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Russia.**ADMINISTRATIVE INFORMATION****Support** - N/A.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023100066**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 October 2023 and was last updated on 19 October 2023.**INTRODUCTION**

Review question / Objective The aim is to unravel the underlying mechanisms, the efficacy, and the potential limitations of each treatment modality, thereby providing an enlightened perspective on the most promising strategies in bone fracture healing.

Rationale Various stimulation methods, including electrical, ultrasound, mechanical, and biological interventions are explored, each leveraging intricate cellular and molecular dynamics to expedite healing. The advent of Stromal Vascular Fraction (SVF) marks a significant stride, offering multifarious benefits in bone healing, from enhanced bone formation to optimal vascular integration, drawing a harmonious balance between innate mechanisms and scientific advancements.

Condition being studied Vascular Integration is achieved as SVF promotes angiogenesis, ensuring

the formation of an integrated vascular network within the healing bone, which is crucial for the supply of essential nutrients and oxygen, and is pivotal for optimal bone regeneration. Lastly, SVF optimizes the Cellular Environment, creating a harmonious niche conducive to the enhanced homing of stem cells and progenitor cells, laying the foundation for efficient and expedited bone healing.

METHODS

Search strategy A systematic and exhaustive search of the literature was conducted utilizing databases such as PubMed, Scopus and Google Scholar. Keywords used for the search included but were not limited to "Bone Fracture Healing," "Stroma Vascular Fraction," "Electrical Stimulation," "Ultrasound Stimulation," "Mechanical Stimulation," "Biological Interventions," "Nutritional and Pharmacological Stimulation," "Bone Morphogenetic Proteins," "Platelet-Rich Plasma," and "Stem Cell Therapy."

The literature search was confined to articles published in English from 2016 to 2023.

Participant or population N/A.

Intervention N/A.

Comparator N/A.

Study designs to be included Peer-reviewed articles, reviews, and clinical trials focusing on SVF or other bone stimulation mechanisms in the context of bone fracture healing.

Eligibility criteria Studies included in this review met the following criteria: Peer-reviewed articles, reviews, and clinical trials focusing on SVF or other bone stimulation mechanisms in the context of bone fracture healing. Studies providing insights into the mechanisms of action, efficacy, clinical applications, and outcomes of the reviewed methods. Publications available in full text.

Information sources A systematic and exhaustive search of the literature was conducted utilizing databases such as PubMed, Scopus and Google Scholar.

Main outcome(s) The comparative analysis provided herein offers a novel insight into the multifaceted therapeutic potentials and limitations of SVF relative to other bone healing modalities, aiming to contribute to the body of knowledge and elucidate optimal strategies in bone regeneration and repair. However, despite the promising findings, it is crucial to acknowledge the limitations such as the scarcity of human studies, potential publication bias, and the nascent state of SVF research. These constraints necessitate cautious interpretation and call for more comprehensive and diversified studies to validate these preliminary observations, substantiate the comparative benefits, and to understand the comprehensive implications of SVF in bone healing strategies. The need for further research is critical to overcome the imbalances and disparities in the available literature, to address the generalizability concerns, and to advance the clinical translation of SVF as a viable and effective bone stimulation method. Meanwhile, the relative safety and lack of complications in reported studies position SVF as a compelling candidate in the array of bone healing modalities, offering a superior and multifaceted approach to bone regeneration and repair, subject to careful evaluation and application in suitable contexts.

Data management From each selected study, the following data were extracted: the author(s), year of publication, study design, sample size, type of bone stimulation mechanism studied, clinical applications, outcomes, and limitations. A data extraction form was developed to ensure uniformity in the extraction process.

Quality assessment / Risk of bias analysis The quality of the included studies was rigorously assessed using appropriate critical appraisal tools. The assessment focused on the study design, methodology, result reliability, and the relevance and validity of the conclusions drawn. Data extracted from the included studies were synthesized and analyzed narratively. Comparative analyses were carried out to evaluate the mechanisms, applications, and outcomes of SVF against the other bone stimulation mechanisms. Emphasis was laid on identifying the advantages, limitations, and potential improvements of each method..

Strategy of data synthesis Each included study was subjected to a critical appraisal to assess the quality of evidence presented. Studies were evaluated based on their methodological rigor, validity of findings, relevance to the review topic, and contribution to the understanding of bone fracture healing stimulation. For each selected article, data were extracted by two independent reviewers (ENG and NM). The data comprised the year of publication, study type, number of participants (for clinical trials), main findings, and conclusions and complications. Any discrepancies between the reviewers were resolved through discussion until a consensus was reached.

Subgroup analysis 22 articles were deemed fit for a more comprehensive assessment for eligibility after first screened 8 articles were selected, 14 were excluded. In last screened series of articles 5 were selected for. Each of these five carefully assessed articles successfully met the predetermined inclusion criteria and were therefore integrated into the review, as delineated in Table 1. The ensemble of selected studies encompasses a diverse array of research methodologies, including prospective and/or retrospective case series, randomized controlled clinical trials and insightful reviews.

Sensitivity analysis N/A.

Language restriction English.

Country(ies) involved Russia.

Other relevant information N/A

Keywords regenerative medicine; stromal vascular fraction; tissue regeneration; graft survival; surgery.

Contributions of each author

Author 1 - Evgeniy Nikolaevich Goncharov - Drafted manuscript, review of data.

Author 2 - Oleg Aleksandrovich Koval - Drafted manuscript, review of data.

Author 3 - Eduard Nikolaevich Bezuglov - Drafted manuscript, review of data.

Author 4 - Mikhail Engelgard - Drafted manuscript, review of data.

Author 5 - Eremin Ilya Igorevich - review of data revision.

Author 6 - Konstantin Velentinovich Kotenko - review of data revision.

Author 7 - Manuel De Jesus Encarnacion Ramirez - review of data revision.

Author 8 - Nicola Montemurro - review of data revision. drafting of manuscript.