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Comparison between Bone Marrow Aspirate Concentrate versus Stromal Vascular Fraction on Osteoarthritis Knee Patients: Meta-Analysis

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ABSTRACT

Background: Osteoarthritis (OA) of the knee is a leading cause of disability, with limited nonoperative treatment options that primarily focus on symptom relief rather than disease modification. Cell-based therapies, including bone marrow aspirate concentrate (BMAC) and stromal vascular fraction (SVF), have emerged as promising alternatives for managing knee OA. However, clinical evidence comparing their efficacy remains limited.

Methods: A systematic review and meta-analysis were conducted according to PRISMA guidelines. PubMed, Scopus, and Web of Science databases were searched for clinical studies reporting outcomes after a single intra-articular injection of autologous BMAC or SVF in patients with varying degrees of knee OA. Studies involving adjunct procedures, culture-expanded cells, or multiple injections were excluded. Pain reduction, assessed by the Visual Analog Scale (VAS), and functional improvement, measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), were the primary outcomes. Standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated using a random-effects model.

Results: Six studies comprising 261 patients (111 BMAC, 150 SVF) were included. Both treatments resulted in significant improvement in pain and function. BMAC reduced mean VAS from 4.5 ± 1.27 to 1.71 ± 0.82 (SMD 2.609; 95% CI, 1.781–3.436), while SVF reduced VAS from 6.1 ± 1.1 to 3.3 ± 1.5 (SMD 3.470; 95% CI, 1.175–5.765). SVF showed significantly greater pain reduction compared with BMAC ($P < 0.0001$). Both BMAC (SMD 1.403; 95% CI, 0.385–2.421) and SVF (SMD 1.125; 95% CI, 0.497–1.754) demonstrated equivalent functional improvement according to WOMAC scores ($P = 0.626$). Study heterogeneity and methodological inconsistencies were noted, particularly in cell preparation and reporting standards.

Conclusion: A single injection of either BMAC or SVF provides short-term symptomatic relief in knee OA. SVF appears superior to BMAC for pain reduction, while both are equally effective in improving function. Given the heterogeneity of preparation protocols and limited high-quality evidence, results should be interpreted with caution. Further standardized, large-scale randomized controlled trials are needed to establish definitive recommendations.

Keywords: Knee osteoarthritis; Bone marrow aspirate concentrate; Stromal vascular fraction; Cell-based therapy

INTRODUCTION

With an estimated 27 million people suffering from clinical OA of some joint, osteoarthritis (OA) is a leading cause of disability and health-care costs worldwide.[1,2] The knee is the most involved body site in this condition, but it can affect any joint. Symptomatic knee OA affects 10% of men and 13% of women over the age of 60.[3] This figure is expected to rise, possibly due to rising life expectancy and the obesity epidemic.

Knee OA is a painful and debilitating condition that has a significant impact on the patient's quality of life.[4] Current non-operative treatment options for knee OA are limited and primarily focus on symptom relief rather than disease cure.[5] Some of the most commonly used nonoperative options for the management of early-onset to moderate OA include analgesia with pharmacologic agents (eg, acetaminophen, nonsteroidal anti-inflammatory drugs, intra-articular injections of corticosteroids and hyaluronates), weight management, supervised exercise programs, and the use of mobility aids and braces.[6]

The progression of OA will eventually result in the failure of nonoperative treatment and the need for definitive treatment with joint replacement surgery.3 As a result, there is an unmet clinical need for novel and effective treatment regimens to address the complex pathology of knee OA.[7]

Cell-based therapies have emerged as a potential treatment option for knee OA in recent years.[8] In preclinical studies, mesenchymal stem cells (MSCs) from various sources have been extensively evaluated for their ability to restore compromised articular cartilage and slow the progression of knee OA.[9] Bone marrow aspirates are the most commonly studied and have been linked to improved pain and knee function, as well as, in some cases, cartilage morphology restoration.[10]

As lipoaspirates are easy to obtain using a minimally invasive procedure with a low complication rate and minimal donor-site morbidity, stromal vascular fraction (SVF) and adipose-derived stem cells have received increased attention as an alternative stem cell source for management of knee OA at any stage.[11,12]

There have been few clinical studies comparing the efficacy of bone marrow aspirate and SVF injections in the knee, with only one study finding no difference in improvement of knee OA symptoms between patients who received micro fragmented adipose tissue and bone marrow aspirate concentrate (BMAC) injection.[13] Given that a significant number of patients with knee OA symptoms may not be surgical candidates or do not choose to undergo surgery, it is critical to determine whether one injection therapy outperforms the other in terms of clinical benefit. It should also be noted that most current cell therapy data for knee OA are from preclinical trials, with only a few results from relevant clinical trials available.[14]

Due to the heterogeneity of preparation protocols, a recent systematic review concluded that there is insufficient evidence to recommend one product over the other in patients with knee OA.[15] The researchers included studies in which BMAC or SVF were combined with platelet-rich plasma injections or surgical procedures (eg, microfractures). In clinical practice, a single BMAC or SVF injection is typically used in patients who are not surgical candidates or who choose nonoperative therapy for knee OA, but the clinical efficacy of these treatments is still being studied.[16]

The goal of this meta-analysis was to identify and compare the clinical efficacy of two biologic interventions after a single injection of BMAC and SVF in the knees of patients with varying degrees of OA. We hypothesized that a BMAC or SVF injection into the knee joints of patients with osteoarthritic changes would have the same clinical effect.

METHODS

We conducted a systematic review of studies on the clinical outcomes of autologous BMAC and autologous adipose tissue-

derived SVF in patients with various degrees of knee OA using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[17]

Search Strategy

A systematic search was conducted using 3 online databases (PubMed, Scopus, and Web of Science) for articles reporting the clinical outcomes after a BMAC or SVF injection into the knee joints of patients with arthritic changes. Multiple combinations of the following terms were used to retrieve potentially relevant articles: ‘‘SVF,’’ ‘‘BMAC,’’ ‘‘autologous,’’ ‘‘knee,’’ ‘‘knee osteoarthritis,’’ ‘‘knee arthritis,’’ ‘‘arthritis,’’ ‘‘pain,’’ ‘‘bone marrow aspirate concentrate,’’ ‘‘bone marrow aspirate,’’ ‘‘stromal vascular fraction,’’ ‘‘adipose derived stromal vascular fraction,’’ ‘‘stromal vascular fraction,’’ ‘‘results,’’ ‘‘outcomes,’’ and ‘‘function.’’ The constraints applied in each database were ‘‘English articles,’’ ‘‘clinical studies,’’ ‘‘any publication date,’’ ‘‘peer reviewed,’’ and ‘‘published in journal.’’

Study Criteria and Screening Process

This meta-analysis included clinical studies that reported the outcomes of patients who received a single BMAC or SVF injection in the knee joint to manage osteoarthritic changes of any severity. Studies that examined patients who received BMAC or SVF injections to the knee in conjunction with other therapies, such as surgical intervention or injection of other pharmaceutical or biologic products, were excluded. Inclusion criteria such as Human studies reporting the outcomes after a single BMAC or SVF injection to the knee joint, Studies in patients with any degree of knee osteoarthritis, Randomized and nonrandomized studies of any level of evidence, BMAC or SVF injection was prepared and injected during a single patient visit, Articles in the English language, Articles published in peer-reviewed journals and exclusion criteria as follows; Studies reporting the outcomes after BMAC injection to the knee combined with other types of injection or surgical procedures, Studies reporting the outcomes after SVF injection to the knee combined with other types of injection or surgical procedures, Studies reporting the outcomes after multiple SVF or BMAC injections (performed within 1 year), BMAC or SVF was not injected during a single patient visit, BMAC or SVF samples underwent culture expansion before injection, Duplicate study population in the literature, Study population <7 patients, Animal studies.

After removing duplicates, potentially relevant articles from the three databases were screened for eligibility using predefined study criteria. A review of the title, abstract, and full text of potentially eligible studies for inclusion was carried out. To ensure that all relevant studies were included, we manually retrieved any related clinical studies from the references of the eligible articles (cross-reference).

STATISTICAL ANALYSIS

For any numerical variable, descriptive statistics such as the mean and standard deviation were recorded. The pre- and post-injection visual analog scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index for function were compared using a random effects model. The random variation within the studies as well as the variation among the studies were incorporated into the random effects model. Any missing standard deviation was calculated using predefined methods.[21] In the meta-analyzed studies, the SPSS statistic was used to assess study heterogeneity, and a funnel plot was used to detect bias risk. The primary outcome was the mean pre- and postoperative VAS. Secondary outcomes included the WOMAC knee index and other outcome scales.

The standardized mean difference was used to calculate the clinical efficacy of injection therapy in each group (SMD). In summary, if the value 0 is not within the 95% CI, the SMD is considered statistically significant at the 5% level (P<.05). A value of 0.2 indicates

a small effect, a value of 0.5, a medium effect, and a value of ≥0.8, a large effect, according to the Cohen rule of thumb for interpreting the SMD statistic. To compare the effect of treatment between the BMAC and SVF groups, an independent-samples Student t test was used. P<.05. was chosen as the level of statistical significance. MedCalc Statistical Software Version 19.2.6 was used for statistical analysis (MedCalc Software Ltd).

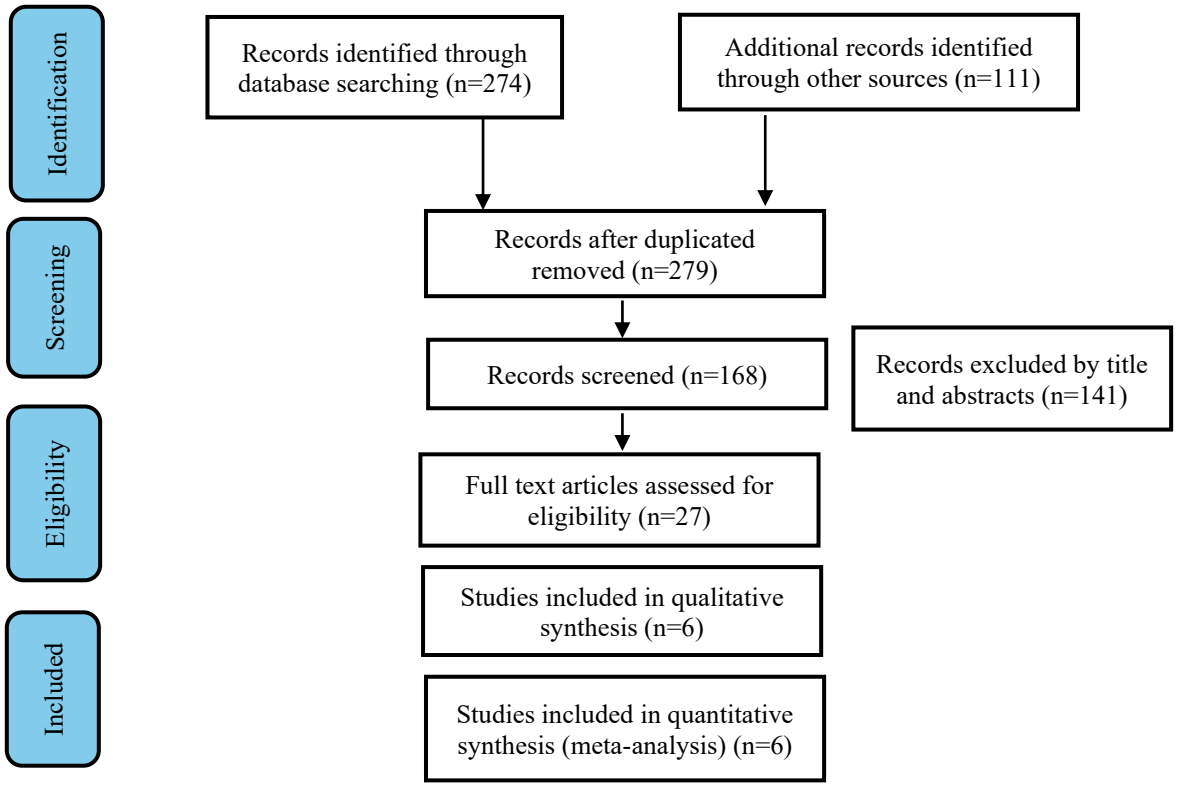

Figure 1. PRISMA (Preferred Reporting Items for Systematic Meta-analyses) Flow Diagram

RESULTS

Search Result and Study Selection

After removing duplicates, 385 potentially eligible studies were retrieved from the three databases. The title, abstract, and full-text screening process yielded six studies (Figure 1) that were eligible for inclusion in this systematic review: One study reported the results of a BMAC injection (Garay, 2018). Three studies reported SVF injection outcomes (Yokota, 2019; Tsubosaka, 2020; Hudetz, 2019), and one study reported comparative outcomes among patients who received either a BMAC or an SVF injection.[13]

The study included 261 patients who received either BMAC (111 patients) or SVF (150 patients). VAS stands for Primary Outcome. Most articles (5/6; 83%) used the VAS score to report the clinical effect of BMAC and SVF injection in patients with knee OA (Tables 1 and 2). The VAS groups consisted of 66 patients who treated using BMAC injections (30 male, 37 females, mean age 57.35±6.6) and 150 patients treated using an SVF injection (75 male, 75 female; mean age, 68,3±9 years). Patients who received an SVF knee injection seemed to be older. The mean follow-up time was quite far between the groups: 21,06 vs 6 months for the BMAC group and 10,75 months (range, 6-13) for the SVF group.

Patients who received a BMAC injection in the knee experienced significantly reduced pain at follow-up (SMD, 2.609; 95% CI, 1.781-3.436 [a large effect]) (Figure 2A). The mean VAS score improved from 4,5±1,27 to 1,71±0,82 in the BMAC group. Similarly, SVF had a large clinical effect (>1,3) on pain reduction when injected into

knees with various degrees of OA (SMD, 3,470; 95% CI, 1.175-5,765) (Figure 2B). The mean VAS score improved from 6.1±1.1 to 3.3±1,5 in the SVF group. SVF injection had a significantly greater effect on pain reduction than did BMAC injection in patients with knee OA ($P < 0.0001$). Evidence of study heterogeneity was detected within the BMAC group ($I^2 = 84.7\%$; $P = 0.001$) and the SVF group ($I^2 = 97.6$; $P < 0.0001$).

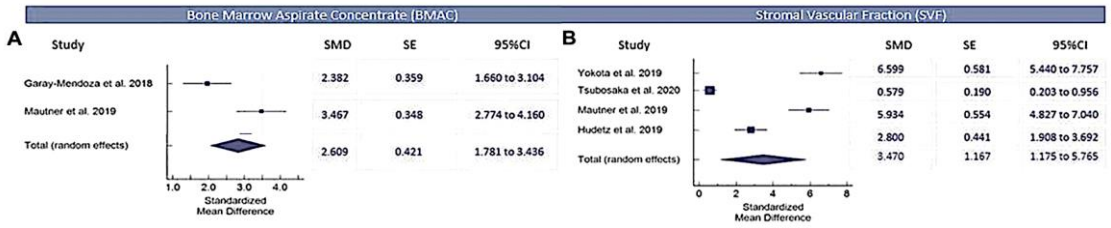

Figure 2. Estimated clinical effect of (A) bone marrow aspirate concentrates and (B) adipose-derived stromal vascular fraction injection on the knee pain of patients with osteoarthritis. SMD, standardized mean difference.

Western Ontario and McMaster Universities Osteoarthritis Index. Of the 6 articles, 4 (67%) used the WOMAC knee index to report clinical outcomes after BMAC or SVF injection (Tables 1 and 2). The WOMAC group consisted of 70 patients who received a BMAC injection (33 male, 38 females; mean age, 55.75 ± 11.75 years) and 116 patients who received an SVF injection to the knee (47 female, 69 male; mean age, 55.8 ± 11.3 years). Based on the WOMAC index, the BMAC injection had a significant effect on the improvement of function in patients with knee OA as compared with the preinjection status (SMD, 1.403; 95% CI, 0.385-2.421) (Figure 3A). Patients who received an SVF injection also experienced significantly improved function after treatment (SMD, 1.125; 95% CI, 0.497-1.754) (Figure 3B). According to the WOMAC index, the clinical effect of BMAC versus SVF injection in patients with knee OA was equivalent ($P = .626$). Study heterogeneity was detected within the BMAC group ($I2 = 85\%$; $P = .009$) and the SVF group ($I2 = 77\%$; $P = .004$).

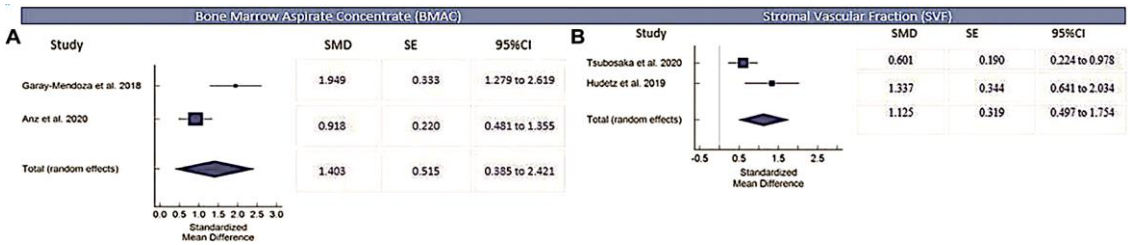

Figure 3. Estimated clinical effect after (A) bone marrow aspirate concentrate and (B) stromal vascular fraction injection to the knee of patients with osteoarthritis, based on the Western Ontario and McMaster Universities Osteoarthritis index. SMD, standardized mean difference.

Other Reported Outcomes. Other reported outcomes included the Knee injury and Osteoarthritis Outcome Score (KOOS; 3 studies)[13,16,22] The mean pre- and post-injection values for the outcome scales are displayed in Tables 1 and 2.

The clinical effect of SVF injection using the KOOS was evaluated in 3 studies with a mean follow-up of 12,3 months.[13,16,22] In the SVF group, the mean postinjection KOOS (59.7) was significantly higher than was the mean preinjection KOOS (42.4). Only 1 study used the KOOS to report the clinical outcome after a BMAC injection at a mean follow-up of 21.6 6 10.5 months.[13] In this study, the mean postinjection KOOS—calculated as the mean value of the 5 KOOS subscales (Pain, Symptoms, Activities of Daily Living, Sport/Recreation, and Quality of Life)—was significantly higher than was the preinjection value (65.5 ± 11.1 and 45.8 ± 16.1).

Table 1. Comparative Outcome Studies After a Single BMAC Injection

Study	Harvest Site	Age (y)	Patients (M, F)	K-L	Latest Follow Up Month	Rehabilitation	Outcome score (Pre vs Post injection)	BMI	Complications
Mautner (2019) LOE 3	PSIS	59 ± 1	41 (24, 17)	1-4	21.06	NR	VAS: 3.9 ± 0.35 vs 2.5 ± 0.35 KOOS: 45.8 ± 16.1 vs 65.5 ± 11.1	NR	NR
Anz (2020) LOE 2	PSIS	55.8 ± 11.3	45 (27, 18)	1-3	12	Partial weightbearing for 2-3 d, ‘‘standard’’ physical therapy for 4 wk at 1 wk after the injection	WOMAC: 35.3 ±18.1 vs 19.4 ± 16.2	27.7 ± 5	NR
Garay-Mendoza (2018) LOE 2	Posterior iliac crest	55.7 ± 12.2	25 (6, 20)	NR	6	NR	VAS: 5.27 ± 2.19 vs 0.92 ± 1.29 WOMAC: 62.61 ± 18.5 vs 91.73 ± 9.45	29.5 ± 12.2	Knee swelling/ pain; knee pain and stiffness (first 48h)

Abbreviation: NR: not reported; ASIS: anterior superior iliac spine; BMAC: bone marrow aspirate concentrate; BMI: body mass index; EMORY: Quality of Life composite; F: female; IKDC: International Knee Documentation Committee; K-L: Kellgren-Lawrence; LOE: level of evidence; M: male; NPS: Numeric Pain Scale; PSIS: posterior superior iliac spine.

Table 2. Outcomes of Patients with SVF Injection

Study	Harvest Site	Age, y	Patients (M, F)	K-L	Latest Follow-up, mo	Rehabilitation	Outcome Scores, Pre- vs Postinjection	BMI	Complications
Tsubosaka (2020) LOE 3	Abdomen or breech	69,4±6,9	57 (41, 16)	1-4	12	NR	VAS: 4,65 ± 2,35 vs 3,28 ± 2,47 WOMAC: 33,4 ± 18,2 vs 22,6 ± 17,5 KOOS: 48,7 ± 15,8 vs 58,6 ± 16,8	25,1 ± 3,1	NR
Yokota (2019) LOE 3	Abdomen	73±9,1	38 (7,31)	1-4	6	Target: 100 bend- and stretch exercises of the knees on the day of SVF injection and each day thereafter	VAS: 8±0,6 vs 4±1,2	24,8±1,9	Mild knee effusion/ swelling: 3 cases. Abdominal pain: 6 cases. Internal bleeding at the incision site: 5 cases. Subcutaneous induration at the abdominal area of harvest: 12 cases
Hudetz (2019) LOE 4	Abdomen	NR	20 (15, 5)	3-4	12	NR	VAS: 7,38 ± 1,41 vs 3,38 ± 1,89 WOMAC: 55,38 ± 18,83 vs 32,25 ± 14,62 KOOS: 35,7 ± 17,9 vs 58,9 ± 17,3	NR	NR

Mautner (2019) LOE 3	Abdomen	63 ± 11	35 (12, 23)	1-4	13	NR	VAS: 4,6 ± 0,3 vs 2,8 ± 0,3 KOOS: 42,8 ± 16,3 vs 61,6 ± 13,4	NR	NR
Abbreviation: y: year; NR: not reported; BMI: body mass index; K-L: Kellgren-Lawrence; VAS: visual analog scale; LOE: level of evidence; WOMAC: western Ontario and mcmaster universities osteoarthritis index; KOOS: knee injury and osteoarthritis outcome score									

Table 3. Characteristics of Cell Isolation Before Intra-Articular Injection

Study	Cell Isolation	Harvest Technique	Harvested/Injected Tissue Volume, mL	CFU Assay	Cell No. and Characterization
Stromal vascular fraction (cellular analysis)					
Tsubosaka(2020)	Celution 800/CRS System	Abdomen or buttocks	100-360/5	NR	2.5 X 10^7 cells injected; cells not characterized
Hudetz (2019)	Lipogems	Abdomen	Unclear/5	NR	CD marker analysis done but results not reported
Mautner (2019)	Lipogems	Abdomen	30/9	NR	NR
Yokota (2019)	Celution 800/CRS System	Abdomen	Abdomen	NR	NR
Bone marrow aspirate concentrate (cellular analysis)					
Anz (2020)	Pure BMC Supraphysiologic Concentrating System (buffy coat and plasma)	PSIS	60/7	138.67 cells/mL	RBCs: 1133 X 10^6/mL; PLTs: 413 X 10^6/mL; WBCs: 44.1 X 10^6/mL; CD34+: 170,924/mL
Mautner (2019)	PureBMC Supraphysiologic Concentrating System	PSIS	60/8	NR	NR
Garay-Mendoza[17] (2018)	Manually (buffy coat)	Bilateral posterior iliac crests (G-CSF administration)	>200/5	NR	Nucleated cells: 302.02 x 107; mononuclear cells: 67.33 x 107; CD34+ cells: 20.56 x 106

Abbreviation: NR: not reported. ASIS: anterior superior iliac spine; CD: cluster of differentiation; CFU: colony-forming unit; G-CSF: granulocyte colony stimulating factor; PLT: platelet; PSIS: posterior superior iliac spine; RBC: red blood cell; SVF: stromal vascular fraction; WBC: white blood cell.

Cell Isolation and Characterization

The posterior iliac crest was reported as the preferred bone marrow harvest site in one of the BMAC studies (Table 3). Patients in the Garay-Mendoza et al study received granulocyte colony-stimulating factor for three days prior to bone marrow harvest for bone marrow stimulation. In the remaining studies, no such stimulation was used.[23] Two studies reported cell isolation and BMA concentration after bone marrow harvest using a commercially available concentrating system that yields a product that is a combination of the buffy coat cell layer and plasma (PureBMC Supraphysiologic Concentrating System; Emcyte).[13,24]

One BMAC study used manual buffy coat isolation under sterile conditions, but the exact process was not reported in sufficient detail to allow replication.[23] Only three of the 49 patients who received a BMAC knee intra-articular injection were subjected to cellular analysis, according to Anz et al. An aliquot of bone marrow aspirate was collected and sent to an outside laboratory for this analysis. Cell count, flow cytometry for CD34 + cells, and colony-forming unit-fibroblast assays were performed and revealed a concentration-dependent increase in platelet, white blood cell, CD34 +, and colony-forming unit-fibroblast counts. Table 3 contains exact figures.[24] Garay-Mendoza et al also noted their product's cell composition with a mean number of 67.33 x 10^7 (31.52 x 10^7–114.02 x 10^7) mononuclear cells, of which 20.56 x 10^6 (range: 5.2 x 10^6–43.36 x 10^6) were CD34 +. No colony-forming unit analysis was performed.[23]

Different harvest sites and isolation protocols were used in the SVF group (Table 3). The abdomen was mentioned in all four studies as a source of adipose tissue harvest, with the buttocks mentioned in one of them.[22] The Celution 800/CRS System (Cytori Therapeutics) was used in two of the four studies: a medical device designed to automate the processing of adipose tissue and SVF cell isolation using a collagenase/Neutral Protease Blend (Celase).[22,25] Furthermore, Lipogems (Lipogems International SpA) was the preferred method of SVF isolation in the last two studies, which is a technique used to obtain microfragmented adipose tissue with an intact stromal vascular niche and MSCs without the use of enzymatic digestion.[13,16]

Postinjection Rehabilitation and Complications

One of two studies (50%) in the BMAC group and one of four studies (25%) in the SVF group detailed the postinjection rehabilitation protocol. After the knee injection, no studies in the BMAC group and 25% in the SVF group reported complications. Table 1 (BMAC group) and Table 2 show post-injection rehabilitation and complications (SVF group).

DISCUSSION

According to this meta-analysis, a single SVF injection in the knee joint of patients with knee OA appears to result in a greater reduction of knee pain than a single BMAC injection at short-term follow-up (12-21 months): specifically, VAS scores improved from 6.1 ± 1.1 to 3.3 ± 1.5 and from 3.9 ± 0.35 to 2.5 ± 0.35, respectively. The clinical effect of these two biologic injections was equivalent in terms of knee joint function (WOMAC knee index), which was evaluated in a subgroup of studies. In patients with mild to severe OA of the knee, BMAC and SVF injections significantly improved pain and function. There was inconsistency in the patient evaluation tools used to report clinical outcomes. The studies also had significant variation in cell isolation methods, as well as serious deficiencies in reporting variables, which could have influenced the published outcomes of cell-based therapies. The cell composition of the biologic product implanted was mentioned in 50% of the studies (2 BMAC, 1 SVF). As a result, the findings of this meta-analysis should be interpreted with caution.

Although multiple studies have found that BMAC and SVF injections improve knee pain and function, there is little evidence that

one therapy is superior to the other. Mautner et al compared the functional outcomes of patients with symptomatic knee OA who received microfragmented adipose tissue, a type of SVF therapy, versus BMAC injection in a retrospective study of 110 patients. The authors reported significant clinical improvement in knee pain and function with BMAC and microfragmented adipose tissue injections, but there was no difference in improvement when these two treatments were compared.

This was the only study in our analysis that compared the clinical effect of BMAC versus SVF in patients with knee OA in the short term (minimum, 6 months) using patient-reported outcomes (VAS, KOOS). SVF injection was more effective than BMAC in reducing pain at short-term follow-up, according to the findings of this meta-analysis. The superiority of SVF over BMAC injection in reducing knee OA pain has not been reported to our knowledge. Furthermore, compared to patients with advanced knee OA (K-L grade 3 or 4), Mautner et al discovered that patients with K-L grade 1 or 2 had a higher response rate to knee injection (ie, patients were considered "responders" if they experienced. Pain was reduced by 25% after the knee injection). We were unable to stratify our findings based on the K-L grade of knee OA due to missing data, which is a limitation. More research is needed to investigate potential differences in outcomes following a BMAC or SVF injection based on the severity of knee OA.

Cell-based therapies are increasingly being used to treat cartilage defects and osteoarthritis of the knee. Because of the unique ability of stem cell populations found in BMAC and SVF to secrete and respond to growth factors and cytokines, possess chondrogenic differentiation potential, and regulate the local immune environment after implantation, they have become a desirable therapeutic regimen in the treatment of knee OA.[5] Despite the excitement surrounding the use of biologics, the precise properties of BMAC and SVF cells, as well as their effects on cartilage healing, remain unknown. There is a lack of agreement in the literature on the optimal preparation protocol and cell composition of the resulting product in cell-based therapies for knee OA.[26]

Similarly, significant flaws were discovered in the reporting of cell processing as well as the number and characterization of cell populations injected in our study. Most studies provided only a hazy description of the methodology used, often only naming the cell isolation device that was used. Only half of the six studies mentioned cell composition (2 in the BMAC group and 1 in the SVF group), and only two attempted a colony-forming unit assay. As a result, there was no way to link cell product composition and progenitor concentration to clinical outcomes. Inadequate reporting of such critical variables can prevent experimental conditions from being replicated, affect clinical outcome interpretation, and make comparing multiple studies nearly impossible.

To reduce confusion and patient misinformation, the American Academy of Orthopaedic Surgeons and the National Institutes of Health issued a consensus statement on the adoption of minimum reporting standards for cell product development and clinical application.[27] They advocated for a clear distinction between autologous minimally manipulated cell products (dubbed "cell therapy") and culture-expanded well characterized stem cell populations, with the precise nature of the offered treatment regimen disclosed and adequately explained to patients.[27] They also agreed to use the minimum information criteria for biologics studies as a guide to standardize protocols and procedures. These proposed minimum requirements include study design, recipient information, tissue harvest, cell processing and/or culture, cell characteristics, postoperative protocols, and results.[14] Finally, they recommended that centers offering biologic therapies create biologic registries to allow for quality assessment.

To reduce confusion and patient misinformation, the Department of Health issued a consensus statement on the adoption of minimum reporting standards for cell product development and clinical application.[27] They advocated for a clear distinction between autologous minimally manipulated cell products (dubbed "cell therapy") and culture-expanded well-characterized stem cell populations, with the precise nature of the offered treatment regimen being disclosed and adequately explained to patients.[27] They also agreed to use the minimum information criteria for biologics studies as a guide to standardize protocols and procedures. These proposed minimum requirements include study design, recipient information, tissue harvest, cell processing and/or culture, cell characteristics, postoperative protocols, and results.[14] Finally, they suggested that centers that provide biologic therapies establish biologic registries to facilitate quality assessment.

Aside from the significant differences in BMAC or SVF injection preparation and administration methods between studies, the post injection rehabilitation protocols also varied. Some studies advocated for full weightbearing of the injected lower extremity after the biologic agent (BMAC or SVF) injection, while others advocated for a brief period of partial weightbearing followed by a gradual increase in patient activity (Tables 1 and 2). There is no agreement on the best rehabilitation protocol for OA patients after a knee injection. Furthermore, little is known about the effect of lower extremity weightbearing status on the biologic effect of BMAC or SVF product in this patient population.[28]

Changes in the mechanical forces applied to the knee joint following a BMAC or SVF injection could, in theory, interfere with the biologic effect of these agents by altering the concentration balance of pro- and anti-inflammatory molecules circulating in the synovial fluid. More research is needed to confirm or disprove this hypothesis.

According to the US Food and Drug Administration, administration-site reactions, the ability of cells to differentiate into inappropriate cell types, clinical failure, and tumor growth are all safety concerns associated with the use of MSC-based therapies in clinical practice. None of the studies reported a serious adverse event, such as the development of tumors, following the BMAC or SVF injection. Knee pain was the most common postinjection side effect, which was sometimes accompanied by knee swelling or stiffness.[25] Patients must be closely monitored for an extended period of time to assess the risk of any stem cell-based therapy for potential carcinogenesis; however, the follow-up time of the included studies was short. Standardized post-injection patient surveillance protocols would also be beneficial.

CONCLUSION

At short-term follow-up, a single BMAC or SVF injection into the knee joints of OA patients resulted in symptomatic improvement. However, SVF appeared to be more effective than BMAC in reducing knee pain. The BMAC and SVF injection preparation techniques used in the studies varied significantly, and there was no stratification of outcomes based on the radiologic classification of OA. As a result, these findings should be interpreted with caution.

Declaration by Authors

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