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ORIGINAL

Evaluate efficacy and safety of stem cells on bone regeneration: a systematic review and meta-analysis

Evaluar la eficacia y seguridad de las células madre en la regeneración ósea: una revisión sistemática y un meta-análisis

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Abstract

Objectives: The present study tries to reach a consensus on the results of studies on the efficacy and safety of stem cells-based scaffolds in disorders related to the jaw bone and Provides sufficient and strong evidence. Therefore, the present study aims to evaluate the efficacy and safety of Stem Cells on bone regeneration.

Methods: Present study is based on PRISMA guidelines; all articles published in international databases such as PubMed, Scopus, Science Direct, ISI Web of knowledge, and Embase between March 2010 and May 2022 are included. 95% confidence interval for effect size with fixed effect modal and in-variance method were calculated. Meta-analysis of data collected from selected studies was performed using STATA.V16 software.

Results: In the initial review, the abstracts of 336 studies were reviewed, two authors reviewed the full text of 136 studies, and finally, ten studies were selected. The prevalence of bone formation due to using stem cell-based scaffolds was 32% (95% CI, 1 % to 63%; p=0.04).

Conclusions: Based on the findings of the present meta-analysis, stem cell-based scaffolds can significantly cause bone formation and regeneration, and as a result, they can significantly improve maxillofacial bone disorders.

Key words: Stem cells, bone regeneration, meta-analysis.

Resumen

Objetivos: El presente estudio trata de consensuar los resultados de los estudios sobre la eficacia y la seguridad de los andamiajes basados en células madre en los trastornos relacionados con el hueso de la mandíbula y trata de proporcionar pruebas suficientes y sólidas. El presente estudio tiene como objetivo evaluar la eficacia y la seguridad de las células madre en la regeneración ósea.

Métodos: El presente estudio se basa en las directrices PRISMA; se incluyen todos los artículos publicados en bases de datos internacionales como PubMed, Scopus, Science Direct, ISI Web of knowledge y Embase entre marzo de 2010 y mayo de 2022. Se calculó el intervalo de confianza del 95% para el tamaño del efecto con el método de efecto fijo y de in-varianza. El meta-análisis de los datos recogidos de los estudios seleccionados se realizó con el software STATA.V16.

Resultados: En la revisión inicial se revisaron los resúmenes de 336 estudios, dos autores revisaron el texto completo de 136 estudios y, finalmente, se seleccionaron diez estudios. La prevalencia de la formación de hueso debido al uso de andamiajes basados en células madre fue del 32% (IC del 95%, 1 % a 63%; p=0,04).

Conclusiones: En base a los resultados del presente meta-análisis, los andamiajes basados en células madre pueden mejorar significativamente la formación y regeneración ósea, y como resultado, pueden mejorar significativamente los trastornos óseos maxilofaciales.

Palabras clave: Células madre, regeneración ósea, meta-análisis.

Introduction

According to the statistics available worldwide, the prevalence of bone disorders of the jaw and face is high and different, and the reason for this difference can be due to economic, cultural, environmental, and social factors[1]. The result of treatment of maxillofacial bone disorders is often unfavorable due to the complexity of the injuries; also, jaw and facial bone disorders may be associated with other injuries such as injuries to the abdomen, spine, head, pelvis, and organs[2]. These disorders may occur due to trauma, congenital abnormalities, or periodontal diseases and cause the loss of alveolar bone[3]. These injuries must be treated because they do not heal alone, and bone grafting must be done[4]. A treatment considered the gold standard for these disorders is an Autogenous bone graft[5]. However, despite the advantages of this method, disadvantages have also been reported, including loss of function, risk of infection, bleeding after surgery, and painful surgery; Therefore, it is very important to use an alternative treatment that minimizes these disadvantages[6]. Recently, tissue engineering has been introduced, a multidisciplinary field of the principles and applications of engineering methods and biological sciences, and is used in connection with the basic understanding of the structure and function of natural and diseased tissues[7]. The purpose of this type of method is to maintain the stable condition of the tissue and better the performance of the target tissue. The use of stem cells is a logical method due to its advantages, such as repair and self-renewal, as well as the ability to differentiate into different cells, and it can affect the host's tissues[8]. Therefore, the use of this method in bone tissue engineering has received much attention[9]. According to the available literature, three components (bone progenitor cells, bone growth factor, and scaffolding) are required for bone tissue engineering[10-12]. Of these three, the most key role is scaffolding, which transfers cells to the lesion site[13]. Scaffolds use an appropriate extracellular matrix to allow cell growth and differentiation to restore tissue function[14]. The use of this new method is very important, and many studies must be done to be able to hope for the treatment results; therefore, the present study tries to reach a consensus on the results of studies on the efficacy and safety of stem cells-based scaffolds in disorders related to the jaw bone and Provide sufficient and strong evidence. Therefore, the present study aims to evaluate the efficacy and safety of Stem Cells on bone regeneration.

Methods

Search strategy

Based on PRISMA guidelines[15], the present study is a systematic review and meta-analysis that includes all articles published between March 2010 and May 2022 in international databases such PubMed, Scopus, Science Direct, ISI Web of Knowledge, and Embase. It used the Google Scholar search engine.

The following keywords were used to search: (((((“Maxillofacial Prosthesis”[Mesh] OR “Oral and Maxillofacial Surgeons”[Mesh] OR “Maxillofacial Abnormalities”[Mesh] OR “Maxillofacial Injuries”[Mesh] OR “Maxillofacial Development”[Mesh] OR “Surgery, Oral”[Mesh] OR “Oral Surgical Procedures”[Mesh]) AND “Bone Diseases”[Mesh]) AND “Stem Cells”[Mesh]) OR (“Stem Cells/surgery”[Mesh] OR “Stem Cells/therapy”[Mesh])) AND “Tissue Scaffolds”[Mesh]) AND “Bone Regeneration”[Mesh].

Inclusion and exclusion criteria

In the current study, human and animal studies were included, and studies using stem cells for jaw and facial bone disorders are considered.

Study selection, Data Extraction, and method of analysis

Studies data were reported by first author name, years, number of Participants, mean of age, cell type, scaffold, location of the lesion, and duration.

STATA.V16 software was used to analyze the data. The level of heterogeneity was evaluated using the I^2 index test (I^2< 50% = low levels, 50<I^2< 75% = moderate and I2>75% = high levels). Calculated was the effect size's 95% confidence interval with a fixed effect mode and invariance.

Results

Four hundred thirty-nine studies were found when the existing literature was reviewed using the studied keywords. Duplicate studies were removed from the original review, and 336 study abstracts were reviewed. Two hundred studies were first excluded because they did not fit the criteria for inclusion, and in the subsequent step, two authors reviewed the full texts of 136 studies. One hundred twenty-six studies had already been removed from the study at this stage for various reasons, including incomplete data, inconsistent research results, poor studies, a lack of full-text access, and data that did not match with the study's objectives. Ultimately, ten studies were selected (**Figure1**).

Characteristics

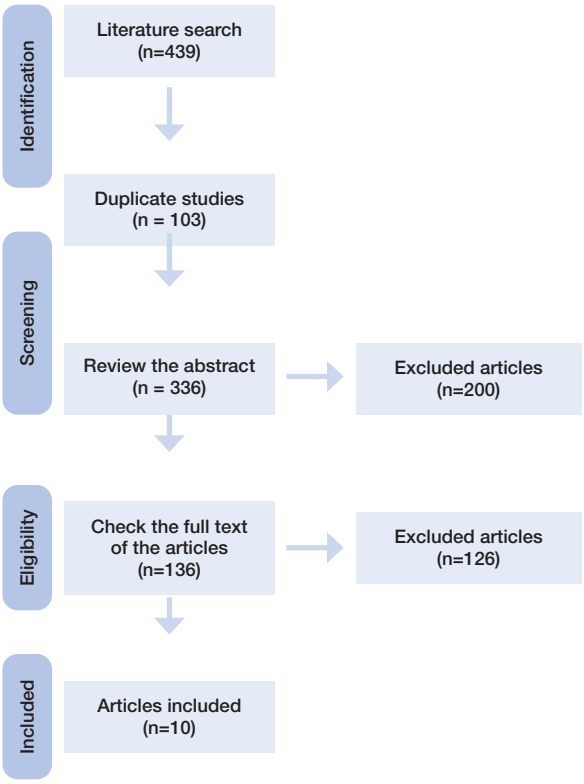
In the present study, nine studies were conducted on animal models, and only one was found in the considered human study period. In animal studies, 16 dogs, 88 rats, 5 rabbits, and 12 pigs were used. A total of 23 patients with a range of 43-74 years were examined in one study. Two studies used ADSCs, and eight studies used BMSCs. The range of study duration was 8-26 weeks. (**Table I**).

Table I: Data extracted from studies.

No.	Study. Years	Sample size		Type of Cell	Scaffold	Location of the lesion		Duration of study
		Animals	Human			Maxilla	Mandible	(weeks)
1	Lee et al., 2021 (16)	10/dog	-	ADSCs	βTCP	-	√	8
2	Prahasanti et al., 2020 (17)	14/rats	-	BMSCs	CAS	-	√	8
3	Zhang et al., 2020 (18)	17/rats	-	BMSCs	βTCP	-	√	8
4	Lopez et al., 2018 (19)	5/rabbits	-	BMSCs	βTCP	-	√	8
5	Moser et al., 2017 (20)	24/rats	-	BMSCs	βTCP	-	√	26
6	Tee et al., 2016 (21)	12/pigs	-	BMSCs	βTCP	-	√	12
7	Lee et al., 2015 (22)	28/rat	-	ADSCs	PLGA	-	√	12
8	Yun et al., 2014 (23)	6/dogs	-	BMSCs	βTCP	-	√	8
9	Yamada et al., 2013 (24)	-	23	BMSCs	PRP	√	-	24
10	Zou et al., 2011 (25)	5/rats	-	BMSCs	βTCP	-	√	8

ADSCs: Adipose-derived mesenchymal stem cells; BMSCs: Bone marrow-derived mesenchymal stem cells; CAS: Carbonate apatite scaffold; PRP: Platelet-rich plasma.

Figure 1: PRISMA flowcharts.



Stem cells-based scaffolds

Meta-analysis showed that stem cell-based scaffolds could significantly cause bone formation and regeneration, and as a result, they can significantly improve maxillofacial bone disorders. Prevalence of bone formation due to using stem cells–based scaffolds was 32% (95% CI, 1 % to 63%; p=0.04) (I^2=0%; P=1.00; low heterogeneity). (**Figures 2, 3**).

Discussion

The present study aimed to evaluate the efficacy and safety of stem cells on bone regeneration. Based on the findings of the meta-analysis, it can be seen that this method is a key factor in the success of tissue engineering, but more studies should be conducted in this field, and more research is needed to introduce this treatment method as an ideal treatment method. BMSCs have been used in most of the selected studies, and these cells are considered a gold standard in bone tissue engineering. Also, BMP2 and PRP have been used as scaffolds. Based on the studies, organic scaffolds, PRP, and natural scaffolds are more popular, and more satisfactory findings are observed using collagen. The present analysis shows that stem cell-based scaffolds can improve bone regeneration, and positive results are observed.

Figure 2: The Forest plot showed the effectiveness of using scaffolds based in stem cells on bone formation.

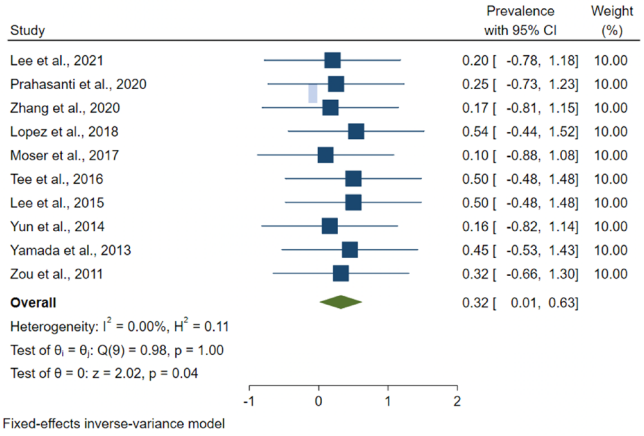
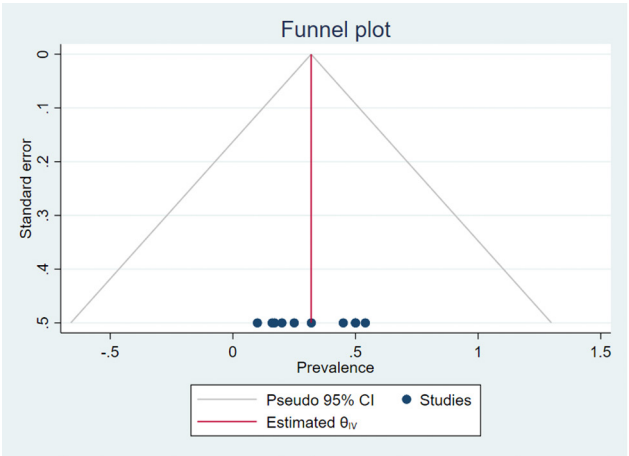


Figure 3: Funnel plot for graphical diagnostics of small-study effect.



Recent studies show that stem cells can be a promising technique for reconstructing bone defects[26]. Also, the results of another study conducted by Dong et al., 2020 showed that MSC-based tissue engineering scaffolds could increase osteogenesis[27]. As mentioned earlier, self-renewal and differentiation are the prominent features of stem cells, making them important in tissue engineering, and mesenchymal stem cells have become important because of their unique properties(28). Based on the available evidence, recent advances have shown that stem cells based on scaffold properties can be considered a very suitable therapeutic option in treating bone defects, although more research is needed[26].

The cell is considered one of the most important and main components of cell tissue engineering, and target tissue cells and stem cells are the two main sources of cells. The findings of the present meta-analysis show that poly (lactic-co-glycolic acid) is most commonly used in treating bone defects. In line with these findings, the results of the study by Zhao et al., 2021 showed that poly (lactic-co-glycolic acid) could be used in bone treatment and regeneration due to its mechanical properties, biocompatibility, and degradability[29]. Also, the present meta-analysis showed that combined scaffolding (PCL/hydroxyapatite) has positive results in bone regeneration. Studies have reported that coral scaffolds have the best therapeutic results[30,31].

Human studies are of great importance to confirm the results of the present study and previous studies and provide stronger evidence for conducting studies with large sample size. Most animal studies have been done on the reconstruction of small lesions, and their findings cannot be generalized to humans; also, the immune system issue should be considered. Using a control group to compare the findings can show the effectiveness of the treatment. Also, the duration of the experiments and research in the studies was very short, so to achieve better results, it is necessary to spend more time and consider all the possible side effects. Also, as discussed in relation to the three components of tissue engineering, all three components were used together in quantitative studies. In the end, it is emphasized that important factors in bone regeneration, such as immunological reactions and angiogenesis, should be considered for this treatment.

Conclusions

So far, an ideal scaffold has not been designed and reported, and important factors in bone regeneration, such as angiogenesis and bone physiology, have not been studied. Therefore, many studies are needed in this field so that an important step in the treatment and regeneration of bone can be taken to confirm the evidence. The rapid prototyping method can be used to construct composite scaffolds with the help of CT and MRI images and genetically modified stem cells.

Conflict of Interest

The authors report no conflicts of interest.

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