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Research Article

Success and use of Stem Cells in Bone Regeneration of the Oral Cavity Systematic Review

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Abstract

Tissue engineering using mesenchymal stem cells (MSCs) is a recent therapy modality that has multiple advantages. One of them is the ability to accelerate hard and soft tissue repair processes thanks to, in part, its proliferative and regenerative capacities, improving morbidity postoperative of the patients. Therefore, the main objective of this review system is to be able to identify the current uses of MSCs in regenerative therapies bones of the oral cavity. In recent years, various articles have been published in where we talk about the advances that have been made in regenerative treatments. The regeneration of lost oral tissues is the objective of research in MSCs. For this reason, it is important that the main characteristics of therapies with MSCs are understood by clinicians so that they can be used in the future.

Objective: To describe the success and use of MSCs for bone regeneration of the oral cavity.

Material and method: A search in the PUBMED, STEM CELLS databases JOURNAL and MICROSOFT ACADEMIC was made to include clinical studies (randomized and controlled), case controls or series of cases that describe the use of human mesenchymal cells (MSC's) for bone regeneration surgeries in the oral cavity, specifically.

Results: 147 articles were found, after reading the title and abstracts 107 articles were selected, 99 were eliminated after evaluating inclusion criteria and exclusion, 8 articles were selected to carry out a complete reading of the text. The selected articles are: 2 randomized clinical cases, 3 cases nonrandomized controlled trials and 3 case series reports. the site for obtaining MSCs that used the most corresponds to the bone marrow. with the results of the articles included in this study, it is observed that the mesenchymal cells intraoral would have the capacity to carry out new formation of bone tissue.

Conclusion: It is necessary to specify a storage and transport protocol for the MSCs. Studies using MSCs extracted from other donor sites are lacking. intraoral. Good results were found in tissue regenerative treatments bone tissue incorporating cellular technology into its procedures.

Introduction

Currently it is common to use oral implantology as an ideal solution in response to the loss of dental structures, consequence of a facial trauma, periodontal disease, resorption or loss of hard and soft tissues; being essential to recover aesthetics and function, returning the original anatomy of lost tissues. But, in most of the cases, the patients do not present the suitable terrain in the area to be treated by implant. So, it becomes essential to go through a stage of bone regeneration surgeries, prior to dental implant installation. To this end, different techniques have been studied, one of these is tissue engineering, which seeks to regenerate lost tissues, through the use of conductive materials in conjunction with autogenous cells with potentials of differentiation, called mesenchymal stem cells (MSCs) [1]. These cells were discovered by Friedenstein in the 1970s, who for two decades carried out studies to determine the biological characteristics of the bone marrow-derived mesenchymal cells, which were capable of differentiate into different cell lineages and thus began a new era of regenerative medicine [2]. Stem cells represent the main pillar of tissue engineering due to their high proliferative capacity and its ability to differentiate into different tissues. The classic definition of a stem cell is based on two principles. The first is that They are cells capable of self-renewal, that is, they replicate by dividing and generating new copies of themselves, and the second is that they are able to differentiate and give rise to mature cells that constitute different tissues and organs depending on of the specific, physiological or experimental conditions in which they are [3]. In 2006 the Mesenchymal and Tissue Stem Cell Tissue Committee of International Society for Cellular Therapy (ISCT)) proposed standards that should meet the cells to be defined as mesenchymal stem cells. Must note that these criteria only apply to human mesenchymal cells [3,4].

First of all, they must adhere to the plastic when they are kept in standardized culture conditions using tissue culture flasks. In Second, >= 95% of the stem cell population must express the CD105, CD73 and CD90 surface antigens, measured by flow cytometry. In addition, there should be little presence (<=2% positive) of the surface antigens CD45, CD34, CD14 or CD11b, CD79a or CD19 and Human Leukocyte Antigens (HLA) class II. Third, these cells must be able to differentiate into osteoblasts, adipocytes and chondrocytes in a differentiated in vitro standardized medium [4]. Stem cells can be classified according to their differentiation potential and origin. Depending on the origin, they present different degrees of differentiation, being classified in adult or embryonic cells. According to their potential for differentiation, they are They can be classified as totipotent, pluripotent, multipotent, and unipotential [4,5]. One of the main functions of these cells is to maintain and repair tissues in found, as well as maintain the cell population. within their most important characteristics is that they have the ability to differentiate into adipocytes, chondrocytes and osteoblasts under in vitro conditions. Furthermore, the MSCs have the ability to not generate a response to the immune system when being immunomodulatory, this means that MSCs are capable of altering the proliferation and effector functions of most cell populations in the innate and adaptive immune system, which gives them the possibility of being used with therapeutic roles [2,6]. But to achieve the reparative process requires a combination of events fundamental, appropriate and sequenced levels of signaling for regulators chemotactic agents, presence of progenitor cells responding to biological signals, an extracellular matrix in appropriate amount and appropriate blood supply [2]. The first area used to obtain MSCs was the bone marrow of patients. Adults. Although its characteristics are optimal, it was observed that; First, the 6 number of progenitor cells in adult tissues was quite low in comparison to the total cells extracted, in a ratio of 1/104-106. For this reason, it is necessary to carry out in vitro

expansions to increase their number. Second, the number of MSCs found in the tissue decreased with increasing age of the patient [6]. Third, obtaining MSCs from bone marrow turns out to be a quite invasive procedure and high morbidity, painful and in some cases see infectious complications. For this reason, they began to look for new sites that had MSCs which allowed a minimum of discomfort for the patient and that there were larger amounts of MSCs [2]. Various sites in the body have been described where MSCs can be isolated, such as the bone marrow, adipose tissue, liver, pancreas, periosteum, synovial membrane, fluid synovium, skeletal muscle, dermis, pericytes, trabecular bone, umbilical cord, lung, amniotic fluid, peripheral blood and oral cavity [2,7]. Following the search other sites, some authors indicate that the oral cavity became one of the sites accessible to obtain MSCs [1], in which different sites have been identified that possess them such as the periodontal ligament, alveolar bone, follicles teeth, extracted teeth, dental pulp, among others [7]. The oral cavity therefore became a great source of MSCs, currently being used in regeneration treatments for both hard and soft tissues, as well as for the treatment of different diseases [6]. In the literature there are many clinical studies carried out on animals and there are little evidence of treatments in humans, in addition to this the studies in Humans are mostly with cells obtained from the bone marrow and there is limited information available using MSCs obtained from another elicitation site such as is the oral cavity [8]. Thus, the objective of our systematic review is to analyze the available evidence in the literature about the success and use of MSC's in bone regeneration surgeries in the oral cavity in humans, trying to check if there is enough evidence to determine that the current use of MSC's in bone regeneration of the cavity oral are predictable and improve the quality and speed of bone regeneration; the same time to find evidence about the donor site and what difference might exist between cells obtained from each site. All that with the intention of shedding light on a updated overview of these regenerative techniques and contribute to the best understanding and decision-making by professionals.

Research Question

What is the current success and use of MSCs in Guided Bone Regeneration of the Oral Cavity?

Objectives

General: Describe the success and use of MSCs for cavity bone regenerations oral.

Specifics:

a. Identify the sites for obtaining used MSC's.
b. Identify protocols for obtaining and transporting MSC's to the ROG site.

Materials and Methods

This systematic review was carried out with the guidelines "Preferred Reporting items for Systematic and meta-analysis protocols" (PRISMA-P) [9].

Selection Criteria - Inclusion Criteria: Randomized controlled clinical papers/studies or descriptive (prospective or retrospective) in humans that include any type of ROG in oral cavity using MSCs, in English or Spanish with Free access.

Exclusion criteria: Literary/systematic reviews, Texts in another language other than English or Spanish, without the possibility of access through the University, texts that are not indexed in mentioned search engines. Duplicates.

Search Strategy

a. A systematic search of the literature was carried out, from the year 1970 to the Currently, in the following databases: PUBMED, STEM CELLS JOURNAL AND MICROSOFT ACADEMIC.
b. Two independent investigators (CSB and FPP) performed the search.
c. The search strategy was as follows, adapting to each of the databases: ((“stem cells”[MeSH Terms] OR (“stem”[All Fields] AND “cells”[All Fields]) OR “stem cells”[All Fields]) AND (“regenerative medicine”[MeSH Terms] OR (“regenerative”[All Fields] AND “medicine”[All Fields]) OR “regenerative medicine”[All Fields]) AND (“mouth”[MeSH Terms] OR “mouth”[All Fields] OR (“oral”[All Fields] AND “cavity”[All Fields]) OR “oral cavity”[All Fields]) AND (“bone regeneration”[MeSH Terms] OR (“bone”[All Fields] AND “regeneration”[All Fields]) OR “bone regeneration”[All Fields])) AND ((ffrft[Filter]) AND (fha[Filter]) AND (ffrft[Filter]) AND (1970:3000/12/12[pdat]).
d. In addition, a review of the references included in the articles was carried out. selected to ensure inclusion of all available articles (Only those indexed in the aforementioned search engines were incorporated).

Obtaining the Information

Two independent investigators (CSB, FPP) compared the results of search to ensure integrity and avoid duplicate articles using the “ZOTERO” software. Analysis was performed on all potential studies. primary where the title and abstract were analyzed. The studies obtained were checked for selection as follows: article title, reading summary, type of study, choice of patients, type and characteristics of bone regeneration surgery performed (vertical/horizontal, if mix was used with alloplastic, xenograft or autograft), site intervened with ROG, criteria for inclusion and exclusion, follow-up time, evaluation of the results, associated complications. Any differences in study selection this was resolved by discussion with a third review author (FMC).

Risk of bias in selected studies

a. Two investigators (CSB - FPP) carried out a methodological evaluation of the quality of the studies. Disagreements were resolved by a third evaluator (FMC).
b. To assess the quality of randomized controlled trials, the used the Cochrane Collaboration tool for assessing risk of bias [10]. The studies were classified as low risk of bias, medium risk of bias and high risk of bias (Table 3).
c. Observational studies were evaluated using the tool Newcastle-Ottawa Quality Assessment Scale tool [11]. this tool includes a questionnaire that is divided into 3 categories: Selection (includes 4 questions), comparability (1 question) and exposure (3 questions). Each study can obtain a maximum of 9 points. The studies were classified in good, medium and low quality, following the scores proposed by the algorithm from the Agency for Healthcare Research and Quality [12].
d. The Joanna Briggs Institute Critical Appraisal tool [13], was used to assess the risk of bias for case reports, which includes 8 questions. a bass risk of bias was considered when ≥50% of the questions were “yes”. High risk is when ≥50% were “no” and unclear risk of bias is when ≥50% of responses were “unclear”.

Results

Consensus among Investigators

Two investigators (CSB - FPP) performed a methodological quality assessment of the studies. Disagreements were resolved by a third evaluator (FMC).

Selection of studies

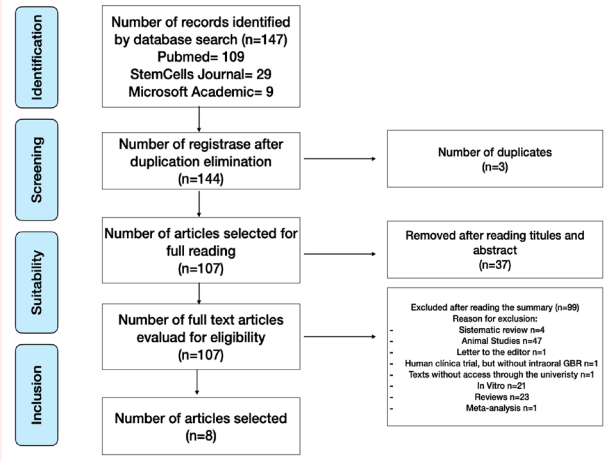

Figure 1: Flowchart of the selection of articles for quialitative analysis of this systematic review.

In the initial search, 147 articles were identified (Figure 1), 144 by eliminating the duplicates. 107 articles were selected after reading titles and abstracts, of which of which 99 were eliminated for the following reasons: 47 were clinical studies in animals,

23 literary reviews, 21 in vitro studies, 4 were systematic reviews, 1 text was related but access was not achieved through the University, 1 article presented a ROG work with MSC's but outside the oral cavity, 1 letter to the editor from a journal and 1 meta-analysis. Finally, 8 articles were selected for analysis after evaluating the inclusion criteria: 3 controlled clinical cases not randomized trials, 3 case series reports and 2 randomized clinical cases.

Study characteristics

The selected studies were non-randomized controlled clinical cases. (n=3), case series reports (n=3) and randomized controlled clinical cases (n=2). All studies were published between 2008 and 2016. The studies were published in dental, periodontal, and stem cell journals. were included, of all the studies, 109 patients. MSC's were used in all the articles. associated with bone substitutes. The characteristics of the studies, the patients and their treatments are included in Table 1. On the one hand, seven of the 8 articles studied performed histomorphometric analysis of bone regeneration carried out, which showed new bone formation, on the other hand, in 1 article only Clinical and radiographic follow-up of the patients was carried out as it was a clinical study. periodontal. Regarding the postoperative follow-up period, we observed that the longest period was 15 months [14], with an average of 7 months, the minimum period of follow-up that we observed was 3 months [15]. When analyzing the types of MSC's used in the studies we found that MSC's were used in 6 of the articles obtained from bone marrow of the iliac crest [14-19], of the remaining 2; one use MSC's extracted from the periodontal ligament of third molars [20] and the other MSC's extracted from a donor cadaver purchased commercially [21]. We observed that Alloplastic particulate bone graft was used in 4 of the articles [14,16,17,19], in 3 used Xenograft [17,18,20], Allograft was used in 1 study [21] and, in the article missing, a protocol called "injectable tissue-engineered bone" (TEB) was described to carry out bone regenerations [15,22]. In their study Smiler et al. [17] show that in order to perform bone regeneration through strategies that are based in cell engineering using MSCs, one must first understand the biology and the potential that these cells have.

Table 1: Characteristics of the included studies.

Author and year	Type of study	Number of patients	Intervention	Type of graft used	MSC's obtention site	Follow up time	MSC's obtention protocol	MSC's transportation protocol
Meijer et al. [14]	Non-randomized controled clinical trial	6 patients	Sinus lift elevation and ROG	Aloplastic	Bone marrow	15 months	Three 3 to 5 ml bone marrow aspirations 24 hours culture	Transported at room temperature in tubes with heparin to prevent coagulation
Shayesteh et al. [16]	Human Randomized controled clinical trial	6 patients	Sinus lift	Aloplastic	Bone marrow	4 months	30 ml of aspirated bone marrow Diluted in 1:3 medium (DMEM/F12), spun at 750Gx20min, washed twice ,suspended in the medium DMEM/F12	Not specified
Smiler et al. [17]	Human case Series Report	5 patientes	Sinus lift, ROG and Alveolar Ridge Preservation (ARP)	Xenograft aliplastic	Bone marrow	4 to 7 months	2-4 ml of bone marrow aspiration from de iliac crest.	not specified
McAlister et al. [21]	Human case Series Report	5 patients	Sinus lift	alograft	Bone Cadaver cels	4 months	Commercially available cells within 24 hours from its death. Cortical bone separated and processed into demineralized particles	Cryopreservation up to 5 years. It's transportation to OR was in dry ice
Rickert et al. [18]	Human Randomized controled clinical trial	12 patients	Sinus lift	Xenograft mixed with autograft or MSC's	Bone marrow	4 months	Iliac crest marrow aspiration with a 60ml syringe with heparin and 8 ml citric acid. Obtained from 52ml of non-mineralized tissue	Not specified
Yamada et al. [22]	Non-randomized Controlled clinical trial	36 patients (GBR) 39 patients (SFE) 12 patients (ARP)	GBR – Sinus lift and ARP	Injectable tissue-engineered bone. (TEB)	Bone Marrow	3 months	Novel method, "injectable tissue-engineered bone" (TEB): MSC's + PRP.	Not specified
Fa-Ming Chen et al. [20]	Human Randomized controled clinical trial	30 patients	GBR	Xenograft	Periodontal ligament	12 months	Obtained from de periodontal ligament from the patients enrolled in the study	Not specified
Katagiri et al. [19]	Human case Series Report	8 patients	GBR – Sinus lift and ARP	Aloplastic	Bought in Loza Inc.	6 months	Bought en Empresa Lonza Inc.	Cels were manteined at 37°C in a 5% CO_2.

Results of individual studies (Table 1 and 2)

Method of obtaining HMSCs: in 5 of the articles the method used to obtain MSC's were autogenous iliac crest marrow aspiration [14-18], and 1 went to through bone marrow MSCs purchased from the company Lonza Inc [19]. in one of In the studies analyzed, the obtaining of MSC's from a bone of a cadaver was observed. donor commercially [21] and finally third party MSCs were obtained molars with indication for extraction of the patients included in the study [20].

Table 2: Study results.

Author and Year	Process	Follow-up	Cell Preparation	Results	Complications
Meijer et al. [14]	Horizontal Guided Bone Regeneration and sinus lift.	15 months	Bone marrow aspiration. The expansion was carried out by seeding the MSCs in culture plates at a concentration of 100,000 cells per cm2, until osteogenic determinations was achieved, then the graft was injected (Pro-Bone 500)	Histomorphometry: in only 1 of the 6 patient they were able to see the creation of bone matrix formed by implanted MSCs.	Non complications, 1 implant was lost.
Shayesteh et al. [16]	Sinus Lift	12 months	Iliac Crest bone marrow aspiration. Diluted in medium 1:3 (DMEM/F12), centrifuged 750Gx20min, washed twice and suspended in DMEM/F12 medium. Culture CD14 cells overnight at 37C with humidity at 5% in 5 flasks. Each one contained DMEM medium + 100 U/ml penicillin, 100U/ml streptomycin and 2.5 ug/ml Amphotericin + Autologous saline.	Histomorphometry: A mean of 41% of new bone formation was seen in the 30 biopsies	No complications. Two implants were lost
Smiler et al. [17]	GBR, ARP, sinus lift	4-7 Months	Iliac Crest bone marrow aspiration.	Histomorphometry: Biopsy analysis showed between 14% to 15% new formed bone (varies according to type of associated graft)	No complications.
McAlister et al. [21]	Sinus Lift	4 Months	Cells extracted from cadaver bone. Cryopreserved and combined with allograft	Histomorphometric: 33% of vital bone	No complications.
Rickert et al. [18]	Sinus Lift	3 months	Iliac Crest bone marrow aspiration.	Histomorphometry: Biopsy analysis showed 17.7% of vital new bone, in sinuses grafted with MSCs	No complications.
Yamada et al. [22]	GBR, ARP, sinus lift	3 months	Iliac Crest bone marrow aspiration.	Histomorphometry: Biopsy analysis shows new bonr formation with a lamellar pattern and abundant vascularization	No complications.
Fa-Ming Chen et al. [20]	GBR	12 months	Periodontal ligament stem cells. Extracted from healthy teeth with indication of extraction	Radiographic assessment, No significant differences were found in bone regenerations performed in both groups	No complications.
Katagiri et al. [19]	GBR, ARP, sinus lift	6 months	MSCs purchased from Lonza Inc. Were cultured al 37C with 5% CO_2 and 95% O_2, Once 70% confluence was reached, modified alpha eagle culture medium containing antibiotics (100U/ml Penicillin G, 100U/ml Streptomycin and 0.25ug/ml Amphotericin B) was added.	Histomorphometry: In the analysis of the biopsies, new bone formation was found in all the patients	No complications.

MSCs transport protocol: we found that in many studies no they do not specify or protocolize the transport of MSCs [15-18,20]. In his studio Meijer et al. [14], mentions that the MSCs are transported in heparin tubes to avoid the coagulation, after 24 hours of culture. One of the ways to storage for commercially obtained MSCs is to cryopreserve them, they are transported to the pavilion stored in dry ice and can wait to be used up to 5 years [20]. Another way described to carry out the transport of MSC's was used by Katagiri et al. [19], where the cells are maintained and transported at 37°C in 5% CO_2 and 95% air.

Surgical Procedures: in the articles analyzed, different types of bone regenerations of the oral cavity. Sinus elevations were observed in 6 articles [14-18,20,21], ROG in 4 articles [14,15,17,20]; and in 3 articles alveolar ridge preservation [15,17,19].

Types of Grafts Used: we observed that bone graft was used in 4 of the articles Alloplastic particulate [14,16,17,19], Xenograft was used in 3 [17,18], Autograft was used in 1 [18], allograft was used in 1 study [21] and, in the missing article, A protocol called "injectable tissue-engineered bone" (TEB) was described for perform bone regeneration treatments [15,22].

Follow-up time: the longest postoperative follow-up period was 15 months [14], with an average of 7 months, the minimum follow-up period that we observed was 3 months [15].

Histomorphometric analysis: in 7 of the 8 articles there was a histomorphometric analysis [14-19,21], in the remaining article there was only radiographic and clinical analysis [20]. In In these 7 articles, neoformation of bone matrix was observed from the MSC's.

Risk of bias in studies

As shown in Table 3, randomized controlled trials that were included in this study [18,20], show a low risk of bias according to the Cochrane Collaboration [10]. For non-randomized controlled clinical cases [14-16] their risk of bias was assessed using the Newcastle-Ottawa tool [11], specified in Table 4, 2 articles being of low risk of bias [14,15] and the remainder, high risk [16]. Finally, for the 3 case report articles [17,19,21] the Joanna Briggs Institute tool [13] was used as shown in Table 5.

Table 3: Quality assessment of randomized controlled trials using the cochrane collaboration tool to asses risk of bias.

Author	Selection Bias		Notification Bias	Performance Bias	Attrition Bias	Other Bias
	Randomization	Blind on Assignment	Selective Report	Blinding of Patients and Staff	Incomplete Data Results	Other Sources of Bias
Rickert et al. [16]	+	+	? (one specific objective not resolved)	? (only deliver envelopes to randomize the type of graft and in which sinus it will be used)	+	? (it does not mention the operators that made de GBR, if it was 1 operator or several)
Fa-Ming Chen et al. [18]	+	+	+	+	+	+

Source: *+=low risk; ?=not clear; -=high risk.

Table 4: Quality assessment of non-randomized controlled clinical cases using the Newcastle-Ottawa scale.

Author	Meijer et al. [14]	Shayesteh et al. [16]	Yamada et al. [22]
Selection			
Representativeness of the clinical study	*	*	*
Selection of comparative groups	*		*
Determination of treatment scheduled	*		*
Evidence that the outcome of interest was not present at the baseline	*	*	*
Comparability			
Presence of a control group for objective analyzed	*		*
Presence of a control group for any other factor	*		
Result			
Result evaluation	*	*	*
Adecuate follow up time.	*	*	*
Acceptable loss to follow-up	*	*	
Final Newcastel-Ottawa score	7	5	7

Table 5: Quality of the evaluation of case reports using the Joanna Briggs Institute tool.

Author	Katagiri et al. [19]	McAlister et al. [21]	Smiler et al. [17]
Were the demographic characteristics of the patients described?	-	-	+
Were clearly described the history of the patients and was presented as a temporal line?	+	+	+
Was the actual clinical situation described in the presentation?	+	-	+
Diagnostic test or assessment methods were clearly described?	+	+	+
Treatment interventions or procedures were clearly described?	+	+	+
Post-interventions clinical conditions were clearly described?	-	-	-
Were adverse events or unforeseen events identified and described?	-	-	+
Case report provides takeaway lessons?	+	+	+

Source: + =yes ; ? = not clear; - = No.

Discussion

Summary of the evidence

The aim of this systematic review was to describe the success and use of MSCs for bone regenerations of the oral cavity. Analyzing the results of the 8 articles studied, where a clinical, radiographic and histomorphometric analysis was performed. With this we can confirm the success in the use of MSCs in bone regeneration. The results showed new formation of bone tissue in areas that were not in contact with the native bone tissue, observed in the histomorphometric analyzes and comparing biopsies of grafted sites prior to the installation of implants [18]. The high percentage of living bone found in morphometric studies, after a period of 4 months of recovery has elapsed, it can give us indications to create a protocol that allows us to load the implants in shorter waiting periods, when considering a bone graft with MSCs [21]. In the studies by Yamada et al. [15], they had good long-term results with the use of TEB, which showed new bone formation, using techniques with MSCsminimally invasive. All patients in this study showed improvements significant in bone volume, without side effects. Regarding the association of MSCs to bone grafting materials in surgical procedures sinus floor elevations, it is shown that biomaterials of the Xenograft type in combination with MSCs have had better results in bone formation comparing mixed xenografts with autografts, 3-4 months after surgery performed. These comparisons were made in the procedures of sinus floor elevations performing a biopsy prior to the installation of implants, thus being able to histologically compare the amount of bone formed in each group [18]. Meijer et al, Shayesteh et al and Katagiri et al. [14,16,19] conducted studies where used alloplastic grafts as a structure to seed MSCs, they achieved demonstrate that MSCs are capable of new bone formation in HA/β-matrices TCP. In the work of Chen et al. [20], he talks about regenerative therapies using PDLSC's on periodontiums with sequelae of periodontal disease. When getting good results in animals, managed to carry out these studies in humans. The results in this study showed that there is no significant difference comparing the control group that was treated only with xenograft and the tested group who used a combination of xenograft with PDLSC's. Katagiri et al. [19] in their article raises problems in the use of MSCs for tissue regenerations; Such as safety and quality in the handling of MSCs, the cost and the strict regulation by the authorities to be able to expand the use of these technologies. Despite these problems, many authors show favorable, effective and safe results in their treatments using cellular engineering.

Sites for obtaining MSCs

In the studies analyzed, different ways and places of obtaining the MSCs, the most used site to obtain MSCs was the bone marrow [14-18] in these studies were obtained using the surgical aspiration technique. Katagiri [19] instead obtained the MSCs from bone marrow, commercially. McAlister et al. [21] obtained the MSCs for their study from cadaver bone tissue. showing another commercial alternative to obtain MSCs, the cells are extracted from the table vestibular. In the work of Fa-Ming Chen et al. [20] he extracted PDLSC's from pieces healthy teeth with an indication to be extracted. From the different obtaining sites that have been exposed by the authors, there are sites such as bone marrow aspiration, in which the obtaining procedure is more complex, since it requires the work multidisciplinary by requiring the use of general anesthesia. It is a more invasive process of high morbidity that requires a longer recovery time, the authors describe from 1 month to 3 months postoperatively. If we compare it with the other collection sites, such as the periodontal ligament or extracted tooth, in which the process is with local anesthesia and the postoperative period goes from 10 to 14 days, Patients reported that they would not undergo bone marrow aspiration again [14]. Contrasting the morbidity observed in the study by Meijer et al. [14], Mcalister et al. [21] with the use of a bone allograft containing MSCs that was purchased on a commercial basis, thus avoiding the need to use a retrieval site MSCs, in addition to showing that they obtained good histomorphometric results in new bone formatio

Protocol for obtaining MSCs

Of the 5 articles [14-18] that used the medullary aspiration method for the obtaining MSC's, they did not protocolize the technique used, they only refer to the fact that They obtained from 4 mL to 30 mL of iliac crest medullary matrix. at work McAllister et al. [21] extracted MSC's from the vestibular table of a cadaver with less than 24 hours after death, the extracted bone tissue is processed into particles demineralized, for use. Katagiri et al. [19] in their work, also used MSCs obtained commercially, the difference is that this type of MSCs are from marrow origin and sent ready for use. In the last job We analyzed the cells that were obtained from the periodontal ligament (PDLSC's), were from healthy pieces with indication of extraction, where after the isolation cell specific markers of MSCs are applied, then they are differentiated and are ready to be used [20].

Types of grafts used

It was found that in most of the studies analyzed [14,16,17,19] the use of Alloplastic graft as a bone substitute to be used as scaffolding in the different feedbacks. This is in search of integrating into these bone substrates the benefits cell phones they don't have. McAllister et al. [21] used allograft as a scaffold for the integration of MSCs. In the studies by Rickert and Faming Chen et al. [18,20] used xenograft in combination with mesenchymal cells within their procedures. In the work of Yamada et al. [15] they create a mixture of concentrates cell phones with MSCs, which he calls "Tissue-engineered bone" (TEB), does not specify if you use any bone substrate as scaffolding for your interventions.

Conclusion

It is necessary to specify or unify the criteria to be able to devise a protocol of storage and transport of the MSCs, that is clear and standardized, this in benefit of clinicians and in favor of reducing errors. We believe that clinical studies omit the morbidity associated with taking MSC's. In addition to not making comparisons of this with the other known sites of Obtaining MSC's. Studies using MSCs harvested from other intraoral donor sites are lacking. With the information obtained we can say that regenerative bone therapies at those that incorporate cellular technology have good results, where he was able to see that there is new bone formation generated by the incorporated MSCs.

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