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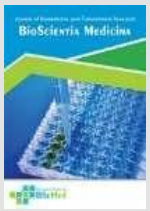

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Efficacy of Exosome Adipose-Derived Stem Cells (ACSs-Exosome) on Skin Flaps Transplantation in Plastic Surgery: A Systematic Literature Review

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A B S T R A C T

Background: Exosomes are a small subset of extracellular vesicles with a size of about 50 nm – 200 nm, which are found in many body fluids. The exosome is rich in various proteins and is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. **Methods:** The literature search process was carried out in various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. **Results:** A total of 5 studies were included in this systematic review. In general, ASCs-exosome administration was more effective in the percentage of flap survival area than in the placebo group. There are 3 studies that state that the effectiveness of flap area survival is more than 70 percent compared to the placebo group, which is only in the range of 30-40 percent. **Conclusion:** ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

1. Introduction

Fat tissue is the main energy depot in the body. In recent years, adipose tissue has been studied to be developed as a control of metabolism, homeostasis, immunity, and regulation of satiety in the body. Fat tissue is generally divided into fat-storing adipose and adipose tissue stromal vascular fraction (SVF).[1-3] SVF is a collection of various immune cells, endothelial cells, and adipose-derived stem cells (ASCs), which were isolated through a series of enzymatic digestion processes. ASCs are very easy to develop and are precursors to being developed into various multipotent progenitor cells, such as osteoblasts, chondrocytes, myocytes, epithelial cells, and neuronal cells.[4-6] In addition, ACSs have various advantages over bone marrow stem cells, namely more accessible and minimally invasive, high proliferation, and secretion of various growth factors, cytokines, and extracellular vesicles.[7,8]

Exosomes are a small subset of extracellular vesicles with a size of about 50-200 m, which are found in many body fluids. The exosome is rich in various proteins, such as cytoskeletal protein, a transmembrane protein, and heat shock protein. Exosomes are also rich in nucleic acids (DNA, mRNA, miRNA, long and short non-coding RNA), lipids, and enzymes (GADPH, ATPase, and PGK1).[9] ASCs-exosome compared to ASCs is in the ability of ASCs-exosome to protect transport activity so as to facilitate

the application of ASCs-exosome on target tissues. In contrast to ASCs, which do not have transportation activity protection facilities, ASCs will be difficult to apply to the target network.[10-12] Exosome is a cargo that carries out the process of transporting and transporting between cells in the context of cell communication. This becomes a potential new therapeutic modality in triggering the modulation and activity of target cells so that ACSs-Exosome becomes a new potential to modulate skin flap transplantation repair in plastic surgery. Currently, there is very little evidence-based data regarding the use of ACSs-exosome in optimizing skin flap transplantation repair in plastic surgery cases.

2. Methods

The literature search process was carried out on various databases (PubMed, Web of Sciences, EMBASE, Cochrane Libraries, and Google Scholar) regarding the use of ASCs-exosome in skin flap transplantation repair in plastic surgery cases. The search was performed using the terms: (1) "mesenchymal stem cell" OR "progenitor cells" OR" adipose-derived stem cells" OR" exosome adipose-derived stem cells" AND (2) "skin flap" OR "skin flaps." The literature is limited to preclinical studies and published in English. The literature selection criteria are articles published in the form of original articles, an experimental model of skin flaps, the control group only received liquid without therapeutic effect or no treatment, studies were conducted in a timeframe from 2012-2022, and the main outcome was the survival rate of skin flaps. Meanwhile, the exclusion criteria were animal models that were not related to skin flaps, the application of ASCs-exosome with other treatments, the absence of a control group, and duplication of publications. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations.

3. Results

A total of 5 studies were included in this systematic review. There were 53 potential studies at the start of the literature search process. A total of 22 studies passed for further screening, and 31 studies did not pass because the studies were conducted outside the 2012-2022 timeframe. A total of 20 studies passed for the next stage, and only 2 studies were excluded because they were case reports. Of the 20 studies that passed the next stage, 15 were excluded because 8 studies could not access full-text, 2 studies were not published in English, and 5 studies did not have a control group (Figure 1).

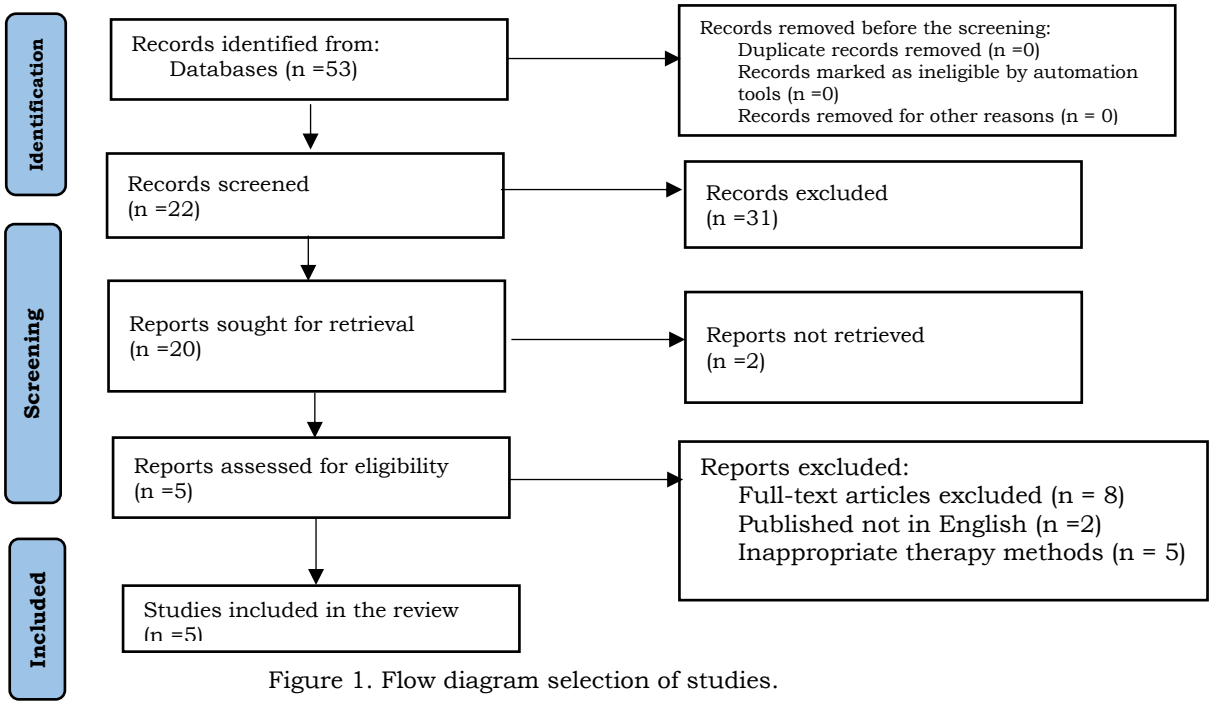

Figure 1. Flow diagram selection of studies.

Table 1 shows the characteristics of the studies included in this systematic review. The majority of studies used a random type of skin flap, and only one used the axial type. The area of the skin flaps varied from 3-60 cm^2 in the study. A total of 3 studies used a xenogenic type transplant, and 2 studies used an allogenic type transplant. The control group almost all received PBS.

Table 1. Study characteristics

Study	Type of skin flap	Skin flap (cm^2)	Cell Type	Transplant type	Method of administration	Placebo	Outcome Flap Survival Area (%) VS Placebo
Feng et al.[13]	Random	9	ASCs-exosome	Xenogenic	Intra-arterial	PBS	78.5±2.3 VS 46.9±3.3
Gao et al.[14]	Random	3	ASCs-exosome	Xenogenic	Subcutaneous Injection	PBS	83.2±2.5 VS 45.7±3.1
Han et al.[15]	Random	14	ASCs-exosome	Allogenic	Subcutaneous Injection	PBS	51.6±2.6 VS 31.2±2.9
Pak et al.[16]	Random	12	ASCs-exosome	Xenogenic	Subcutaneous Injection	PBS	67.8±2.4 VS 39.6±2.8
Reichenberger et al.[17]	Axial	60	ASCs-exosome	Allogenic	Intravenous Injection	PBS	73.9±3.3 VS 33.3±2.7

Table 1 shows that, in general, ASCs-exosome administration was more effective in the percentage of flap survival area than in the placebo group. There are 3 studies that state that the effectiveness of flap area survival is more than 70 percent compared to the placebo group, which is only in the range of 30-40 percent.

4. Discussion

Flap transplantation is a reliable repair modality in cases of trauma and organ reconstruction. Optimization of the flap transplantation process is highly dependent on the process of neovascularization and ischemia-reperfusion.[18] The better the neovascularization and the better ischemia-reperfusion, the better the flap transplantation process. ASCs-exosome has great potential to prevent ischemia-reperfusion injury in order to optimize flap transplantation. ASCs exosome is able to optimize the angiogenesis process to increase the viability of chondrocutaneous composite grafts for the application of defects in the nose, earlobe, and skin.[19,20]

Various studies above show that ASCs-exosome is able to optimally improve the survival status of skin flaps. ASCs-exosome was able to increase the expression of miRNA-760 and decrease the expression of miRNA-423-3p, which would lead to the regulation of the expression of ITGA5 and HDAC5, which led to the initiation of vascularization in skin flaps.[21] Another study showed that the ASCs-exosome is rich in the cytokine IL-6, where IL-6 is very important in the process of angiogenesis and flap repair. In addition, the cytokine IL-6 has an anti-viral effect that can provide infection protection for patients.[22] Another study showed that ASCs-exosome induced with low dose hydrogen peroxide was able to improve neovascularization and was able to suppress the inflammatory process and tissue damage after ischemia-reperfusion injury.[23]

5. Conclusion

ASCs-exosome has the potential to be developed to improve the survival rate of skin flap transplantation in the case of plastic surgery.

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