume retention and faster attainment of results.

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Uso de injertos de grasa enriquecidos con células madre en la reconstrucción facial: ¿han demostrado superioridad sobre los injertos de grasa autólogos?

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RESUMEN

La cirugía plástica y reconstructiva, ha dado pasos agigantados desde la década de los años 90, con la implementación de nuevas técnicas y recursos para su realización. En los casos de defectos pequeños donde se busca la restauración, se puede hacer uso de la biocirugía, que involucra el uso de células madre, biomateriales, ingeniería química y de tejidos. El trasplante de células madre, tiene el potencial de estimular la capacidad innata regenerativa del tejido, así como de generar una respuesta persistente a lo largo del tiempo, minimizando el trauma quirúrgico y la reintervención. A pesar, de la ventaja plausible, la calidad y cantidad de la evidencia publicada al respecto es muy escasa, ocasionando divergencia de opiniones, sugerencias y recomendaciones. Con base en lo anterior, el objetivo de esta revisión consiste en realizar un análisis de la evidencia más reciente sobre los resultados en el uso de injertos de grasa enriquecidos con células madre en la reconstrucción facial, comparado a los injertos de grasa autólogos. A través de la revisión de la literatura, se pudo evidenciar que, aunque la evidencia es heterogénea a la fecha, existe una tendencia marcada en que el uso de injertos de grasa enriquecidos con células madre, podría ser superior a los injertos autólogos en la reconstrucción facial, con potenciales beneficios en la retención de volumen a mediano plazo y mayor celeridad en la obtención de resultados.


1. INTRODUCTION

Enormous progress has been made in plastic and reconstructive surgery since the 1990s, with the implementation of new techniques and resources for its performance [1, 2]. For instance, facial reconstruction, being one of the most complex interventions in this discipline due to the involvement of numerous structures and organs, as well as functional and aesthetic outcomes, has rapidly evolved with the inclusion of new grafts [2, 3]. Autologous fat grafts have traditionally been one of the options used because of their good tissue tolerability and satisfactory outcomes. However, the response during the rehabilitation and anatomical normalization phase, as well as the extent and severity of the defect to be reconstructed, also plays a crucial role [4, 5].

In cases of small defects requiring restoration, biosurgery can be employed, involving the utilization of stem cells, biomaterials, chemical engineering, and tissues [6-10]. The potential to stimulate the innate regenerative capacity of tissue and generate a persistent response over time, minimizing surgical trauma and reoperation, lies with stem cell transplantation [10]. Despite its plausible advantage, the quality and quantity of published evidence on this matter are very limited, resulting in divergent opinions, suggestions, and recommendations.

However, the most recent and high-quality evidence seems to offer a broader perspective on the trend of outcomes obtained when comparing the use of fat grafts enriched with stem cells to the use of autologous fat grafts [11]. Given the need for a scientifically sound basis to facilitate decision-making in clinical practice, especially in severe cases requiring extensive reconstruction, the objective of this review is to analyze the most recent evidence regarding the outcomes of using fat grafts enriched with stem cells in facial reconstruction, as opposed to autologous fat grafts.

2. MATERIAL AND METHODS

A literature search was conducted using the terms ‘stem cell-enriched fat grafts,’ ‘autologous fat grafting,’ and ‘facial reconstruction,’ along with their synonyms, which were combined using Boolean operators, in the PubMed and Scopus databases. Any full-text articles that compared the outcomes of using fat grafts enriched with stem cells in...
facial reconstruction to autologous fat grafts were included, with priority given to original studies and systematic reviews and meta-analyses. Articles published up to the year 2023 were included. A total of 34 articles were identified, including some describing basic theoretical concepts. The estimated values and calculations found were reported in their original measurements, including frequencies, percentages, confidence intervals (CI), difference of means (DM), relative risk (RR), odds ratio (OR), or hazard ratio (HR).

3. RESULTS

3.1. USE OF STEM CELLS IN PLASTIC SURGERY: ADVANTAGES OVER TRADITIONAL APPROACHES

With the advent of technology in health research involving stem cells, the potential of these cells has been demonstrated through tissue engineering based on their properties [12, 13]. Achieving their purification requires various processes, starting with the extraction of these cells from the epidermal tissue. Initially, cellular cultures, enzymatic restoration, and purification are performed, and growth factors, physical, and chemical factors are added to facilitate their appropriate adaptation when applied to the skin [13-15]. Consequently, different cellular subtypes can be obtained, allowing for more effective tissue reconstruction and promoting a healthier cellular transition. As a result, the transplantation of these cells has the capacity to induce immunomodulation, recruit keratinocytes and fibroblasts, and promote angiogenesis, nerve regeneration, synthesis of elastin and collagen, and even hair regeneration [12, 13, 15-17]. In contrast, achieving these advantages using traditional techniques is very difficult or even impossible when working with tissue lacking prior regeneration and differentiation. In such cases, only the facial structure is restored without addressing crucial details that significantly contribute to the patient’s aesthetics [15]. The administration of stem cells can initiate an anti-aging mechanism through cellular reprogramming, reducing cell wear and senescence, and restoring the proteodynamics of previous cells. These benefits extend to soft tissues, bone, cartilage, and more [15-17]. Thus, they can be applied during bone reconstruction, wound healing, augmentation and regeneration of soft tissues, peripheral nerve, and cartilage (Figure 1). These benefits are particularly associated with the specific use of mesenchymal stem cells [18]. However, it is essential to consider some limitations when using these cells. The U.S. Food and Drug Administration (FDA) has reported concerns about the inherent risk of contamination and damage to cultivated and distributed cells [19]. Therefore, strict and restricted regulation is necessary in the commercialization of stem cell-based products to ensure patient safety. This is primarily due to a significant gap in the evidence from trials that thoroughly studied the factors associated with potential harmful effects.
of stem cells during cultures or translational applications [12, 16]. This risk begins with the extraction of tissue and donor cells, continues through laboratory manipulation, and extends to eventual administration. Even the use of substrates and compounds in cultures should be of the highest quality. Thus, it is essential to always verifying that the provider possesses all certifications and discloses the actual components of their products [12-14].

Another risk lies in the potential for these reprogrammed cells to undergo malignant transformation. Undoubtedly, like all pluripotent cells, they are susceptible to mutagenesis and the eventual acquisition of malignant properties, especially mesenchymal stem cells. However, specific evidence studying this phenomenon is currently unknown [15, 20]. Nevertheless, the benefits of using these cells and the impact they can have on health outcomes, such as morbidity, functional capacity, and quality of life, are evident.

3.2. CLINICAL EVIDENCE ON THE USE OF STEM CELL-ENRICHED FAT GRAFTS VS. AUTOLOGOUS FAT GRAFTS

To date, clinical evidence studying the use of stem cell-enriched fat grafts versus autologous fat grafts is scarce. However, there is a marked trend favoring the benefit of using grafts enriched with stem cells.

Among the most recent studies, Bourne et al [21] conducted a randomized controlled trial with 12 subjects who had at least two craniofacial deficiencies and underwent surgery for correction using stem cell-enriched fat grafts compared to traditional grafts. They found no statistically significant differences in volume retention between the intervention group and the control group, both overall (50.3% vs. 57.3%; p=0.269) and in the malar region (51.4% vs. 56.7%; p=0.494). No association was found between any sociodemographic or clinical factor and volume retention. The cellular subpopulation was predominantly composed of adipocytes derived from stem cells (60.1% ± 11.2%), and a strong correlation was only found between the presence of pericytes and volume retention (p = 0.027) [21]. The authors concluded that although both interventions were effective and safe (due to the absence of adverse events), there was no significant advantage in favor of using stem cells.

In previous years, these same researchers evaluated surgical outcomes in the transfer of autologous fat for craniofacial deformity reconstruction in a prospective cohort study of 20 subjects [22]. The authors did not observe adverse events but identified that volume retention at three months significantly predicted volume retention at nine months (p <0.001). Those undergoing a second intervention had similar retention to the first intervention (p=0.05), and as in the previous study, there was no association between any sociodemographic or clinical factor and retention, except for smoking, which was associated with higher retention (74.4% vs. 56.2%; p=0.009). Physical appearance (p=0.002), social relationships (p=0.02), and functionality (p=0.05) significantly improved at nine months. Considering that there were no significant differences between this intervention and the use of stem cells, it is presumed that these outcomes are similar to those that can be achieved with the use of stem cells, with a notable impact on the patient’s functional capacity and self-image [22].

Importantly, without the presence of serious adverse or secondary events.

Sasaki et al [23], through a case-control study, evaluated the efficacy and safety of cell-assisted fat grafts versus traditional grafts, using 3D evaluation. Volunteer candidates selected their preferred technique for facial volume augmentation. The study determined that graft enrichment with stem cells significantly improved the mean volume retention at nine months (p <0.01) [23]. Rasmussen et al [24], through a systematic review, evaluated the effect, viability, and clinical relevance of using stem cell-enriched fat grafts in large interventions, including 38 studies. The researchers observed that the use of stem cell-enriched grafts increased volume retention by more than 1.5 times compared to other techniques. However, they stated that the evidence was highly heterogeneous, making it difficult to determine the clinical relevance, although the results are promising [24]. Sterodimas et al [25], in a randomized controlled trial involving 20 participants with facial defects, compared the performance of autologous fat grafts to stem cell-enriched fat grafts. They found that the entire stem cell-enriched graft group required only one treatment session to achieve aesthetically acceptable results and high levels of satisfaction. In contrast, in the control group, only three patients achieved these results during the first session. It should be highlighted that at 18 months, there were no statistically significant differences between both groups, leading to the conclusion that the benefit of using stem cell-enriched grafts lies in obtaining favourable results more quickly [25].

In China, Yin et al [26] also conducted a randomized controlled trial with 50 patients (equally divided into two groups) to evaluate the effect of stem cell-enriched grafts versus standard fat grafts in facial reconstruction. They
demonstrated that the survival rate of stem cell-enriched grafts was significantly higher than that of the control group (77.6% vs. 56.2%; p < 0.001). Additionally, skin quality based on texture was significantly better in the intervention group at 6 months post-surgery (15.8 vs. 10.3; p < 0.01). Satisfaction was similar at the end of the study in both groups [26]. Interestingly, studies using platelet-rich plasma-added grafts and assessing the same outcomes as previously mentioned evidence have obtained very similar results, showing an added benefit to the cellular modification of the transplanted tissue [27]. Bashir et al [28] in Pakistan evaluated outcomes in the use of traditional grafts versus stem cell-enriched grafts for facial deformity reconstruction in 25 individuals, observing that the use of enriched grafts had similar outcomes in terms of soft tissue thinning at 6 months post-intervention, with equal satisfaction [28]. Krastev et al [29], through a systematic review and meta-analysis of 52 studies with 1568 patients, evaluated the safety and efficacy of autologous fat transfer, showing that patient satisfaction and surgeon satisfaction were approximately 91% and 88%, respectively. The number of sessions required to achieve.

3.3. FUTURE PERSPECTIVES

In the field of plastic surgery, particularly in the utilization of biomaterials enriched with stem cell properties, research lines and future perspectives warrant deep translational application evaluation due to the scarcity of evidence regarding marker expression or tissue changes in this technique, and its associated factors [30, 31]. Several authors [32], who emphasize the significant gap, especially in low and middle-income countries, where evidence pertaining to this subject is nearly absent, have supported this viewpoint. Importantly, it should be emphasized that the advancement of these techniques and biomaterials extends beyond the mere aesthetics of the procedure. The primary objective is the restoration of the patient's quality of life and functional capacity [32]. Consequently, this area could be defined as a research priority in the reconstruction of congenital or acquired facial defects, especially in children and adolescents, where the emotional impact of the defect could be greater and could affect other domains of their lives [33, 34]. Particularly, because the evidence related to this topic that has exclusively studied children is very limited [34]. The potential of bioprinting and regenerative medicine lies in surpassing organ regeneration and ensuring the preservation of all the functionality and organic properties of the tissue. This implies a remarkable progress in tissue engineering and regeneration. The utilization of 3D tools and regeneration may revolutionize the traditional paradigm and prognosis for managing burned patients or healing extensive wounds [35, 36]. The establishment of more research centers and specialized care in plastic and reconstructive surgery is necessary to enable the inclusion of patients as research subjects and overcome the barrier of sample size limitation observed in previous studies.

4. CONCLUSIONS

Despite the heterogeneity of the evidence to date, a pronounced trend suggests that the utilization of fat grafts enriched with stem cells may be superior to autologous grafts in facial reconstruction, offering potential benefits in mid-term volume retention and faster achievement of results.

5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

6. REFERENCES
