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MESTRADO INTEGRADO EM MEDICINA

# The Use of Bone Marrow Aspirate in Lumbar Spinal Fusion

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M

2023

# The Use of Bone Marrow Aspirate in Lumbar Spinal Fusion

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Maio 2023

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Porto, maio de 2023

**Acknowledgements**

Firstly, I would like to express my gratitude to my supervisor, Prof. Dr. Ricardo Rodrigues Pinto, not only for his guidance through this process but also for inspiring me with his daily work and commitment.

Likewise, I would like to thank my family and friends for always being by my side and encouraging me.

**Resumo**

**Introdução:**

A dor lombar afeta um quarto da população portuguesa, sendo a doença degenerativa da coluna vertebral a etiologia mais prevalente. Caso o tratamento conservador seja ineficaz, deve considerar-se a fusão vertebral para estabilizar a coluna e reduzir a lombalgia. No entanto, uma percentagem significativa dos doentes não obtêm a fusão desejada, levando a dor persistente e possivelmente cirurgia de revisão.

O *gold standard* desta cirurgia utiliza osso autólogo (do local de descompressão ou da crista ilíaca do doente) ou alogénico e/ou substitutos ósseos. Para potenciar a fusão óssea, estudos têm investigado métodos como a incorporação de aspirado de medula óssea, que contém células estaminais mesenquimatosas e fatores osteogénicos, como fatores de crescimento. Estas células já demonstraram ter propriedades regenerativas, tornando-se uma alterativa promissora para atingir taxas de fusão mais elevadas e taxas de pseudartrose mais baixas.

**Objetivo:**

Avaliar a biologia das células estaminais mesenquimatosas e a sua aplicação em Ortopedia, especificamente na fusão lombar. Serão identificados estudos clínicos que utilizaram aspirado da medula óssea para potenciar a fusão lombar, analisando os seus resultados clínicos, taxa de fusão e complicações.

**Métodos:**

Pesquisa bibliográfica no PubMed e análise de dados relativamente ao uso de aspirado de medula óssea ou derivados para potenciar a artrodese lombar. Avaliação dos dados relativos aos resultados clínicos deste procedimento, especialmente taxas de fusão, resultados clínicos e complicações.

**Resultados:**

Os princípios por trás da utilização de aspirado da medula óssea em Ortopedia, especialmente na cirurgia de fusão lombar, foram analisados e discutidos. Foram identificados onze estudos clínicos a avaliar a fusão lombar utilizando aspirado da medula óssea. Os estudos comparativos obtiveram taxas de fusão superiores ou semelhantes no grupo em que foi utilizado o aspirado de medula óssea, comparativamente aos grupos em que não foi utilizado. Nos estudos não comparativos, todos obtiveram boas taxas de fusão, à exceção de um. Todos os que avaliaram os resultados clínicos obtiveram resultados satisfatórios, sem um aumento aparente de complicações associado ao uso de aspirado de medula óssea.

**Conclusão:**

Embora sejam necessários mais estudos, a literatura existente sugere que ao adicionar aspirado de medula óssea (concentrado) a um autoenxerto ou aloenxerto se obtêm melhores resultados, ou pelos menos igualmente satisfatórios, comparativamente à ausência do aspirado, sem aumento aparente da taxa de complicações associada a este procedimento.

**Palavras-Chave:**

Fusão espinal; vertebras lombares; transplante autólogo; transplante ósseo; transplante de medula óssea; substitutos ósseos; transplante de células estaminais mesenquimatosas; proteína morfogenética óssea 2.

**Abstract**

**Introduction:**

Low back pain affects a quarter of the Portuguese population, with degenerative spinal disorders being the most prevalent aetiology. If conservative treatment is ineffective, spinal fusion should be considered to stabilise the spine and reduce low back pain. However, a significant percentage of patients do not achieve the desired fusion, leading to persistent pain and possibly revision surgery.

The gold standard for this surgery uses autologous (from the patient's decompression site or iliac crest) or allogenic bone and/or bone substitutes. To potentiate bone fusion, studies have investigated methods such as the incorporation of bone marrow aspirate, which contains mesenchymal stem cells and osteogenic factors, such as growth factors. These cells have already been shown to have regenerative properties, making them a promising alternative to achieve higher fusion rates and lower pseudoarthrosis rates.

**Objective:**

Evaluate the biology of mesenchymal stem cells and their application in Orthopaedics, specifically in lumbar fusion. Clinical studies that have used bone marrow aspirate to enhance lumbar fusion will be identified, analysing their clinical outcomes, fusion rate, and complications.

**Methods**:

Bibliographic search in PubMed and data analysis regarding the use of bone marrow aspirate or derivates to promote lumbar arthrodesis. Evaluation of data regarding the clinical results of this procedure, especially fusion rates, clinical results, and complications.

**Results**:

The principles behind the use of bone marrow aspirate in Orthopaedics, especially in lumbar fusion surgery, were analysed and discussed. Eleven clinical studies evaluating lumbar fusion using bone marrow aspirate were identified. The comparative studies obtained higher or similar fusion rates in the group in which bone marrow aspirate was used, compared to the groups in which it was not used. In the non-comparative studies, all but one achieved good fusion rates. All those that evaluated clinical outcomes obtained satisfactory results, without an apparent increase in complications associated with the use of bone marrow aspirate.

**Conclusion**:

Although further studies are needed, the existing literature suggests that adding bone marrow aspirate (concentrate) to an autograft or allograft achieves better, or at least equally satisfactory, results compared to the absence of aspirate, with no apparent increase in the complication rate associated with this procedure.

**Keywords:**

Spinal Fusion; Lumbar Vertebrae; Transplantation, Autologous; Bone Transplantation; Bone Marrow Transplantation; Bone Substitutes; Mesenchymal Stem Cell Transplantation; Bone Morphogenetic Protein 2.

**List of abbreviations**

b-TCP - beta-tricalcium phosphate
BCP - biphasic calcium phosphate
BM - bone marrow
BMA - bone marrow aspirate
BMAC - bone marrow aspirate concentrate
BMP - bone morphogenetic proteins
BSF - Brantigan, Steffee, Fraser
CT - computerised tomography
DBM - demineralised bone matrix
fig. - figure
IB - interbody
LBOS - low back outcome score
MSC - mesenchymal stem cells
No - number
ODI - Oswestry disability index
PDGF - platelet-derived growth factors
PLF - posterior lumbar fusion
PLIF - posterior lumbar interbody fusion
rhBMP-2 - recombinant human bone morphogenetic protein-2
TFG-β - transforming growth factor-β
TLIF - transforaminal lumbar interbody fusion
VAS - visual analogue scale
XR - X-ray

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## Introduction

One of the most common health problems that causes considerable disability, use of health services and work absenteeism is low back pain. In Portugal, low back pain affects 26.4% of the population, making it the most prevalent rheumatic and musculoskeletal disease. This not only has high costs for society but also dramatically impacts disability, perceived health, and quality of life for the individual. There are many causes for low back pain, and the most prevalent organic ones are degenerative spinal disorders, such as degenerative disc disease, spondylolisthesis, degenerative scoliosis, and recurrent disc herniations. Initially, conservative measures should be attempted. These include pain medication, intensive exercise therapy, or physiotherapy. [1] In case of failure of these measures, if neurologic or structural components of the spine are compromised, operative intervention should be considered, particularly spinal fusion. [2]

Lumbar fusion, or arthrodesis, is the procedure where two or more vertebrae are fused to achieve spinal stability. [3] This process intends to eliminate painful movement of the vertebrae by making a rigid fixation, creating definitive lumbar fusion. [2] This technique has many indications, including obvious or suspected instability of the affected spine segments, such as in degenerative diseases, trauma, tumours, and spondylodiscitis. [3]

Although the clinical practice has shown the achievement of good long-term results, lumbar fusions have been associated with some complications, [3] such as failure of bone formation, remodelling or union, resulting in pseudoarthrosis. [4] The definition of pseudoarthrosis is the absence of solid bony fusion more than six months after surgery, occurring at least in 15% of primary lumbar fusions, [2] an extremely high incidence for a surgery that is so widely performed. [5] This often leads to persistent back or radicular pain because of the continuous movement. If this is the case, recurrent or persistent pain may be determinant when deciding whether to perform spinal revision surgery. Pseudoarthrosis can also be asymptomatic or associated with atypical symptoms, [2] and may be associated with some risk factors, such as smoking, steroid use, diabetes, and younger age. [6]

In the past, the posterior or posterolateral fusion was performed by attaching autologous iliac crest cancellous bone to the transverse processes and facet joints. Currently, lumbar fusion is mostly performed using a pedicle-screw-rod system (internal fixator) and autologous or allogenic bone and/or bone substitutes. [7] Intervertebral disc spacers may be inserted into the intervertebral disc spaces to achieve better ventral support, better correction of sagittal alignment and a higher fusion rate. These are usually industrially manufactured implants, known as cages. [3]

Furthermore, to achieve spondylodesis, the deposition of bone and/or bone substitutes is essential. Autologous bone is the gold standard for fusion, and it can be obtained from the decompression or bone harvested from the anterior or posterior iliac crest, depending on the approach and local availability. Nevertheless, harvesting autologous iliac crest bone may be associated with higher morbidity and complications such as haematomas, fractures, infections, hypertrophic scars and, above all, pain and dysaesthesia at the donor site. To avoid this issue, many surgeons have switched to using the local bone from the decompression site for short fusions. Allogenic bone is also being increasingly used, providing great osteoconductive potential and being available in almost unlimited quantities, even though it has a low osteoinductive potential. [3] An example of an allograft is demineralised bone matrix that can be used as an extender together with the autograft. [8] To increase the osteoinductive potential of the demineralised bone matrix, recombinant human BMP-2 (rhBMP-2) can be added. [9]

Methods to promote fusion may be necessary to physically manipulate the intended site, promoting vascularisation, osteoinduction, osteoconduction and osteogenic potential. When the osteogenic response integrates and replaces the grafted bone with a newly formed matrix comparably rigid to the host bone, union is achieved. When lamellar bone along new lines of stress is able to carry physiological loads without suffering an injury, fusion is considered present. [4]

Methods such as adding bioactive growth factors to the autografts or allografts have been studied to potentiate bone fusion. An example of this is the addition of bone marrow aspirate (BMA), which contains not only mesenchymal stem cells (MSC) but also other osteogenic factors such as platelets and growth factors. These cells have been demonstrated to hold benefits when it comes to tissue regeneration, including the musculoskeletal, by providing osteoinductive potential. Although recent, this technique has been used in the Orthopaedic field, particularly in lumbar fusion. [10]

The main purposes of this study were to:

1) Describe the biology behind the use of BMA and its applicability in Orthopaedics, specifically in lumbar fusion;
2) Analyse current evidence from available clinical studies to understand if BMA may be a good alternative or adjunct to current fusion methods in spinal surgery.

**Methods**

A comprehensive literature review was performed to analyse current evidence on the use of BMA or its derivates in the promotion of lumbar arthrodesis/fusion.

The articles were searched in the PubMed database, with no restrictions concerning the country or publication date. The search was based on the combination of the following keywords: Spinal Fusion; Lumbar Vertebrae; Transplantation, Autologous; Bone Transplantation; Bone Marrow Transplantation; Bone Substitutes; Mesenchymal Stem Cell Transplantation; Bone Morphogenetic Protein 2.

Data on the biological basis for this procedure and on similar applications in the Orthopaedic field was collected and analysed. Clinical studies in which BMA or concentrate has been used were collected. The following data were collected and analysed from each study: clinical outcomes, particularly regarding the fusion rate, side effects and complications.

## Results

### Bone marrow aspirate in spinal fusion:

Many methods to overcome the problem that is the significant incidence of non-union have been investigated. One of them is the utilisation of mesenchymal stem cells to increase fusion rates and decrease complications. [2]

Autologous bone grafts have viable stem cells and progenitors with osteogenic potential. However, due to the harvesting and implantation process, only few survive, having to thrive through metabolic competition with other cells. This has led to trials where autologous bone marrow alone or combined with supplement bone graft is used at the fusion site to evaluate the fusion rate when compared to autograft alone. [4] Therefore, as studies in regenerative medicine progress, there has been increasing interest in bone marrow-derived mesenchymal stem cells. [11]

The human bone marrow is a source of MSCs, growth factors and cytokines that have anti-inflammatory and regenerative properties. [12] It is located in the centre of long and axial bones and is a semisolid tissue composed of molecular and cellular components. These components can be separated into nonhematopoietic, such as osteoblasts and adipocytes, and hematopoietic, such as neutrophils and osteoclasts. In addition, there are also stem cells: hematopoietic and mesenchymal. [13]

Adult stem cells can be divided into hematopoietic stem cells, which derive from the blood and are able to differentiate into blood cells, and mesenchymal stem cells, which are derived from other tissue sources. [14] Adult MSCs can be collected from the bone marrow, peripheral blood, adipose tissue, and dental pulp. In addition, there are also neonatal tissue-derived MSC, also called embryonic, that are obtained from the umbilical cord, placenta, and amnion. [15] MSCs have advantages and disadvantages depending on the source. Embryonic stem cells have true pluripotent properties, but on the other hand, there are issues regarding their regulation. *In vitro*, multipotent adult MSCs can express different characteristics of multiple tissues, such as bone, cartilage, adipose tissue, and skeletal muscle. [16]

MSCs are multipotent stem cells that can self-renew and differentiate into other specialised cell lines. [14] Although they cannot differentiate into different tissues *in vivo*, they secrete trophic and immunomodulatory factors that create a regenerative microenvironment, instructing tissue-specific progenitor cells to regenerate the injured tissue, being this the main reason for their utility in the field of Orthopaedics and other areas of medicine. [15]

MSCs increase the production of interleukin 10 and inhibit interferon-gamma and tumour necrosis factor-alpha, promoting the lymphocyte T helper response. Furthermore, they also alter antigen-presenting maturation and inhibit T-cell recognition and expansion. [15] A heterogenous population of stem and progenitor cells is present in every tissue and provides the capacity to proliferate and promote the formation of new connective tissue. [17] MSCs (fig. 1) are, therefore, optimal for tissue regeneration, as they have the beneficial immunoregulatory capacity to relieve abnormal immune responses, produce growth factors with paracrine or autocrine functions, and differentiate into target cells. [18]

Another limitation of the autologous cancellous bone is that the concentration and prevalence of the connective tissue progenitors in this tissue source is limited, highlighting even further the advantages of the BMA. This aspirate is associated with lesser morbidity since it can be collected via a percutaneous approach and processed intraoperatively. [17] The processing consists of increasing the concentration of the connective tissue progenitors by eliminating the blood components that dilute them (such as plasma and red cell mass) with a centrifugation technique that promotes density separation. [19] In this way, the concentration of cells produces an enriched cellular composite graft, improving graft's efficacy. [20] Nucleated cells whose contribution to the graft is detrimental can also be removed by selective retention or magnetic separation, removing cells that can induce inflammation or release inhibitory factors with their death at the receptor site. They can also compete with the connective tissue progenitors by consuming the oxygen available at the transplantation site. [17]

**Applicability in the field of Orthopaedics:**

For MSCs to be used in the field of Orthopaedics, they must be isolated, expanded *in vitro* and later implanted into the patient. This has been used in many studies of therapy for bone defects based on MSCs, describing several clinical applications of MSCs in bone reconstruction, such as in dentistry for alveolar cleft defects, jaw defects reconstruction and maxillary sinus augmentation, and in Orthopaedics in bone defects or in cases of non-union. [18]

Repairing cartilage defects is another substantial challenge for orthopaedic surgeons because of the cartilage's avascular nature and limited ability to repair itself. MSCs can differentiate into chondrocytes, offering a new strategy for repairing damaged cartilage. Cartilage reconstruction demands a combination of multiple stimulating factors; the co-culture of chondrocytes and MSCs would accomplish superior results than the application of MSCs alone. In chronic knee osteoarthritis, the transplantation of expanded autologous bone marrow stem cells promoted good-quality cartilage, despite no significant clinical improvement. There are also studies of the

injection of allogeneic MSCs into joints, relieving some of the symptoms, even though the repair of the damaged cartilage was not always evident. [18]

There are also studies on the use of MSCs for regenerating musculoskeletal tissues, such as tendons and ligaments, meniscus, and intervertebral discs, however better evidence of their effectiveness in these settings still needs to be improved. As the population ages, and given the high prevalence of disc degeneration-related conditions, MSCs may be promising candidates for their regeneration. Some clinical studies even demonstrate that it has various advantages and a better prognosis than the current gold-standard treatments. [15, 18, 21, 22]

Regarding the use of MSCs, studies of the rebuilding of the central and peripheral nervous system, restoration of the myocardium, regeneration of the liver and reconstruction of the cornea, trachea, and skin are also taking place. [18]

However, there are also some potential risks when implanting MSCs, as MCSs have pro-angiogenic functions; may lead to fibrosis, for example, if they differentiate into myofibroblasts; and proinflammation, due to the immunosuppressive effects that the MSCs have when exposed to elevated levels of proinflammatory cytokines. [18]

An alternative method is the use of BMA, a method that has become popular in Orthopaedics at the end of the last century and the beginning of the present. This orthobiologic product has been used in many treatments of some musculoskeletal disorders, such as non-union, bone defects, arthritis, ligament tears, and osteonecrosis of the femoral head. [13, 17, 23]

BMA contains MSCs, hematopoietic stem cells, endothelial progenitor cells, among others, and growth factors such as platelet-derived growth factors (PDGF), bone morphogenetic proteins (BMP), transforming growth factor-β (TFG-β), interleukin-8, interleukin-1 receptor antagonist, and vascular endothelial growth factor. BMA is considered a safe procedure with a low complication rate and can be harvested from different sites, such as the posterior or anterior iliac crest, the calcaneus, or the proximal or distal tibia. The iliac crest is the most frequent aspiration source since it offers a significant amount of material and has more osteoblastic progenitors than the other two sites. [13]

Different harvesting techniques lead to different results regarding the amount of progenitor cells. [13] The volume aspirated should be small, around 1-2mL at each site, to obtain a total of around 90-120 mL, since some studies demonstrate that by increasing the aspirate volume, the volume of peripheral blood also increases, contributing to the dilution of the sample. That is why harvesting at most 4mL from each site is recommended. [23] It is also recommended to modify

the aspiration site by 5 to 10 mm (fig. 2) to optimise the yield of connective tissue progenitors [17] and to aspirate subcortically since it is where the stem cell progenitors are mostly located. [13]

As the sample is obtained, the aspirate tends to coagulate rapidly because of the present coagulation factors, platelets, and megakaryocytes. Therefore, there are anticoagulant agents inside the syringes, such as heparin. However, there is some discordance concerning this part of the procedure because when coagulation occurs, there is platelet degranulation that consequently releases osteotropic cytokines and growth factors at the injured site, which might be beneficial. Some contraindications to this procedure include anaemia, active hematologic neoplasm, systemic infection, and patients who cannot be adequately positioned for the procedure. [13]

MSCs represent only a small fraction of the nucleated cells in the bone marrow (BM), being variable among different articles, such as 0.001-0.01% according to Dan et al. [24], and 0.01-0.02% according to Brozovich et al. [25] To address this concern, there have been protocols developed to concentrate the BMA, maximising the procedure's efficacy. Doing so can improve the recuperation of nucleated cells from the BMA and decrease the number of non-nucleated cells, such as red blood cells. This technique is up-and-coming since it is a rich source of MSCs and growth factors, such as PDGF and TFG-β. [12] The bone marrow aspirate concentrate (BMAC) contains MSCs and nucleated cells that might have paracrine effects by the delivery of growth factors and cytokines into the site and direct endogenous bone repair. [26] To obtain the concentrate, the BMA must undergo a density separation centrifuge, ending up with more marrow-derived cells. Since it is a process that includes various stages, some variations may be present, leading to differences in the BMAC composition. Depending on the processing method, growth factors, platelets, and cytokines may also differ between protocols and studies. For this reason, it is challenging to compare how effective the BMAC is among individual studies. [27]

After obtaining the BMA, to obtain a concentrate, BMA is processed intraoperatively by using a dedicated centrifuge for 15 minutes. This separates the sample in leukocytes with platelets and erythrocyte fractions. The leukocytes, together with the MSCs and growth factors, can be concentrated approximately ten times. Using sterile pipettes, the isolated buffy coat is collected and mixed with the autologous bone or biomaterial, which is then deposited on each side of the decorticated spine. [10] However, even though the use of these cells is auspicious, there still needs to be a systematic optimisation of this method in clinical practice. [17]

**Applicability in the spine surgery field:**

Lumbar fusion has been performed for many years with either local bone from decompression or iliac crest bone graft, as autograft is considered the gold standard for this procedure. However, as aforementioned, non-union rates are as high as 15%; therefore, other methods have been the target of many studies. These aim to have fewer comorbidities related to the harvesting of the iliac crest and a better or, at least, similar fusion rate. One alternative is using BMA (concentrated in some studies) combined with autologous bone, such as the iliac crest or the bone obtained from the decompression site, or allografts such as hydroxyapatite, beta-tricalcium phosphate (b-TCP), and demineralised bone matrix. [28]

Autograft has the three necessary capacities for a successful fusion: osteoconduction, osteoinduction, and osteogenesis. Therefore, the ideal bone graft substitute should have these as well. The graft substitutes, such as hydroxyapatite, present osteoconductive properties, providing a scaffold that enables osteogenesis. The demineralised bone marrow provides osteoinductive properties. The BMAC would therefore add to the insufficient capacity to produce osteogenic cells. [29]

The literature search identified eleven clinical studies using BMA or BMAC to promote spinal fusion (Table I). In nine studies [10, 24, 28-34], posterolateral fusion (PLF) was performed, with the addition of transforaminal interbody fusion to PLF in two [29, 34] of them. In three [31, 35, 36], a posterior lumbar interbody fusion (PLIF) was performed. The surgeries were performed on only one level in two studies [32, 35]; in the remaining, they were performed in one to three levels. Also, two [29, 34] studies were retrospective, and the other nine were prospective, some being randomised [10, 28, 32] and others not. In all studies, the bone marrow was aspirated from the iliac crest, in some anteriorly and others posteriorly, always with an aspiration of small samples from different sites to avoid haemodilution. Furthermore, in the studies where the iliac crest was used to obtain BMA and autograft [28, 30-32, 35], different iliac crests were used, one to mix with the BMA and the other as the autograft. The BMA was afterwards concentrated in 5 [10, 24, 28, 29, 34] studies. All surgeries were instrumented with pedicle screws.

The surgeries were performed mainly due to similar pathologies. In eight studies[10, 24, 28, 29, 32-36], there was a degenerative disease of the lumbar spine, including degenerative disc disease, lumbar spinal stenosis, degenerative spondylolisthesis and lumbar instability. Bansal et al. [30] performed the surgeries to patients with unstable dorsal and lumbar spinal fractures, and Gan et al. [24] performed the surgeries to patients with degenerative disease of the lumbar spine as well as unstable thoracolumbar fracture. Niu et al. [32] performed the surgeries for lumbar spinal stenosis

and degenerative or spondylolytic spondylolisthesis or segmental instability. Finally, Neen et al. [31] did not specify the patients' pathologies.

Some studies used a comparison group (Table II) to assess the results between the presence and absence of the BMA, concentrated or not. The comparison group was either another group of different patients, or the same patients in which different materials were used on each side of the spine.

Hart et al. [10] compared the use of spongious allograft chips alone in 40 patients (group I) with the use of the same material with the addition of BMA concentrate in other 40 patients (group II). Bansal et al. [30] compared the results between the use of hydroxyapatite plus beta-tricalcium phosphate with BMA on one side (side I) of the spine in 30 patients and the use of iliac crest autograft on the other side (side II) in the same patients. Neen et al. [31] compared 50 patients (group I) who were submitted to surgery with BMA with Healos®, a type I collagen/hydroxyapatite matrix, and 50 other patients (group II) in which iliac crest autograft was used. Niu et al. [32] submitted 43 patients to a PLF in which on one side of the spine, the test side, laminectomy bone chips mixed with BMA were used in 21 patients (group 1) or calcium sulphate pellets soaked in BMA in 22 patients (group 2) and on the other side, the control side, iliac crest autograft was used. Johnson [28] evaluated 24 patients with a PLF with autologous BMAC plus allograft cancellous bone on one side of the spine and, on the other side, iliac crest autograft. Moro-Barrero et al. [33] had 35 patients undergoing PLF with the use of autologous bone graft from decompression on one side of the spine (side 1) and biphasic calcium phosphate (BCP) ceramic with BMA on the other (side 2). Kitchel et al. [35] had 25 patients who underwent a PLIF performed with a mineralised collagen bone graft soaked with BMA on one side of the spine and iliac crest autograft on the other.

Ajiboye et al., Gan et al., and Thaler et al. [24, 29, 34, 36] had no comparison group in their studies (Table III), having applied in all patients BMA concentrate with allograft plus demineralised bone matrix (DBM) in two of them [29, 34], and BMA (concentrated in Gan's et al. [24]) with beta-tricalcium phosphate in the other two [24, 36].

All patients from these selected studies were evaluated with both X-ray and computerised tomography (CT) scans, except in two studies, Neen et al. [31] and Ajiboye et al. [29], in which only X-rays were performed at 12 and 24 months and only at 12 months, respectively. In the remaining studies, CT scans and X-rays were obtained at one and/or two years postoperative (with some studies having even more events). A few of the studies used some classifications to assess the radiographic fusion rate, such as a 3 grade system defined by the Brantigan, Steffee, Fraser (BSF) [34]

[29], in which BSF-3 is considered a radiographic fusion and the Lenke classification [34] [29], in which Lenke A represents the presence of definitely solid with bilateral trabeculated stout fusion mass.

In addition, some of the studies also evaluated the clinical outcomes (Table VI) with modified Odom's criteria (excellent, good, satisfactory, and poor outcomes) [29, 34]; an analogue scale of function evaluation [36]; the Oswestry Disability Index (ODI) [35, 36]; Low Back Outcome Score (LBOS: excellent, good, fair, and poor) [31]; a Patient Satisfaction Score, which has in account a pain relief score, whether the patient would repeat the surgery if needed, if they would recommend it, and the satisfaction with the process of surgical care[31]; and the Prolo Economic Score (after Schnee). [31]

In table IV, the fusion scores of studies with comparison group are compared. Hart et al. [10] and Bansal et al. [30] had a superior fusion score in the group where BMA/BMAC was used. In contrast, Neen et al. [31] had lower fusion scores in the BMA group in radiological evaluation; however, they had similar clinical outcomes in both groups. When comparing the side of the spine in which BMA was added, Niu et al. [32] had a superior fusion score (85.5%) in the laminectomy bone chips with BMA group and inferior (45.5%) in the calcium sulphate pellets with BMA group. The group in which there was no BMA added had similar (90.5% and 90.9%, respectively) fusion rates independently of the material used on the other side of the spine. Furthermore, Johnson [28], Moro-Barrero et al. [33], and Kitchel et al. [35] all found similar results between the two comparing groups.

Ajiboye et al. [34], Ajiboye et al. [29], and Gan et al. [24] did not have a comparison group (Table V); however, they considered that good outcomes were achieved. In contrast, Thaler et al. [36], also without a comparison group, only had a solid fusion in 26.67% of the levels. Nonetheless, the beta-tricalcium phosphate yielded good clinical outcomes one year after the surgery.

All studies reported some complications associated with the surgery except for one [28, 35], as shown in Table VII. Different complications were listed, and in some studies, some patients required revision surgery [10, 33, 34, 36]. In Hart's et al. [10] study, each group had two patients that developed a hematoma following revision surgery and were submitted to drainage in the first week postoperatively. In Bansal's et al. [30] study, seven patients had complications, all of them in the autologous bone graft side of the spine. One with lucency and breakage of the distal pedicle screw, five with donor site pain, and one with sensory loss over the lateral aspect of the thigh. In Neen's et al. [31] study, there were no complications in the Healos® with BMA group, whereas in the iliac crest autograft group, 14% of the patients had persisting donor site pain. In Moro-Barrero's et al. [33] study, one patient with pseudoarthrosis required reoperation, allowing the obtainment of biopsies with evidence of compact bone tissue on the BMA with biphasic calcium phosphate. In Kitchel's et

al. [35], although there were no reported complications or complaints of BMA site aspiration pain, four patients had a non-union, and seven referred donor graft site pain at 24 months.

Regarding the non-comparative studies, in Ajiboye's et al. [34] study, one patient developed a seroma, one had clinical pseudarthrosis, and five, including these previous two, had to undergo surgery again. In Ajiboye's et al. [29] study, there were some complications, such as hardware bursitis in seven patients, postoperative infection in two, and clinical pseudoarthrosis in two. In Gan's et al. [24] study, only four patients had some exudation or moderate swelling of the wounds and recovered with conservative treatment. In Thaler's et al. [36] study, five patients developed some complications, such as transient paresis of L5, dura leakage, migration of the cage, and seroma, and one patient required revision surgery.

Hence, Hart et al. [10] and Bansal et al. [30] concluded that using BMA, concentrated in Hart's et al., was preferable to the comparing group in its absence. Hart et al. [10] concentrated the BMA in the operating room by centrifuging it for 15 minutes, leading to a concentration of 10 times of MCSs. The concentrate was afterwards mixed with the spongious allograft chips. One- and two-years postoperatively, respectively, evaluated with X-ray, there were between 0% and 10% fusion cases in the spongious allograft chips group (I) in comparison with 15% and 35% in the spongious allograft chips with BMAC group (II). Furthermore, when evaluated by a CT scan at two years postoperatively, group I achieved fusion in 40% of the cases, while group II reached 80%, a significant difference. Also, all single-level fusions achieved solid fusion, while in multilevel, only 63,6% had the same result.

Bansal et al. [30] used beta-tricalcium phosphate, which is resorbed by a biological route, leaving newly produced bone tissue, and hydroxyapatite, which is typically thought to be very marginally resorbable. When combined, in this case, with a 1:9 ratio, respectively, these provide a scaffold for the formation and remodelling of bone over time. It was observed that at three months post-surgery, 100% of both sides of the spine already had bridging bone mass when evaluated by X-ray, which became more prominent at six months, getting to one year with a good fused mass in 30/30 in side I (side with the BMA) and 29/30 in side II (autograft side). One patient ended up with a poor fusion mass on side II, with lucencies and implant failure.

In the study by Ajiboye et al. [34] the surgeries were performed on 31 elderly (> 65 years) patients, with an average age of 71.5 years and an overall solid fusion rate of 83,9% was found one year after surgery (evaluated using X-ray and CT scan). The aim of the study objective was to define the outcomes of adding BMA concentrate to DBM since it has been established that the MSC population in bone marrow decreases with age. The bone marrow was aspirated and then twice

run through a graft chamber with the DBM and allograft chips, with a device that selectively retains the cells. Fusion rates in PLF and interbody (IB) were also compared. In PLF, 83,3% and 85,7% were obtained in single and multilevel fusions, respectively, and in IB, 95,8% and 100%, respectively. Clinically, the outcomes were distributed according to a four-grade system named Odom's criteria. 83,9% of the patients achieved 'excellent' or 'good' outcomes at one-year postoperative, and 6.5% achieved 'poor' outcomes. Thus, prosperous fusion rates, clinical outcomes, and a low rate of complications were reported.

Ajiboye et al. [29] submitted 80 patients to a PLF with TLIF with BMA concentrate, DBM and allograft chips. The BMA was processed the same way as in Ajiboye's et al. [34] study. A solid fusion was obtained in 81,3% of the patients at one-year post-surgery, evaluated with X-ray. According to Odom's criteria, 'excellent' or good' outcomes at one-year were reported in 72,5% of the patients and 'poor' in 13,7%. This way, a successful fusion was achieved, with excellent functional outcomes and minor complications.

Gan et al. [24] analysed 41 patients who were submitted to a PLF with BMA concentrate with beta-tricalcium phosphate, obtaining good spinal fusion results in 95,1% of patients at 34,5 months. In this procedure, the MSCs were enriched perioperatively and combined with b-TCP with negative pressure and a short-time incubation while the operation took place. Bony fusion in the interlaminar or intertransverse processes became apparent in the X-rays performed at six months. Upbeat bony fusion could be observed at 12 months with an X-ray and CT scan.

In the study by Thaler et al. [36], 34 patients, with a total of 45 levels, underwent a PLIF with BMA with b-TCP and were evaluated one year postoperatively with X-ray and CT scan and clinically. Solid fusion was identified in 26,67% of the total levels, and inadequate fusion in 38,63% of levels, a high rate of pseudoarthrosis, which, however, did not reflect in the clinical results, which were reported to be good.

Neen et al. [31] applied the BMA to each strip of Healos® and left it soaking for 20 minutes. Each group had 15 patients that underwent PLF, 13 PLIF and 22 360º front and back fusion. They were evaluated radiographically at 12 and 24 months postoperatively and clinically at 24 months postoperatively. Radiologically, the fusion rate was lower in group I (Healos® with BMA), with 84%, while group II (iliac crest autograft) had a fusion rate of 94%. However, most of the difference accounted for the inferior performance of the Healos® with BMA when utilised as an interbody cage filler. If the results of the interbody fusion are deducted from the study, group I had no poorer outcomes than group II. Furthermore, the clinical results were similar between the two groups.

Regarding Niu's et al. [32] study, in group 1 (laminectomy bone chips), the side with the addition of BMA had 85,7% of fusion and the control one 90,5%, and in group 2 (calcium sulphate pellets), the side with the addition of BMA had 45,5% of fusion and the control one 90,9%. Thus, the autograft achieved the expected high fusion rates, and laminectomy bone with BMA performed just as well. However, the calcium sulphate pellets soaked in BMA had significantly lower results than the control side.

Johnson [28] concentrated the BMA in the operating room, leading to a concentration of 3 to 4 times of all cellular elements, and afterwards mixed it with crushed cancellous allograft, recombinant thrombin and calcium chloride. The patients were followed radiographically for one year, presenting no statistical difference in fusion scores between the two sides of the spine.

Moro-Barrero et al. [33] mixed the BMA with the biphasic calcium phosphate in a sterile bowl, leaving it soaking for 10 minutes. On side 1 (autologous bone graft from decompression), at 24 months, there was a good fusion in 31/35 and 28/35 of the patients, evaluated with X-ray and CT scan, respectively. On side 2 (BCP ceramic with BMA), there was a good fusion in 31/35 patients at 24 months, either in X-ray or CT scan, therefore no statistically substantial difference between the two sides.

The radiologic results of Kitchel et al. [35] at 12 and 24 months were similar, with a fusion rate of 84% on the autologous side and 80% on the bone graft substitute side. Clinically, the outcomes were not different between the 21 patients with lumbar fusion and the four patients with a non-union. Also, the disability and pain scores demonstrated significant improvements, and there were no peri or postoperative complications.

**Discussion**

Non-union remains a significant orthopaedic issue. This has led to the development of many studies to find better alternatives other than the current gold standard, or that may complement it. The use of MSCs obtained from bone marrow is a significant subject of interest since they are believed to own multipotent plasticity. As such, they are able to differentiate into various cell lines, including bone, cartilage, tendon, nerve, and muscle. Furthermore, the concentration of the BMA has also shown to have potential benefits as some cell lines are obtained in higher concentrations.[26]

In this study, several conclusions can be made regarding this matter. Firstly, when it comes to the comparative studies, Hart et al. [10] and Bansal et al. [30] concluded that the group in which BMA/BMAC was used had higher fusion rates than the comparing group in its absence, therefore being a promising alternative to the current gold standard. In addition, Hart et al. [10] considered that the significant difference between the two groups, in which BMAC with the allograft achieved much superior results, could be explained by the fact that the spongious allograft chips that were used alone in the comparison group lack the osteoinductive potential and osteogenic cells.

Neen et al. [31] reported radiologically lower fusion rates in the BMA group. However, they observed that most of the difference in the results between the two groups accounts for the inferior performance of the Healos® with BMA when utilised as an interbody cage filler. If the results of the interbody fusion were deducted from the study, the group where Healos® with BMA was used would not have had poorer outcomes than the other one. Furthermore, the clinical results were similar between the two groups. Niu et al. [32] concluded that the autograft achieved the expected high fusion rates, and laminectomy bone with BMA performed just as well. However, the calcium sulphate pellets soaked in BMA had significantly lower results than the control side. This result must be, therefore, carefully considered since the lower fusion rate might be due to the calcium sulphate pellets used. Johnson [28], Moro-Barrero et al. [33], and Kitchel et al. [35] found similar results between the two comparative groups. Furthermore, Kitchel et al. [35] also demonstrated significant improvements in disability and pain scores overall.

In the studies in which no comparison group was used, three [24, 29, 34] of them reported adequate fusion rates with the utilisation of a graft plus the BMAC. The remaining one, Thaler et al. [36], recommends against using b-TCP with BMA as a substitute for the gold standard technique. However, the fusion rates did not reflect the clinical outcomes, in which there was a positive evolution. Additionally, according to the manufacturer of the b-TCP, bone transformation should occur in 6 to 18 months, and in this study, the follow-up time was only 12 months. That being said, it is not possible to know if there was an adequate fusion between 12 and 18 months. Also, Gan et

al. [24] used the same materials (b-TCP with BMAC), and the fusion was evaluated later than in Thaler's et al. [36], at 34,5 months, with adequate fusion rates. This might support the fact that Thaler's et al. [36] evaluation might have been too early.

However, Hart et al. [10] study was the only one in which the only difference between the comparative groups was the addition of BMA. In the other comparative studies, there were more variations other than adding the BMA/BMAC, since the bone graft used differed between the two groups. In the control group, iliac crest autograft was used, except for Moro-Barrero's et al. [33] study, in which autologous bone from the decompression site was used; and in the test group, a different graft from the control was used, such as hydroxyapatite with beta-tricalcium phosphate [30] or Healos® [31], for example. This makes it more challenging to evaluate the benefits of adding BMA/BMAC since more variables my bias the study findings.

Also, in some of the comparative studies, the different materials with the addition or not of the BMA/BMAC were applied in the same patient but on different sides of the spine [28, 30, 32, 33, 35]. This also makes it more challenging to evaluate since it is not possible to know if the results of one side of the spine influence the opposite side, enhancing or impairing its results. However, in Niu et al. [32] study, iliac crest autograft was used on one side of the spine and on the other side, laminectomy bone chips (group 1) or calcium sulphate pellets (group 2), both with BMA, were used. In group 1, the fusion rates were similar between the two sides, however in group 2, the side of the iliac crest autograft, had a much higher fusion rate than the calcium sulphate side. This leads to the conclusion that the autograft side did not influence (at least significantly) the other side. Further conclusions cannot be made in the remaining studies since both sides of the spine achieved similar fusion rates.

Furthermore, in the non-comparative studies [24, 29, 34, 36], some complications were difficult to assess and had limited generalizability of their results. This is because it is not possible to know if they were due to the surgery itself, the allograft used or even the use of BMA/BMAC since there was no comparing group to evaluate if the same complications would arise. Some of these complications, such as dural leaks or cage migration, are very likely to result of the surgical technique rather than from the use or not of BMA/BMAC.

In the comparative studies, specifically in Hart's et al. [10] because the only difference between the groups was the addition of BMA, both groups had similar rates of complications; however, in Neen's et al. [31], there were no complications in the Healos® with BMA group, while in the iliac autograft group, there is persisting donor site pain in 14% of the patients. This is also true in Bansal's et al. [30] study, where the group in which autologous bone was harvested presented

complications such as donor site pain and sensory loss over the lateral thigh. This supports the fact that using BMA with a bone substitute may be a good alternative to reduce the morbidity associated with the harvesting of the bone from the iliac crest. The remaining comparative studies did not specify in which group the complications arose.

Moreover, in Johnson [28], Bansal et al. [30], Kitchel et al. [35], Moro-Barrero et al. [33], Ajiboye et al. [34], and Thaler's et al. [36] studies, the sample size was relatively small (35 patients or less). Also, Thaler's et al. [36] study needed a longer follow-up period to ensure that the fusion assessment was done when the advised time from the manufacturer for bone transformation had passed. Additionally, retrospective studies [29, 34] have more limitations. Ajiboye's et al. [34] study also has the limitation of the study being conducted only on older people.

Compared to the remaining studies in which CT scans were also used, Ajiboye et al. [29] and Neen et al. [31] evaluated their patients only with X-rays. It has been demonstrated that evaluation with a CT scan is the most sensitive radiographical method since it can detect a significantly higher rate of pseudoarthrosis than radiographs. [36]

Another factor to consider is that the technique of obtaining and concentrating the bone marrow still needs a standardised protocol. This would make the comparisons between the individual studies more meaningful since they all used different methods, quantities, among other variables. This leads to different compositions of the samples, for example, when it comes to the number of progenitor cells, and may influence the results. [13, 27]

Additionally, BMA and BMAC have some differences, as aforementioned. Fortier et al. [37] compared the composition of both in an equine model, where the bone marrow was aspirated from the horses' sternum, and found that in BMAC there is a significant increase in white blood cells and platelets and a reduction in red blood cells. Although they did not quantify growth factors, there is a clear positive correlation between anabolic growth factors and platelets. The stem cells themselves were also not quantified, as there was no specific cell surface marker for them. However, the flow cytometry suggested their presence in BMAC. Also, it would be interesting to determine if a larger quantity of stem cells correlates to higher bony fusion or tissue repair. Therefore, as there have been no comparative studies directly comparing the application of BMA versus BMAC in lumbar fusions, it is challenging to compare them based on individual studies such as those presented here. This is because various variables can differ between studies, making it difficult to make definite conclusions.

Even though most of these studies had their limitations, it is possible to conclude that the use of BMA or BMAC in addition to an autograft or allograft mostly achieves superior or at least

equivalent results. Additionally, in the studies where iliac bone autograft was not used, it was possible to avoid one of the major complications of the current gold standard, the donor site pain which often results from harvesting autologous bone.

Finally, BMA or BMAC in association with autologous bone graft seems to be effective in enhancing spinal fusion without increased surgical risks. In the future, it would be helpful to have studies directly comparing the use of the same autograft or allograft with BMA versus BMAC so there would not be confounding variables and the actual benefits of each method can be evaluated and compared.

## Tables

*Table I: Summary of analysed studies. No.: Number. PLF: Posterior lumbar fusion. PLIF: Posterior lumbar interbody fusion. TLIF: Transforaminal lumbar interbody fusion.*

| Studies | Technique | No. of levels | Study | Bone Marrow Aspirate |
|---|---|---|---|---|
| **Hart et al., 2014** [10] | PLF | 1-3 | Prospective | Concentrated |
| **Bansal et al., 2009** [30] | PLF | 1-3 | Prospective | Not Concentrated |
| **Neen et al., 2006** [31] | 15: PLF;<br>13 PLIF;<br>22: 360º front and back fusion | 1-3 | Prospective | Not Concentrated |
| **Niu et al., 2009** [32] | PLF | 1 | Prospective | Not Concentrated |
| **Johnson, 2014** [28] | PLF | 1-3 | Prospective | Concentrated |
| **Moro-Barrero et al., 2007** [33] | PLF | 1-3 | Prospective | Not Concentrated |
| **Kitchel et al., 2005** [35] | PLIF | 1 | Prospective | Not Concentrated |
| **Ajiboye et al., 2015** [34] | PLF + TLIF | 1-3 | Retrospective | Concentrated |
| **Ajiboye et al., 2016** [29] | PLF + TLIF | 1-3 | Retrospective | Concentrated |
| **Gan et al., 2008** [24] | PLF | 1-3 | Prospective | Concentrated |
| **Thaler et al., 2013** [36] | PLIF | 1-3 | Prospective | Not Concentrated |
| **Total of studies** | | 11 [10, 24, 28-36] | | |

*Table II: Identification of comparative groups. BMA: Bone marrow aspirate. BMAC: Bone marrow aspirate concentrate. BCP: biphasic calcium phosphate.*

| Study | Without BMA/BMAC | With BMA/BMAC |
|---|---|---|
| **Hart et al., 2014** [10] | 40 patients: spongious allograft chips (group I) | Other 40 patients: spongious allograft chips with BMA concentrate (group II) |
| **Bansal et al., 2009** [30] | 30 patients: iliac crest autograft on one side of the spine (side II) | Same 30 patients: hydroxyapatite plus beta-tricalcium phosphate with BMA on one the other side of the spine (side I) |
| **Neen et al., 2006** [31] | 50 patients: iliac crest autograft (group II) | Other 50 patients: Healos® with BMA (group I) |
| **Niu et al., 2009** [32] | 43 patients: iliac crest autograft on one side of the spine (control side) | Same 43 patients on the other side of the spine (test side):<br>- 21 patients: laminectomy bone chips with BMA (group 1)<br>22 patients: calcium sulphate pellets with BMA (group 2) |
| **Johnson, 2014** [28] | 24 patients: iliac crest autograft on one side of the spine | Same 24 patients: allograft cancellous bone with BMAC on the other side |
| **Moro-Barrero et al., 2007** [33] | 35 patients: autologous bone graft from decompression on one side of the spine (side 1) | Same 35 patients: BCP ceramic with BMA on the other (side 2) |
| **Kitchel et al., 2005** [35] | 25 patients: iliac crest autograft on one side of the spine | Same 25 patients: mineralized collagen bone graft with BMA on the other side |

*Table III: Identification of non-comparative groups. BMA: Bone marrow aspirate. BMAC: Bone marrow aspirate concentrate.*

| | |
|---|---|
| **Ajiboye et al., 2015** [34] | 31 patients: BMAC with demineralised bone matrix and allograft. |
| **Ajiboye et al., 2016** [29] | 80 patients: BMAC with demineralised bone matrix and allograft chips. |
| **Gan et al., 2008** [24] | 41 patients: BMAC with beta-tricalcium phosphate. |
| **Thaler et al., 2013** [36] | 34 patients: BMA with beta-tricalcium phosphate. |

*Table IV: Fusion rates achieved in the surgeries of comparative studies. BMA: Bone marrow aspirate. BMAC: Bone marrow aspirate concentrate. Mo.: months. XR: X-ray. CT: computerised tomography. LBOS: Low back outcome score. ODI: Oswestry Disability Index. IB: Interbody.*

| Study | Fusion rate (Without BMA/BMAC) | Fusion rate (With BMA/BMAC) |
|---|---|---|
| **Hart et al., 2014** [10] | XR 12 mo.: 0 fusion cases (0%);<br>XR 24 mo.: 4 (10%);<br>CT 24 mo.: 16 (40%). | XR 12 mo.: 6 fusion cases (15%);<br>XR 24 mo.: 14 (35%);<br>CT 24 mo.: 32 (80%). |
| **Bansal et al., 2009** [30] | 3 mo.: 0/30 bridging bone mass;<br>6 mo.: 30/30 mass more prominent;<br>1 year: 29/30 good fused mass. | 3 mo.: 30/30 bridging bone mass;<br>6 mo.: 30/30 mass more prominent;<br>1 year: 30/30 good fused mass. |
| **Neen et al., 2006** [31] | 94%. | 84%. |
| **Niu et al., 2009** [32] | Group 1: 90.5%;<br>Group 2: 90.9%. | Group 1 (laminectomy bone chips with BMA): 85.7%;<br>Group 2 (calcium sulphate pellets with BMA): 45.5%. |
| **Johnson, 2014** [28] | Gutter: 1.6 +/- 0.1;<br>Facet: 1.7 +/- 0.1. | Gutter: 1.6 +/- 0.1;<br>Facet: 1.6 +/- 0.1. |
| **Moro-Barrero et al., 2007** [33] | XR: good: 89%; poor: 11% ;<br>CT: good: 80%; poor: 20%. | XR: good: 89%; poor: 11%;<br>CT: good: 89%; poor: 11%. |
| **Kitchel et al., 2005** [35] | 84% (21/25) | 80% (20/25) |
| | IB: 92% (23/25) | |

*Table V: Fusion rates achieved in the surgeries of non-comparative studies. Mo.: months. ODI: Oswestry Disability Index. IB: Interbody. PLF: Posterior lumbar fusion. BSF: Brantigan, Steffee, Fraser. VAS: Visual analogue scale.*

| Study | Fusion rate |
|---|---|
| **Ajiboye et al., 2015** [34] | Solid fusion: 83.9% (26/31);<br>PLF: 83.3% (20/24) in single and 85.7% (6/7) in multilevel;<br>IB: 95.8% (23/24) in single and 100% (7/7) in multilevel;<br>PLF: Lenke A – 83.9% (26/31);<br>IB: BSF-3 – 96.8% (30/31). |
| **Ajiboye et al., 2016** [29] | Solid fusion: 81.3% (65/80);<br>PLF: 79,7% (47/59) in single and 85.7% (18/21) in multilevel;<br>IB: 93,2% (55/59) in single and 90,5% (19/21) in multilevel;<br>PLF: Lenke A – 81.3% (65/80);<br>IB: BSF-3 – 92.5% (74/80). |
| **Gan et al., 2008** [24] | 34,5 mo.: 95,1% good spinal fusion. |
| **Thaler et al., 2013** [36] | Solid fusion: 12/45 levels (26,67%);<br>Indeterminate fusion: 15/45 levels (34,09%);<br>Inadequate fusion: 17/45 levels (38,63%). |

*Table VI: Clinical results. LBOS: Low back outcome score. ODI: Oswestry Disability Index. b-TCP: beta-tricalcium phosphate. VAS: Visual analogue scale.*

| Studies | Clinical results |
|---|---|
| **Hart et al., 2014** [10] | Not evaluated. |
| **Bansal et al., 2009** [30] | Not evaluated. |
| **Neen et al., 2006** [31] | Group I (Healos® with BMA): LBOS: 92%; patient satisfaction index: 94%; prolo economic score: 90%;<br>Group II (iliac crest autograft): LBOS: 88%; patient satisfaction index: 92%; prolo economic score: 88%; |
| **Niu et al., 2009** [32] | Not evaluated. |
| **Johnson, 2014** [28] | Not evaluated. |
| **Moro-Barrero et al., 2007** [33] | Not evaluated. |
| **Kitchel et al., 2005** [35] | ODI scores improved 57.2% at 12 months and 55.6% at 24 months, compared with baseline. |
| **Ajiboye et al., 2015** [34] | Odom's criteria at one-year postoperative: excellent/good: 83,9%; poor: 6,5%. |
| **Ajiboye et al., 2016** [29] | Odom's criteria at one-year postoperative: excellent/good: 72,5%; poor: 13,7%. |
| **Gan et al., 2008** [24] | Not mentioned apart from the complications. |
| **Thaler et al., 2013** [36] | b-TCP yielded a good clinical outcome 1 year after surgery. ODI and VAS for leg and back scores improved significantly. |

*Table VII: Complication rates and the need for revision surgery. BMA: bone marrow aspirate.*

| Studies | Complications | Approach |
|---|---|---|
| **Hart et al., 2014** [10] | Group I: 2/40 (5%): hematoma;<br>Group II: 2/40 (5%): hematoma. | Group I: 2/40 (5%): revision surgery and drainge;<br>Group II: 2/40 (5%): revision surgery and drainage. |
| **Bansal et al., 2009** [30] | Side I (BMA): 0/30 (0%);<br>Side II (iliac crest autograft): 1/30 (3,33%): lucency and breakage of the distal pedicle screw; 5/30 (16,67%): donor site pain; 1/30 (3,33%): sensory loss over lateral tight. | Not specified. |
| **Neen et al., 2006** [31] | Group I (Healos® with BMA): 0/50 (0%);<br>Group II (iliac crest autograft): 7/50 (14%): persisting donor site pain. | Not specified. |
| **Niu et al., 2009** [32] | Not specified. | Not specified. |
| **Johnson, 2014** [28] | 0/24 (0%) | 0/24 (0%) |
| **Moro-Barrero et al., 2007** [33] | 1/35 (2.86%): pseudoarthrosis. | 1/35 (2,86%): revision surgery. |
| **Kitchel et al., 2005** [35] | 4/25 (16%): non-union. | Not specified. |
| **Ajiboye et al., 2015** [34] | 1/31 (3,23%): seroma;<br>1/31 (3,23%): pseudoarthrosis. | 5/31 (16,13%): revision surgery due to a seroma, pseudoarthrosis, adjacent segment pathology (3/31; 9,68%). |
| **Ajiboye et al., 2016** [29] | 7/80 (8,75%): hardware bursitis;<br>2/80 (2,5%): postoperative infection;<br>2/80 (2,5%): pseudoarthrosis. | Not specified. |
| **Gan et al., 2008** [24] | 4/41 (9.76%): wounds with little exudation or moderate swelling. | Not specified. |
| **Thaler et al., 2013** [36] | 9/45 (20%) levels: pseudoarthrosis;<br>1/34 (2,94%): transient paresis of L5;<br>1/34 (2,94%): dura leakage;<br>1/34 (2,94%): migration of the cage;<br>2/34 (5,88%): seroma. | 1/34 (2,94%): revision surgery due to pseudoarthrosis. |

**Figures**

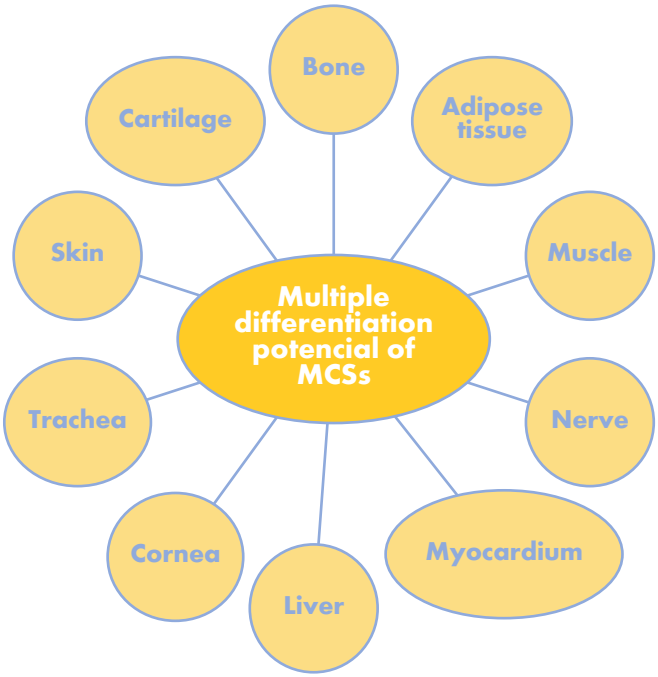


*Figure 1: Numerous differentiation potentials of mesenchymal stem cells into various tissues. MCS: Mesenchymal stem cells.*

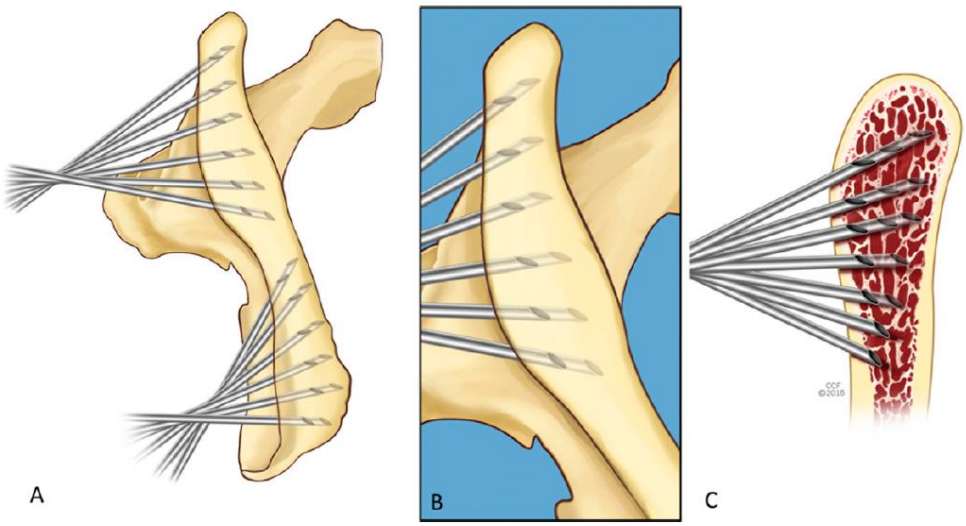


*Figure 2: The technique of harvesting bone marrow aspirate with the advancement of around 5mm of the needle from site to site. In 1A and 1B, there is an axial view representation and in 1C, a coronal view. Used with permission of Nicolas S. Piuzzi, MD.* [17]

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