Original Article
Adipose-derived stromal vascular fraction (SVF) in scar treatment: a systematic review protocol

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Abstract: Background: Autologous adipose-derived stromal vascular fraction (SVF) is an emerging therapy that is being pioneered as a potential treatment for keloids and hypertrophic scars. Up to this point, there isn't a cure for keloids and hypertrophic scars yet they comprise the commonest benign skin disorders. Despite published studies reporting potential therapeutic benefits of SVF, their use and efficacy on scar improvement are not clearly described. The aim of this review is to describe the clinical practice involved in harvesting, processing, utilization of SVF, and associated efficacy in scar treatment. Methods: We shall include published clinical articles evaluating the efficacy of SVF on improving scar characteristics and assessment scores among adults with keloids or hypertrophic scars. Article search of Medline/PubMed, Cochrane Library and Embase using Mesh terms of "scars" and "stromal vascular fraction" combined with the Boolean operators ("AND", "OR") will be performed by two independent researchers following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement. The primary outcome measure will be the mean difference in the Scar characteristics including Scar assessment scores, scar thickness among others. Data synthesis: Descriptive data synthesis and mean differences between treatment arms will be calculated for the primary outcome of the scar assessment scores. In case more than three studies provide consistent characteristics of the scar assessment scores, a meta-analysis will be conducted. Discussion: Evidence obtained from the systematic review will form the foundation upon which further clinical trials research will be conducted in evaluating the efficacy of autologous adipose-derived stromal vascular fraction in keloid and hypertrophic scar. The systematic review has been submitted to the PROSPERO database and is currently under review.

Keywords: Stromal vascular fraction, keloids, scars, adipose stem cells, systematic review

Introduction

Scars are a natural result of wound healing and they often undergo regression with minimal cosmetic disruption [1]. In some instances, the natural scar regression fails and results in the continued excess production of the scar tissues to cause keloids or hypertrophic scars [2].

More commonly these keloids occur in colored populations with an estimated prevalence of up to 16% among blacks [3, 4], the majority of whom live in Low- and Middle-income countries [5, 6].

To date, hypertrophic scars and keloids are still difficult to treat and existing therapies have variable degrees of scar volume regression and symptom relief. These therapies often require several repeat dosages which upon termination invariably result in recurrence [2]. Keloids are usually treated non-surgically with pressure compression, local intra-lesional infiltration of corticosteroids such as Triamcinolone, anticancer agents such as 5-Fluorouracil, cryotherapy among others [4]. Surgery as monotherapy carries a very high recurrence and is therefore often augmented with adjuvant medical therapies [7].

Adipose Derived Stromal Vascular Fraction (SVF) is a new and emerging potential therapy for scar treatment that has been recognized to result in hypertrophic scare regression and flat-

tening [8, 9]. Autologous adipose derived stromal vascular fraction is the cellular extract obtained from processed fat tissue following liposuction and contains mesenchymal stem cells [10] that are capable of trilineage cellular differentiation in addition to immunomodulation of chronic inflammatory processes that characterize keloid development [11]. It's these properties that confer the therapeutic potential of the SVF in promoting scar regression and symptom relief [12]. These cells produce through a paracrine mechanism several chemokines which have anti-apoptotic, anti-inflammatory, pro-angiogenic, immuno-modulatory and anti-scarring effects which directly promote scar regression [11-13]. These anti-fibrosis cytokines [14] decrease the α-SMA and collagen type I gene expression seen in keloids [15].

Previously, systematic reviews have been performed on the use of autologous fat-grafts where the un-processed lipoaspirate is injected directly into the scar [16]. Fat grafting involves infiltration of the lipoaspirate which comprises of both the unnecessary fat in addition to the stromal cells which in this case are the active components. SVF which are more the processed and active extract of the lipo-aspirate reduces the bulky nature and deformity associated with fat grafts. On the contrary fat grafts act as lipo-fillers especially in facial deformities [17].

Rationale for review

In 2017, a systematic review of autologous fat grafting and its role in scar treatment was conducted by Riyat et al [18] with the key emphasis being the use of fat graft and at that time, there were limited high evidence studies to support the use of autologous fat in scar therapy. The last four years have since seen a tremendous increase in interest of adipose derived stromal vascular fraction (SVF) in favor of the autologous fat graft. The SVF is a more refined form of the autologous fat graft, less bulky and carries less risk of fat necrosis that is associated with fat grafting [19].

With significant advances in the role of SVF in scar therapy in the last five years [8, 20], it will be important to evaluate the current practices and efficacy in scar therapeutics.

Objectives

Primary objective: The primary objective of this review is to establish the efficacy of Adipose derived stromal vascular fraction in comparison to non-surgical therapies in the treatment of scars among adults in LMICs.

Secondary objectives: 1. To establish the adverse events associated with SVF use in scar treatment. 2. To describe the medical administration of SVF in scar therapy: a. To establish the dosing and dosing frequency of SVF. b. To describe the various techniques for lipo-aspirate processing to obtain SVF.

Methods/design

Study design

This systematic review will evaluate the existing clinical research involving the use of autologous adipose-derived stromal vascular fraction in the treatment of scars.

This will follow the registration of this review under the PROSPERO international register of systematic reviews. The study will be conducted following the principles of Preferred Report Items of Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) [21].

Eligibility criteria

Inclusion and exclusion criteria: We shall use the PICOS (Participants, Interventions, Comparisons, outcomes and study design) framework to identify relevant articles to include in the review.

For articles to be included in the review, they will have to meet the requirements as described below: 1. The studies have to be clinical including randomized controlled clinical trials, cohorts, case controls comparing adipose-derived stromal vascular fraction to an established non-surgical scar treatment modality including intralesional corticosteroids, cryotherapy, anti-cancer, cutaneous radiotherapy, laser therapy among others. 2. The studies should have been conducted among adults and published in peer reviewed journals between 2000 and 2020. 3. The outcome measure of the study should be the scar assess-

ment score comparing a baseline scar score to an end of follow-up score.

Exclusion criteria: Articles reporting the use of autologous non-processed fat-graft (lipoaspirate), allogenic use of stromal vascular fraction will be excluded.

Language

There will be no restriction on the language applied to the review.

Information sources

We shall perform a search in the following databases: Medline/PubMed, SCOPUS, EMBASE, CINAHL. We shall search for grey literature using Google scholar and websites of professional bodies. In addition, we shall search trial registries including ClinicalTrials.gov. We shall also conduct reference searching of studies included in the review.

Search strategy and key search terms

The article selection will involve articles limited to publications between January 2000 to December 2020 as there was no consensus to the definition of Adipose-derived stromal vascular fraction prior to the year 2000.

We will use keywords including Medical Subject Heading (MeSH) terms related to Adipose Derived Stromal Vascular Fraction (SVF) and keloids to identify the articles in the electronic databases. Boolean operators "AND" and "OR" will be used to combine the search term.

The keywords and a preliminary PUBMED search string have been included (Supplementary File 1).

Study records

Data management, selection and collection processes: Two experienced reviewers (AK and SR) will independently screen the relevant search titles and abstracts and select those deemed relevant. Selected articles will be exported to Rayyan©, merged and duplicate studies will be removed.

In the second phase, two independent reviewers (RM & IK) will independently screen the selected articles for eligibility for inclusion in the review following the inclusion and exclusion criteria. The PRISMA Flow guide will be used to determine the final outcome of the article search and selection. Studies that pass the inclusion criteria will then be identified for review. The flow guide is adapted from the PRISMA Statement [22] (See **Figure 1**).

For any disagreements between the reviewers, consensus will be sought through discussions and in case a resolution is not reached, a third researcher (HML) will act as the tie-breaker.

Data collection process

Pilot testing: We shall pilot the data extraction form on five articles. The pilot forms will be reviewed for areas of ambiguity and these will be further refined to optimize the quality of data captured.

Data extraction: The study characteristics will be obtained from text, tables and figures including graphs and entered into the electronic data extraction form.

Data items: The data items will be broadly fit into the areas below.

Study characteristics: a. Study design, participant characteristics: Study design, sample size, length of follow up, participant demographic characteristics including the age, sex, ethnicity will be obtained. b. Baseline keloid and scar characteristics including: The scar volume (mm^3), height (mm), and the Scar assessment scores. c. The SVF intervention methodologies: Description of the intervention methods including harvesting, process and infiltration techniques. The comparison/control arm methods. Processing technique for obtaining SVF or AD-SCs. d. End of follow-up keloid and scar characteristics: The scar volume (mm^3), height (mm), and the Scar assessment scores. e. End of Follow-up adverse effects: Any recorded adverse effects and their categorization.

Outcomes

The primary outcome of this review is the mean difference between baseline and end of follow-up in scar assessment scores in the SVF and the Comparator arms.

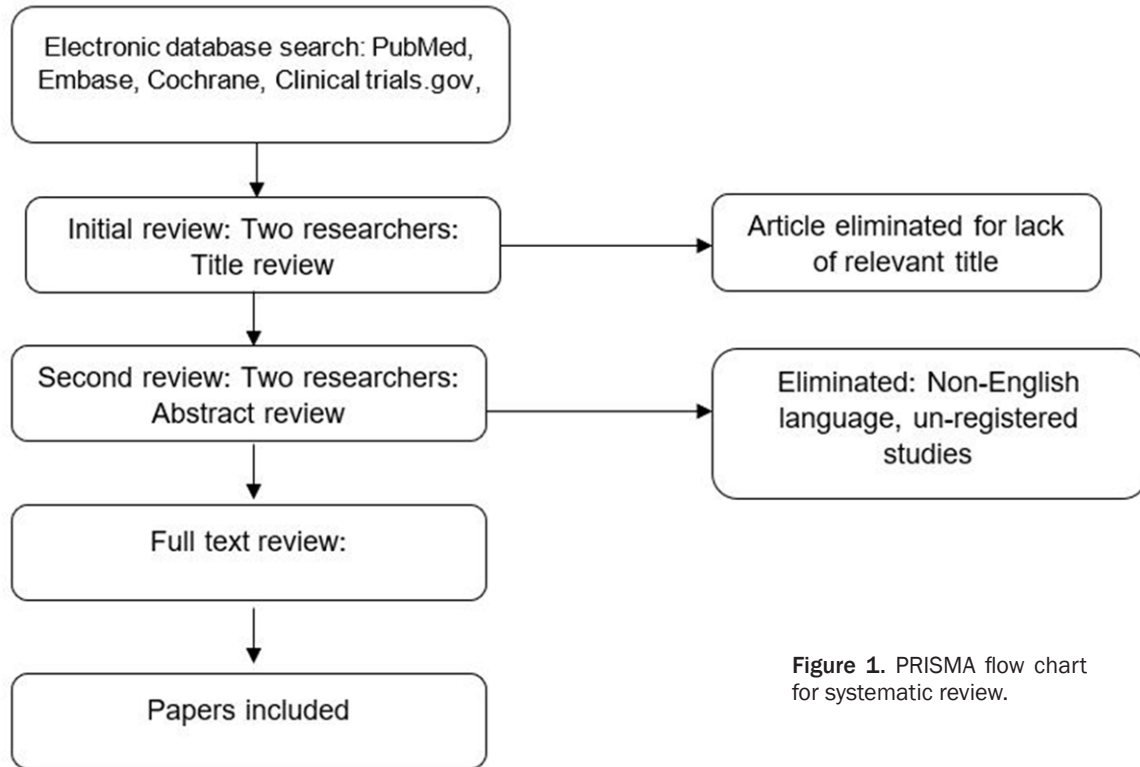The Secondary outcomes include the adverse events that will be reported in each study, the

Figure 1. PRISMA flow chart for systematic review.

dosing and dosing frequency, lipoaspirate volume, lipoaspirate processing techniques and the duration of treatment the scar volume and height in millimeters.

Evaluation of risk of bias

Risk of bias in individual studies/iInternal validity: The two researchers will participate in the evaluation of risk of bias for each of the selected studies. We shall base on the Cochrane Collaboration tools for assessing for risk of Bias.

For Randomized control trials, we shall use the "Revised Cochrane risk-of-bias tool for randomized trials (RoB2)" [23] while for the non-randomized studies, the "Risk of Bias in Non-Randomized studies of intervention (ROBINS-I) tool" [24] will be used. For observational studies, the Risk of Bias tool for observational studies (ROBINS-E) tool will be used [23, 24].

The Risk of Bias will be assessed based on the domains included in the tools above including the randomization process, deviation from intended interventions, missing outcome data, measurement of outcome, report result.

The risk of bias in each study will be reported as 'Low' risk or 'High' risk or 'Some concern'.

Individually for each randomized controlled trial, Selection bias, performance bias, detection bias, attrition bias, reporting bias and any other source of bias will be reviewed.

Assessment of external validity

In order to assess how generalizable, the findings in the different studies, we shall evaluate how the study populations were selected including the sampling methods and sample characteristics.

The study ID, including authors, year of publication, the characteristics of the study design, the characteristics of the population, the SVF characteristics including harvesting site, storage and processing and the outcome variables will all be used to evaluate for external validity.

Qualitative research: For qualitative research, critical appraisal will include the evaluation of the reliability of the findings of the studies as well as their validity basing on the existing body of knowledge as well as the investigators' origi-

nal intentions for conducting the study respectively.

We shall also evaluate for credibility based on how well the findings of the study are represented correctly.

Implications

All studies will be scored for the level of the risk of bias and subsequent analysis of the findings will be stratified into the three categories of risk of bias.

Summary measures

Difference of means will be used as the summary of measures for the Scar assessment scores and any other variables collected from the study.

Data synthesis

Difference of means will be used as the summary measure for volume of keloids, height and the Scar Assessment score as well as any other variable collected from the studies.

First, we shall summarize the characteristics of the included studies based on the PICOS elements which we shall include in the "characteristics of included studies" table.

The intervention description of the study characteristics will be structured using the Template for Intervention Description and Replication (TIDIeR) checklist [25, 26].

The primary and secondary outcome measures

The keloid volume and height in addition to the scar assessment scores will be analyzed using descriptive statistics of means and proportions.

In case more than three studies provide consistent characteristics of scar volume or height regression or Scar assessment scores, we shall conduct a meta-analysis of those studies. Subgroup analysis of SVF and ADSC will be performed should there be more than three studies in each subgroup. Sub-group analysis will also be conducted in case significant heterogeneity occurs between the scar assessment scores.

Where possible, analysis of the effect measures will be conducted to obtain mean differences and the standardized mean differences with a confidence interval of 95% for all the continuous variables.

In order to prevent multiplicity arising from more than one follow-up interventions, we shall obtain the average of the effect estimates and the standard error of this will be obtained by obtaining the averages of the effect estimates. In studies where more than one outcome is reported, we shall select the primary outcome of interest for our study.

We shall use the Random effects model (Der Simonian-Laird model) [27, 28] to evaluate all the outcome measures while heterogeneity will be evaluated using the I^2 statistics and the result will be categorized into one of the three: Low (25-50%), Moderate (50-75%), High (>75%).

We shall assess heterogeneity in two subgroups i.e., the clinical interventional trials and the observational studies.

In case the degree of statistical heterogeneity is high, we shall conduct sub-group analysis for dosing, frequency of stem cells infiltrated, the follow up period and the scar assessment score type.

In the event that it's not feasible to conduct a meta-analysis, we shall obtain all results and use qualitative synthesis to describe a narrative of the studies in regard to the outcomes of interest.

In case meta-bias is detected in specific studies, we shall contact the study authors to provide extra information such as the missing data.

All authors will appraise the quality of evidence in all the included studies for each primary outcome of interest. The Grading of Recommendations Assessment, Development and Evaluations (GRADE) process will be used to rate the quality of the scientific evidence as well as develop recommendations.

Discussion

With the growing interest of adipose-derived stromal vascular fraction in scar therapeutics [29, 30], coupled with the varying success

reports, it is timely to review the efficacy of this emerging and potentially efficacious treatment.

Several studies have reported varying results with no clear standardization of the effect measures and this variability in treatment success needs to be interrogated [8, 9, 30].

We therefore intend to systematically evaluate for the efficacy of SVF in comparison to other scar treatment modalities in order to establish whether SVF can be an alternative modality in scar and keloid therapy.

We shall evaluate for the effect of the SVF on the scar assessment score as well as evaluate the safety profiles and different procedural methodologies.

The most used scar assessment tools include the Patient and Observer Scar Assessment Scale (POSAS) [31], Vancouver Scar Assessment scale [32] and will constitute the scar assessment scales that we shall compare among others validated scar assessment forms.

We have identified a previous systematic review that evaluated for fat grafting in scar treatment [16] but unlike this systematic review where both SVF and fat grafting studies were reviewed, our study will specifically look at the use of the SVF. Given that the majority of these un-treated scars are in Low and Middle Income countries and yet the majority of research is in High Income countries [33, 34], we shall look at the use of the SVF in Low and Middle Income Countries where there may be limitations in the access of various components and reagents [35]. This review will therefore highlight aspects involved in stromal vascular fraction use and any unique practices in LMICs and how they would significantly differ from the high-income study findings.

Similarly, systematic reviews evaluating for the pre-clinical studies have been sufficiently described but there seems to be a translational disconnect in the clinical areas to build sufficient evidence of the clinical benefit of the SVF [36, 37].

Our conclusions will be based on a thorough evaluation of all appropriately conducted stud-

ies and therefore should be strong and informative. Secondly any existing grey areas in SVF will be highlighted and meaningful recommendations generated.

Disclosure of conflict of interest

None.

Abbreviations

ADSC, Adipose Derived Stem Cells; SVF, Adipose Derived Stromal Vascular Fraction; PRISMA-P, Preferred Report Items of Systematic Reviews and Meta-Analyses protocols; TIDIeR, Template for Intervention Description and Replication.

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Supplementary File 1

Search strategy for systematic review

Adipose-derived stromal vascular fraction (SVF) in scar treatment: a systematic review protocol

(((((((((((Adipose Derived Stromal Vascular Fraction[Title/Abstract]) OR (Stromal Vascular Fraction[Title/Abstract])) OR (Adipose Derived Stem Cells[Title/Abstract])) OR (Fat stem cells[Title/Abstract])) OR (Mesenchymal stem cell*[Title/Abstract])) OR (SVF[Title/Abstract])) OR (Adipose Derived Mesenchymal stem cells[Title/Abstract])) OR (Adipose Tissue Derived Stromal cell*[Title/Abstract])) OR (Adipose-Derived Mesenchymal Stromal Cell[Title/Abstract])) OR (Adult stem cell*[Title/Abstract])) OR (Stromal cells[Title/Abstract])) AND (((((((Scar[Title/Abstract]) OR (Scars[Title/Abstract])) OR (hypertrophic scar*[Title/Abstract])) OR (hypertrophic scar[Title/Abstract])) OR (keloids[Title/Abstract])) OR (cicatrix[Title/Abstract])) OR (contracture[Title/Abstract]))