

Concentrated Bone Marrow Aspirate for Knee Osteoarthritis

Technology Overview

Adopted by:

The American Academy of Orthopaedic Surgeons Board of Directors
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Disclaimer: This Technology Overview was prepared using systematic review methodology and summarizes the findings of studies published as of March 14, 2021 on the use of concentrated bone marrow aspirate for the treatment of knee osteoarthritis. As a summary, this document does not make recommendations for or against the use of concentrated bone marrow aspirate. It should not be construed as an official position of the American Academy of Orthopaedic Surgeons. Readers are encouraged to consider the information presented in this document and reach their own conclusions about concentrated bone marrow aspirate for the treatment of knee osteoarthritis.

Contents

Development Work Group Roster	4
Voting Members	4
AAOS Staff	4
Work Group Disclosures	5
Concentrated bone marrow aspirate Data Summary	7
Introduction	7
Summary of Findings	7
Benefits & Harms	8
Important/Priority Outcomes	9
Cost Effectiveness/Resource Utilization.....	9
Acceptability.....	9
Feasibility	9
Future Research	10
Study of Attrition Flow Chart	12
SOF: concentrated bone marrow aspirate vs. Control/Placebo	13
Composite.....	13
Function.....	13
Other	14
Pain.....	15
OA Progression.....	15
Quality of Life	16
SOF: concentrated bone marrow aspirate vs. Other Tx	17
Composite.....	17
Function.....	18
Pain.....	18
Quality of Life	19
Adverse Events.....	19
Data Tables	20
Table 1: concentrated bone marrow aspirate vs. Control/Placebo- Composite	20
Table 2: concentrated bone marrow aspirate vs. Control/Placebo- Function.....	21
Table 3: concentrated bone marrow aspirate vs. Control/Placebo- OA progression	22
Table 4: concentrated bone marrow aspirate vs. Control/Placebo- Other.....	23
Table 5: concentrated bone marrow aspirate vs. Control/Placebo- Pain.....	26
Table 6: concentrated bone marrow aspirate vs. Control/Placebo- QOL.....	28
Table 7: concentrated bone marrow aspirate vs. Other Tx- Adverse events.....	29
Table 8: concentrated bone marrow aspirate vs. Other Tx- Composite.....	30
Table 9: concentrated bone marrow aspirate vs. Other Tx- Function.....	32
Table 10: concentrated bone marrow aspirate vs. Other Tx- Pain.....	38
Table 11: concentrated bone marrow aspirate vs. Other Tx- QOL.....	40

Quality Appraisal	41
Randomized Study Appraisal Form.....	41
Observational Study Appraisal Form	41
PICO Question	44
Literature Search Strategy	45
Included References	50

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Concentrated Bone Marrow Aspirate Data Summary

Introduction

Concentrated bone marrow aspirate (CBMA) is a novel cell-based therapy containing mesenchymal stromal cells (MSCs), platelets, and other regenerative cells (hematopoietic stem cells, white blood cells, macrophages, and various cytokines/chemokines) with cartilage trophic potential. CBMA can be derived from autologous or culture-expanded source. This review will focus on autologous source as cultured CBMA are considered non-commercial experimental technology with limited availability and jurisdiction in the United States. Autologous CBMA injected locally in the synovium of affected joints exhibit anti-inflammatory and immunomodulatory properties modifying the local microenvironment to aid in cartilage repair. Basic science studies have shown promising results with increased anabolic function of cartilage with limited high quality randomized clinical trial data. This therapeutic potential has stimulated interest in autologous CBMA's ability to treat osteoarthritis (OA).

When interpreting the findings presented below, one must consider the heterogeneity of the included studies. Similar to other cell-based therapies, various factors such as patient age, comorbidities, severity of disease, the manner in which the therapy is prepared, the quantity and quality of MSCs obtained, what it is mixed with, and the route of administration may influence treatment outcome. The ability to draw strong conclusions on the utility/efficacy of CBMA is limited by the inability to control for these variables in the current available literature.

Summary of Findings

The published literature about OA patients receiving autologous point-of-care CBMA returned twelve articles. There are three high quality articles (Hernigou 2018, Shapiro 2017, Shapiro 2019) four moderate quality articles (Anz 2020, Centeno 2018, Goncars 2017, Hernigou 2020) and five low quality articles (Estrada 2020, Jin 2020, Kim 2020, Mautner 2019, Yang 2021). The ability to draw strong conclusions on the utility/efficacy of CBMA for knee OA is limited by shortcomings of the current literature.

Concentrated Bone Marrow Aspirate versus Placebo Treatment

Two high quality studies by the same author studying the same patient cohort compared a single CBMA plus platelet poor plasma intraarticular injection versus saline intraarticular injection (Shapiro 2019, Shapiro 2017) in patients with bilateral symptomatic knee OA (Kellgren-Lawrence grades I-III) while two low quality studies evaluated CBMA versus placebo in patients with medial unicompartmental knee OA who underwent high tibial osteotomy (Jin 2020, and Kim 2020). In both high-quality articles, the authors found no significant difference in function, pain, and quality of life between the two groups but noted significant improvement from baseline within 1 week of injection. Shapiro, 2017 found CBMA relieved pain similar to saline placebo contralateral knee injection at 1 week, 3 months, and 6 months. In a subsequent 1 year follow-up study by Shapiro (2019), pain remained decreased in both groups and quality of life improvement in CBMA injected knees was comparable to placebo without any cartilage regeneration noted in 6 month follow-up MRI quantitative mapping. Of the two low quality studies evaluating CBMA versus placebo, there was no difference in clinical outcome in the treatment group. Jin, 2020 evaluated microfracture plus CBMA in patients with moderate to severe knee OA (Kellgren-Lawrence grades III-IV) versus microfracture alone and found greater cartilage regeneration in the treatment group as assessed via second-look arthroscopic cartilage repair assessment. Kim 2020 reported allograft bone chips with autologous CBMA resulted in better osteotomy filling and osteoconductivity as assessed radiographically at 6 weeks and 3 months. Although, both low quality articles noted either better histological, arthroscopic, or radiological features, this did not translate into any appreciable benefit in functional outcome scores between the treatment and placebo group.

Concentrated Bone Marrow Aspirate versus Other Treatment Modality

Eight articles (Hernigou 2018, Centeno 2018, Hernigou 2020, Gocars 2017, Anz 2020, Estrada 2020, Mautner 2019, Yang 2021) compared CBMA to various other treatment modalities. One of these studies was of high quality (Hernigou 2018), four of moderate quality (Anz 2020, Centeno 2018, Gocars 2017, Hernigou 2020), and three of low quality (Estrada 2020, Mautner 2019, Yang 2021). A high quality study by Hernigou, 2018, which assessed young patients (18-41 years old) with steroid induced osteonecrosis found fewer surgical and medical complications in patients with bilateral secondary knee OA (Kellgren-Lawrence grades I-IV) treated with CBMA subchondral administration compared to contralateral TKA done during the same anesthetic event. They also reported increase in bone marrow volume size assessed via MRI at the site of subchondral injections. Similar results were published by Hernigou in 2020 (moderate quality) at which point they noted single CBMA subchondral injections decreased knee pain enough to postpone TKA in patients with bilateral knee OA (Kellgren-Lawrence grades I-IV). Over a mean of 15-year follow-up among 140 patients, the overall incidence of TKA in the CBMA treatment group was 1.19% per person-year. However, a limitation of these two studies addressed by the authors was the potential beneficial effect of subchondral injections performed within subchondral bone for patients with osteonecrosis. As a distinct disease process, these results may not be applicable to a broader osteoarthritis population. Centeno, 2018 reported CBMA plus platelet product intraarticular injection 1x resulted in better outcomes scores than patients receiving exercise therapy in patients with mild to moderate knee OA (Kellgren-Lawrence grades II-III). At the end of 3 months, all patients randomized to exercise therapy crossed over to the CBMA treatment group.

Of the other moderate quality studies, Gocars, 2017 reported significantly improved clinical outcome scores with CBMA 1x intraarticular knee injection compared to intraarticular sodium hyaluronate injection 3x at 1 year in patients with moderate to severe (Kellgren-Lawrence stage II-III) knee OA. Anz, 2020 reported no significant difference in outcome scores (WOMAC and IKDC) between patients with mild to moderate knee OA (Kellgren-Lawrence grades I-III) who received platelet rich plasma (PRP) versus autologous CBMA intra-synovial injection 1x, though they noted improvement in both groups compared to baseline. Of the three low quality studies, Mautner, 2019 evaluated patients with knee OA (Kellgren-Lawrence grades I-IV) who either received CBMA or microfragmented adipose tissue (MFAT) with both groups having similar functional outcome (KOOS and EQOL) and pain (VAS) scores that was significantly better than pre-procedure. Similarly, Estrada, 2020 retrospectively compared PRP versus CBMA versus adipose derived MSC for knee OA (Kellgren-Lawrence grades I-III) with treatment group allocation based on severity of knee OA. In the end all three groups has similar clinical outcome scores (KSS, and IKDC) that were significantly better than baseline. Yang, 2021 compared patients with medial compartment OA (Kellgren-Lawrence grade III) who underwent high tibial osteotomy. The comparison groups in this study received either CBMA or human umbilical cord blood-derived mesenchymal stromal cell (hUCB-MSC). At 33 weeks, both groups showed improvement on functional scores (IKDC, KOOS, SF-36, and Tegner activity scores) from preoperative baseline, but with no significant differences between groups. The hUCB-MSC group did, however, show significantly better healing of regenerated cartilage, measured by second look arthroscopy, than the CBMA group.

Benefits & Harms

There was minimal evidence of significant harm from this intervention. Most articles showed no significant difference in outcomes. There was some benefit in young patients (18-41 years old) with steroid induced osteonecrosis as demonstrated in Hernigou 2018 and Heringou 2020 using CBMA for composite score, osteoarthritis progression and adverse events.

Important/Priority Outcomes

Of the high-quality articles, two determined intraarticular injection of CBMA plus platelet poor plasma 1x was no better than placebo saline injection in terms of function, MRI based cartilage appearance, or pain control. The other high-quality study reported CBMA plus platelet product intraarticular injection did functionally better than exercise therapy, and that CBMA subchondral injection 1x had a lower complication rate and quicker recovery than TKA. In Hernigou 2018, twice as many patients with CBMA injection favored the cell-therapy knee compared to their TKA (21 versus 9 patients). In the three moderate-quality articles, two reported that CBMA intraarticular injection 1x did not perform clinically better than sodium hyaluronate injection 3x, nor PRP but did significantly better than baseline. Two of these studies reported CBMA significantly helped with pain relief.

Cost Effectiveness/Resource Utilization

The cost of the equipment to concentrate bone marrow aspirate is negotiated with each health system by the equipment manufacturers and therefore can vary widely. A reasonable estimate of the equipment cost can be on the order of >\$1,000 per episode. CBMA resource utilization can be minimal when used in the operating room. Most companies have a representative that will concentrate the bone marrow aspirate. However, some hospitals require the use of a phlebotomist to perform the concentration. Using CBMA in the outpatient clinic setting utilizes more resources for patient monitoring, analgesia, and sterile preparation. CBMA is not covered by insurance and therefore the cost is either absorbed by the hospital or by the patient.

Acceptability

CBMA has gained acceptance as a safe biologic because it is autologous and there are very few complications reported with CBMA harvesting. However, it is not widely accepted as efficacious for knee OA because of lack of data supporting its use.

Feasibility

The feasibility of using CBMA relies on surgeon comfort with obtaining bone marrow in the operating room or in the clinical setting. Bone marrow is typically harvested from the iliac crest (anterior or posterior) but can also be harvested from the proximal tibia or calcaneus. Aspiration only takes a few minutes. However, concentration can take on the order of 15-30 minutes. Companies specializing in this industry provide a centrifuge and special sterile equipment in order to concentrate the bone marrow.

Conflicts of Interest

Reference	Financial Conflicts of Interest
Anz, A. W., 2020	EmCyte funding
Centeno, C., 2018	Funded by Regenexx, LLC and the Centeno-Schultz Clinic
Estrada, E., 2020	
Goncars, V., 2017	
Hernigou, P., 2018	
Hernigou, P., 2020	
Jin, Q. H., 2020	
Kim, H. J., 2020	
Mautner, K., 2019	

Shapiro, S. A., 2017	Funding for this study was from the Center for Regenerative Medicine, Mayo Clinic. M.I.O. holds stock in and is an unpaid consultant for Accelalox Inc and is a paid consultant for Zimmer.
Shapiro, S. A., 2019	

Future Research

The focus of this report was on CBMA for knee OA and did not consider the use of CBMA in other joints or uses of CBMA for pathology other than OA, such as bone repair/remodeling. Compared to other biologics such as platelet rich plasma (PRP), the general quantity and quality of studies on CBMA in knee OA was low. There are several emerging paradigms in CBMA that should be considered when designing clinical research studies:

- 1) Comparison Groups: Controlled studies with a comparison group are essential to determine equivalence or superiority to another biologic or drug.
- 2) Isolated Treatments (single variable): CBMA and the comparator should each be single component injections (ie, CBMA alone) rather than a combination of products (ie, CBMA with PRP).
- 3) Quantity of Treatments: Future studies must specify the quantity of treatments, and the time period over which treatments are given.
- 4) Specifics of Treatments: Future studies must identify the type of CBMA (or other biologic) administered, how it was obtained (aspiration method and location), how it was processed (centrifuge brand and protocol), and ideally, cell analysis of the product after concentration.
- 5) The Concept of MSCs: CBMA is often stated to have few mesenchymal stromal cells (MSCs). However, there is presently no study indicating an optimal dose of MSCs for cartilage repair or for treatment of OA. With the contemporary understanding of the immunomodulatory function of MSCs and that both MSC secretome and CBMA can recruit MSCs (Holmes HL, 2018), the literal quantity of MSC in CBMA is unlikely of significant consequence. Increased focus on the bioactive immunomodulatory/anti-inflammatory molecules in CBMA through proteomic studies is more likely to reveal the mechanism of action of CBMA and therefore identify a biomarker to define quality of CBMA. To that end, a future study design could compare proteins in A) CBMA given to patients with knee OA that had a good clinical response versus B) CBMA given to patients with knee OA that did not have a good response. This comparative study design of “responders” to “non-responders” can begin to identify target molecules of interest as recently demonstrated in a PRP study (Zahir, In Press). Only then can comparisons of “quality” between harvest sites and defining of dose be studied.

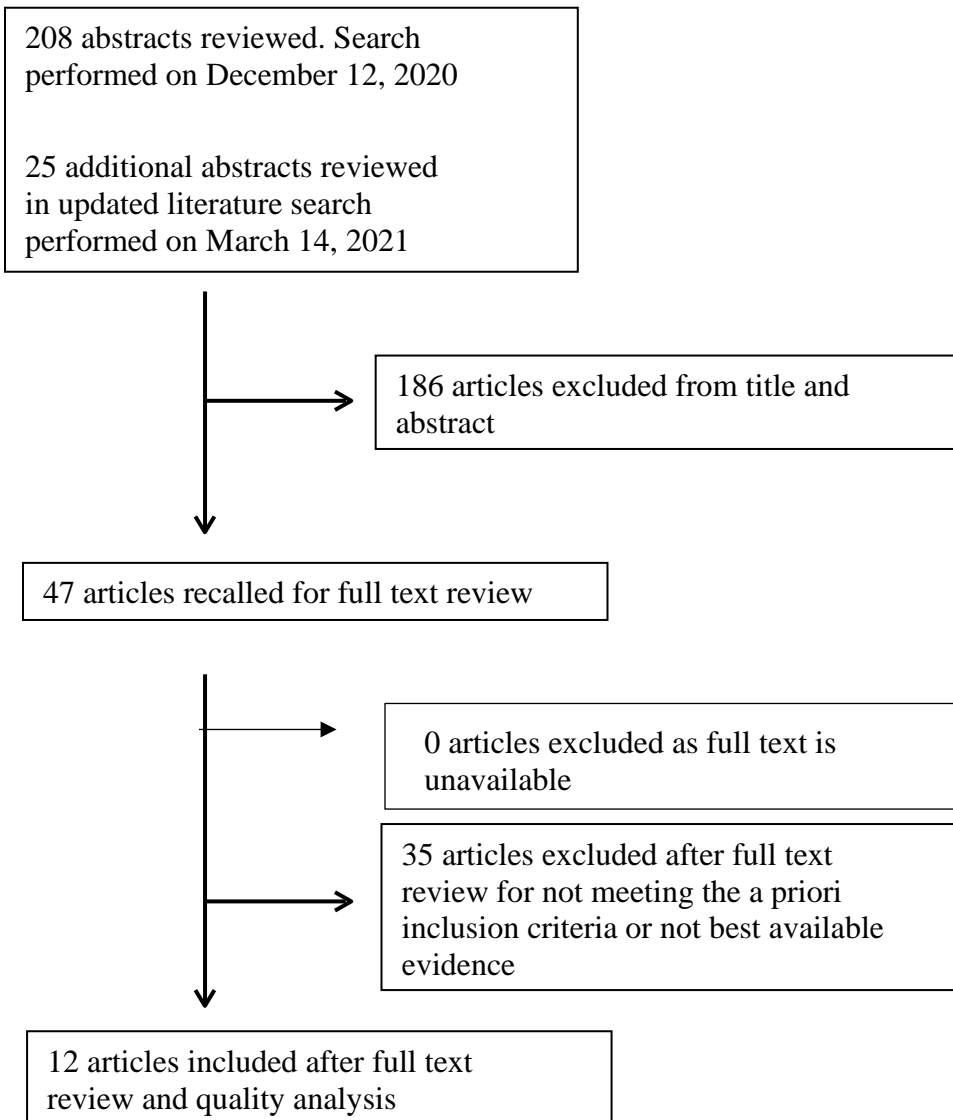
Donor (patient) Variability: Donor variability (Chahla J, 2016) (Cassano JM, 2018) (Siegel G, 2013) is concerning when trying to assimilate the body of literature for CBMA in knee OA. Patient variabilities including age, sex, physiology, medical comorbidities, prior surgeries, prior injections, and genetics (among other factors) are likely contributing factors to outcome. These patient-specific factors must be considered when designing future research studies. One potential opportunity to account for variability would be to administer biologic in one healthy knee versus one knee with OA, applying the biologic (or control) to both knees, in an animal model.

- 6) Joint Alignment and Stability: Any chondrogenic or chondroprotective effect mediated by CBMA are only likely of benefit if there is mechanical stability and alignment in the joint. Joint stability and alignment should be included as patient-specific factors in analyses.
- 7) Impact of Pathogenesis of OA: Improved stratification of the knee OA disease process. OA is not a static disease, but rather fluctuates in symptomology. In addition, radiographic features of knee OA do not always correlate with clinical symptoms. Furthermore, some knees with OA may be inflamed and respond differently to a biology treatment, versus other knees that have the same radiographic classification of OA, but are not inflamed (no effusion or warmth, for example). It remains unclear as to how the timing of CBMA injection(s) reflect the immunomodulatory/inflammatory status of the joint. Future studies/trials need to consider this when establishing study methods.

Conclusions

The use of concentrated bone marrow aspirate (CBMA) for the treatment of osteoarthritis of the knee may show promise in future clinical application, however, the current state of published literature includes limitations. Among the papers identified for this analysis, studies comparing CBMA to placebo did not identify statistically significant improved outcomes beyond 1 week (Shapiro, 2017; Shapiro, 2019). Studies comparing CBMA to non-placebo treatments frequently identified improvement from baseline, but rarely showed statistically significant outcome improvement over other treatments (Hernigou 2018, Centeno 2018, Hernigou 2020, Gocars 2017, Anz 2020, Estrada 2020, Mautner 2019, Yang 2021). Future higher quality research will be necessary to identify the true efficacy of CBMA as an alternative to conventional treatment modalities. Due to the heterogeneity of the available data and the variable nature of cell-based therapies which are influenced by numerous host, preparation, and delivery factors, the ability to draw strong conclusions on the utility/efficacy of CBMA for knee OA is limited.

Study of Attrition Flow Chart



SOF: concentrated bone marrow aspirate vs. Control/Placebo

Composite

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
↑ Better Outcomes ↓ Worse Outcomes ● Not Significant				
Composite				
IKDC			●	
WOMAC Total			↑	
KL Grade 1	●			
KL Grade 2	●			
KL Grade 3	●			

Function

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
↑ Better Outcomes ↓ Worse Outcomes ● Not Significant				
Function				
Hip-Knee-Ankle (valgus, degrees)			●	
Posterior Tibial Slope (degrees)			●	
Femoral Mechanical Axis (degrees)			↑	
Tibial Mechanical Axis (degrees)			●	
KSS Function			●	

Other

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>				
Other				
Algometer - Medial Joint Line Measurement	●			
Algometer - 1cm Above Medial Joint Line Measurement	●			
Algometer - 1cm Below Medial Joint Line Measurement	●			
Medial Femoral Condyle	●			
Lateral Femoral Condyle	●			
Medial Tibial Plateau	●			
Lateral Tibial Plateau	●			
Patella	●			
Activity Level		●		
Postoperative weight-bearing line %				●
Postoperative mFTA (degree)				●
Opening angle (degree)				●
Opening gap (mm)				●
Osteotomy filling				↑
Osteoconductivity modified van Hemert's Score				↑

Pain

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
↑ Better Outcomes ↓ Worse Outcomes ● Not Significant				
Pain				
KSS Pain			↑	
VAS Pain	●	●		
WOMAC Pain				
KOOS Pain				
ICOAP - Constant Pain	●	●		
ICOAP - Intermittent Pain	●	●		
ICOAP - Total Pain	●	●		
Does your knee pain limit your activity level? (Not at all/Mildly)	●			
Does your knee pain limit your activity level? (Moderately)	●			
Does your knee pain limit your activity level? (Severely/Extremely)	●			
Improvement in Knee Pain	●			

OA Progression

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
↑ Better Outcomes ↓ Worse Outcomes ● Not Significant				
OA progression				
HSS Score				●
Knee Society KS				●
Knee Society FS				●

Quality of Life

	High		Low	
	Shapiro, 2019	Shapiro, 2017	Jin, 2020	Kim, 2020
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>				
QOL				
ICOAP - How much has constant knee pain affected quality of life? (% that improved)	●			
ICOAP - How much has intermittent knee pain affected quality of life? (% that improved)	●			

SOF: concentrated bone marrow aspirate vs. Other Tx

Composite

	High		Moderate			Low	
	Centeno, 2018	Hernigou, 2018	Hernigou, 2020	Anz, 2020	Goncars, 2017	Estrada, 2020	Mautner, 2019
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>							
Composite							
IKDC				●		↓	
WOMAC Total				●			
KOOS Total					●		
Emory Quality of Life - Composite							●
WOMAC General							

Function

	High		Moderate		Low		
	Centeno, 2018	Hernigou, 2018	Hernigou, 2020	Anz, 2020	Goncars, 2017	Estrada, 2020	Mautner, 2019
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>							
Function							
KSS Function	●				●	↑	
KSS Knee	↑	●	●		●	↓	
WOMAC Stiffness				●			
WOMAC Function				●			
KOOS Symptoms					↑		
KOOS Sports/Rec					●		●
Emory Quality of Life - Mobility							●
Emory Quality of Life - Self-Care							●
Emory Quality of Life - Usual Activities							●
KOOS ADL					●		●
LEAS	↑						
SF-12 Physical Component Summary	●						
ROM (degrees)	●						
Use of Crutches (days)		●					

Pain

	High		Moderate		Low		
	Centeno, 2018	Hernigou, 2018	Hernigou, 2020	Anz, 2020	Goncars, 2017	Estrada, 2020	Mautner, 2019
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>							
Pain							
VAS Pain	●		●				●
WOMAC Pain				↓			
KOOS Pain					●		●
Emory Quality of Life - Pain/Discomfort							●

Quality of Life

	High		Moderate			Low	
	Centeno, 2018	Hernigou, 2018	Hernigou, 2020	Anz, 2020	Goncars, 2017	Estrada, 2020	Mautner, 2019
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>							
QOL							
KOOS QOL						●	●
Emory Quality of Life - Anxiety							●
SF-12 Mental Component Summary	●						

Adverse Events

	High		Moderate			Low	
	Centeno, 2018	Hernigou, 2018	Hernigou, 2020	Anz, 2020	Goncars, 2017	Estrada, 2020	Mautner, 2019
<p>↑ Better Outcomes</p> <p>↓ Worse Outcomes</p> <p>● Not Significant</p>							
Adverse events							
Adverse Events		↑					

Data Tables

Table 1: concentrated bone marrow aspirate vs. Control/Placebo- Composite

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Jin, 2020	Low	IKDC	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	4.3 (-0.18, 8.78)	NS
Jin, 2020	Low	WOMAC Total	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	-4.1 (-8.11, -0.09)	concentrated bone marrow aspirate w/ Microfracture
Shapiro, 2019	High	KL Grade 1	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	1.00(0.15,6.55)	NS
Shapiro, 2019	High	KL Grade 2	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	0.63(0.36,1.10)	NS
Shapiro, 2019	High	KL Grade 3	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	1.86(0.89,3.86)	NS

Table 2: concentrated bone marrow aspirate vs. Control/Placebo- Function

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Jin, 2020	Low	Hip-Knee-Ankle (valgus, degrees)	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	0.4 (-0.44, 1.24)	NS
Jin, 2020	Low	Posterior Tibial Slope (degrees)	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	1.2 (-0.42, 2.82)	NS
Jin, 2020	Low	Femoral Mechanical Axis (degrees)	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	1.2 (0.41, 1.99)	concentrated bone marrow aspirate w/ Microfracture
Jin, 2020	Low	Tibial Mechanical Axis (degrees)	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	0.8 (-0.69, 2.29)	NS
Jin, 2020	Low	KSS Function	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	2.2 (-1.59, 5.99)	NS

Table 3: concentrated bone marrow aspirate vs. Control/Placebo- OA progression

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Kim, 2020	Low	HSS Score	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	HSS Score	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	HSS Score	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	HSS Score	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society KS	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society KS	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society KS	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society KS	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society FS	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society FS	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society FS	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Knee Society FS	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS

Table 4: concentrated bone marrow aspirate vs. Control/Placebo- Other

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Shapiro, 2019	High	Algometer - Medial Joint Line Measurement	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Algometer - 1cm Above Medial Joint Line Measurement	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Algometer - 1cm Below Medial Joint Line Measurement	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Medial Femoral Condyle	6 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Lateral Femoral Condyle	6 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Medial Tibial Plateau	6 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Lateral Tibial Plateau	6 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Patella	6 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2017	High	Activity Level	1 wks	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= >.99	N/A	NS
Shapiro, 2017	High	Activity Level	3 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= >.99	N/A	NS
Shapiro, 2017	High	Activity Level	6 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= >.51	N/A	NS
Kim, 2020	Low	Postoperative weight-bearing line %	.	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Kim, 2020	Low	Postoperative mFTA (degree)	.	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS
Kim, 2020	Low	Opening angle (degree)	.	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS
Kim, 2020	Low	Opening gap (mm)	.	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS
Kim, 2020	Low	Osteotomy filling	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported - 4.000000000000001E-3	N/A	concentrated bone marrow aspirate
Kim, 2020	Low	Osteotomy filling	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported - 5.000000000000001E-3	N/A	concentrated bone marrow aspirate
Kim, 2020	Low	Osteotomy filling	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS
Kim, 2020	Low	Osteotomy filling	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	Allograft chip: n/a	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 1)	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported - 2.500000000000001E-2	N/A	concentrated bone marrow aspirate
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 2)	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 3)	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 4)	6 wks	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 1)	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported - 3.1E-2	N/A	concentrated bone marrow aspirate
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 2)	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 3)	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 4)	3 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 1)	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 2)	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 3)	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 4)	6 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 1)	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 2)	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 3)	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS
Kim, 2020	Low	Osteoconductivity modified van Hemert's Score (Zone 4)	12 mos	Allograft bone chips mixed with autologous BM aspirated: n/a	1. Placebo/Control	Author Reported	N/A	NS

Table 5: concentrated bone marrow aspirate vs. Control/Placebo- Pain

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Jin, 2020	Low	KSS Pain	Postop	concentrated bone marrow aspirate w/ Microfracture: 1x	Control (Microfracture Alone): 1x	Mean Difference	2.9 (0.09, 5.71)	concentrated bone marrow aspirate w/ Microfracture
Shapiro, 2019	High	ICOAP - Constant Pain	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	ICOAP - Intermittent Pain	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	ICOAP - Total Pain	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	VAS Pain	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	Does your knee pain limit your activity level? (Not at all/Mildly)	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	0.94(0.61,1.45)	NS
Shapiro, 2019	High	Does your knee pain limit your activity level? (Moderately)	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	1.00(0.41,2.43)	NS
Shapiro, 2019	High	Does your knee pain limit your activity level? (Severely/Extremely)	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	1.50(0.27,8.22)	NS
Shapiro, 2019	High	Improvement in Knee Pain	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	RR	1.14(0.72,1.80)	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Shapiro, 2017	High	ICOAP - Constant Pain	3 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= 0.53	N/A	NS
Shapiro, 2017	High	ICOAP - Intermittent Pain	3 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= 0.09	N/A	NS
Shapiro, 2017	High	ICOAP - Total Pain	3 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= 0.24	N/A	NS
Shapiro, 2017	High	VAS Pain	3 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .88	N/A	NS
Shapiro, 2017	High	ICOAP - Constant Pain	6 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .89	N/A	NS
Shapiro, 2017	High	ICOAP - Intermittent Pain	6 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .49	N/A	NS
Shapiro, 2017	High	ICOAP - Total Pain	6 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .54	N/A	NS
Shapiro, 2017	High	VAS Pain	6 mos	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .44	N/A	NS
Shapiro, 2017	High	ICOAP - Constant Pain	1 wks	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .67	N/A	NS
Shapiro, 2017	High	ICOAP - Intermittent Pain	1 wks	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .41	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Shapiro, 2017	High	ICOAP - Total Pain	1 wks	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .57	N/A	NS
Shapiro, 2017	High	VAS Pain	1 wks	Fifty-two milliliters of bone marrow was aspirated from the iliac crests and concentrated in an automated centrifuge: n/a	Saline Injection: 15 mL	Author Reported - p= .47	N/A	NS

Table 6: concentrated bone marrow aspirate vs. Control/Placebo- QOL

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Shapiro, 2019	High	ICOAP - How much has constant knee pain affected quality of life? (% that improved)	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS
Shapiro, 2019	High	ICOAP - How much has intermittent knee pain affected quality of life? (% that improved)	12 mos	concentrated bone marrow aspirate: 1x, 5ml concentrated bone marrow aspirate, 10ml Platelet-Poor Bone Marrow Plasma	Placebo (Saline): 1x, 15ml	Author Reported - Paired Wilcoxon Signed Rank Test	N/A	NS

Table 7: concentrated bone marrow aspirate vs. Other Tx- Adverse events

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Hernigou, 2018	High	Adverse Events	6 mos	BMMSCs: 6500 MSCs/ml (CFU-F 3420 to 9830)	TKA: n/a	Author Reported - Student's t -test, Wilcoxon Signed-Rank test	N/A	BMMSCs

Table 8: concentrated bone marrow aspirate vs. Other Tx- Composite

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Estrada, 2020	Low	IKDC	90 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	-1.2 (-3.04, 0.64)	NS
Estrada, 2020	Low	IKDC	180 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	1.1 (-0.67, 2.87)	NS
Estrada, 2020	Low	IKDC	360 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	-2.2 (-4.12, -0.28)	PRP
Estrada, 2020	Low	IKDC	90 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-0.8 (-2.52, 0.92)	NS
Estrada, 2020	Low	IKDC	180 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-5.6 (-7.33, -3.87)	Adipose Tissue-Derived Stem Cells
Estrada, 2020	Low	IKDC	360 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-6.6 (-8.52, -4.68)	Adipose Tissue-Derived Stem Cells
Anz, 2020	Moderate	IKDC	1 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.1 (-7.95, 8.15)	NS
Anz, 2020	Moderate	IKDC	3 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	2 (-5.35, 9.35)	NS
Anz, 2020	Moderate	IKDC	6 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-1.3 (-9.96, 7.36)	NS
Anz, 2020	Moderate	IKDC	9 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.6 (-8.40, 9.60)	NS
Anz, 2020	Moderate	IKDC	12 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.6 (-8.05, 9.25)	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Anz, 2020	Moderate	WOMAC Total	1 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.3 (-6.31, 6.91)	NS
Anz, 2020	Moderate	WOMAC Total	3 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-3 (-9.18, 3.18)	NS
Anz, 2020	Moderate	WOMAC Total	6 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	3.2 (-3.71, 10.11)	NS
Anz, 2020	Moderate	WOMAC Total	9 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-0.8 (-7.94, 6.34)	NS
Anz, 2020	Moderate	WOMAC Total	12 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	2.6 (-4.51, 9.71)	NS
Mautner, 2019	Low	Emory Quality of Life - Composite	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	0.061 (-0.02, 0.14)	NS
Goncars, 2017	Moderate	KOOS Total	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Total	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Total	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Total	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Table 9: concentrated bone marrow aspirate vs. Other Tx- Function

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Hernigou, 2020	Moderate	KSS Knee	3 mos	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Mean Difference	2.3 (-1.71, 6.31)	NS
Hernigou, 2020	Moderate	KSS Knee (most recent follow-up)	Postop	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Mean Difference	2 (-2.22, 6.22)	NS
Estrada, 2020	Low	KSS Knee	90 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	0.3 (-1.61, 2.21)	NS
Estrada, 2020	Low	KSS Knee	180 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	-1.3 (-3.30, 0.70)	NS
Estrada, 2020	Low	KSS Knee	360 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	-0.7 (-2.61, 1.21)	NS
Estrada, 2020	Low	KSS Function	90 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	4.7 (2.31, 7.09)	concentrated bone marrow aspirate
Estrada, 2020	Low	KSS Function	180 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	0.5 (-1.75, 2.75)	NS
Estrada, 2020	Low	KSS Function	360 days	concentrated bone marrow aspirate: 1x, 30ml	PRP: 1x, 10ml	Mean Difference	2.3 (0.15, 4.45)	concentrated bone marrow aspirate
Estrada, 2020	Low	KSS Knee	90 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-2.3 (-4.36, -0.24)	Adipose Tissue-Derived Stem Cells
Estrada, 2020	Low	KSS Knee	180 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-5.4 (-7.40, -3.40)	Adipose Tissue-Derived Stem Cells
Estrada, 2020	Low	KSS Knee	360 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-8.9 (-10.79, -7.01)	Adipose Tissue-Derived Stem Cells

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Estrada, 2020	Low	KSS Function	90 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	7.9 (5.55, 10.25)	concentrated bone marrow aspirate
Estrada, 2020	Low	KSS Function	180 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	1.3 (-0.86, 3.46)	NS
Estrada, 2020	Low	KSS Function	360 days	concentrated bone marrow aspirate: 1x, 30ml	Adipose Tissue-Derived Stem Cells: 1x, 25ml	Mean Difference	-1.1 (-3.26, 1.06)	NS
Anz, 2020	Moderate	WOMAC Stiffness	1 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0 (-0.62, 0.62)	NS
Anz, 2020	Moderate	WOMAC Stiffness	3 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-0.1 (-0.72, 0.52)	NS
Anz, 2020	Moderate	WOMAC Stiffness	6 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.2 (-0.46, 0.86)	NS
Anz, 2020	Moderate	WOMAC Stiffness	9 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.3 (-0.39, 0.99)	NS
Anz, 2020	Moderate	WOMAC Stiffness	12 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.5 (-0.16, 1.16)	NS
Anz, 2020	Moderate	WOMAC Function	1 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.2 (-4.39, 4.79)	NS
Anz, 2020	Moderate	WOMAC Function	3 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-2.7 (-7.19, 1.79)	NS
Anz, 2020	Moderate	WOMAC Function	6 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	1.3 (-3.47, 6.07)	NS
Anz, 2020	Moderate	WOMAC Function	9 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-0.9 (-5.92, 4.12)	NS
Anz, 2020	Moderate	WOMAC Function	12 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	1.5 (-3.61, 6.61)	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Mautner, 2019	Low	Emory Quality of Life - Mobility	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.101 (-0.33, 0.13)	NS
Mautner, 2019	Low	Emory Quality of Life - Self-Care	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.011 (-0.12, 0.10)	NS
Mautner, 2019	Low	Emory Quality of Life - Usual Activities	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.165 (-0.44, 0.11)	NS
Mautner, 2019	Low	KOOS Symptoms	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	1.8 (-9.06, 12.66)	NS
Mautner, 2019	Low	KOOS ADL	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	3.6 (-5.36, 12.56)	NS
Mautner, 2019	Low	KOOS Sports/Rec	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	9.8 (-7.07, 26.67)	NS
Centeno, 2018	Moderate	LEAS	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	concentrated bone marrow aspirate w/ Platelet Products
Centeno, 2018	Moderate	KSS Knee	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	concentrated bone marrow aspirate w/ Platelet Products
Centeno, 2018	Moderate	KSS Function	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	NS
Centeno, 2018	Moderate	SF-12 Physical Component Summary	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	NS
Centeno, 2018	Moderate	ROM (degrees)	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Hernigou, 2018	High	Use of Crutches (days)	Periop .	BMMSCs: 6500 MSCs/ml (CFU-F 3420 to 9830)	TKA: n/a	Mean Difference	-18 (-39.38, 3.38)	NS
Hernigou, 2018	High	KSS Knee	3 mos	BMMSCs: 6500 MSCs/ml (CFU-F 3420 to 9830)	TKA: n/a	Mean Difference	2.3 (-6.36, 10.96)	NS
Hernigou, 2018	High	KSS Knee ("most recent follow-up; average 12 years, range 8-16 years")	Postop	BMMSCs: 6500 MSCs/ml (CFU-F 3420 to 9830)	TKA: n/a	Mean Difference	2 (-7.12, 11.12)	NS
Goncars, 2017	Moderate	KOOS Symptoms	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Symptoms	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Symptoms	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	BMDMC
Goncars, 2017	Moderate	KOOS Symptoms	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	BMDMC
Goncars, 2017	Moderate	KOOS ADL	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS ADL	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS ADL	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Goncars, 2017	Moderate	KOOS ADL	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Sports/Rec	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Sports/Rec	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Sports/Rec	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Sports/Rec	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Knee	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Knee	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Knee	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Knee	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Function	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Goncars, 2017	Moderate	KSS Function	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Function	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KSS Function	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Table 10: concentrated bone marrow aspirate vs. Other Tx- Pain

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Hernigou, 2020	Moderate	VAS Pain	3 mos	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Author Reported - Student t-test, Wilcoxon Rank-Sum test, Kaplan-Meier Survival Curves, Univariate Cox Proportional-Hazards Models, Multivariate Cox Proportional-Hazards Models	N/A	NS
Hernigou, 2020	Moderate	VAS Pain	6 mos	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Author Reported - Student t-test, Wilcoxon Rank-Sum test, Kaplan-Meier Survival Curves, Univariate Cox Proportional-Hazards Models, Multivariate Cox Proportional-Hazards Models	N/A	NS
Hernigou, 2020	Moderate	VAS Pain	12 mos	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Author Reported - Student t-test, Wilcoxon Rank-Sum test, Kaplan-Meier Survival Curves, Univariate Cox Proportional-Hazards Models, Multivariate Cox Proportional-Hazards Models	N/A	NS
Hernigou, 2020	Moderate	VAS Pain	15 yrs	BMMSCs: 20ml; 10 in medial condyle, 10 in medial tibial plateau. 7800 MSCs/ml (3120-11560)	TKA: n/a	Author Reported - Student t-test, Wilcoxon Rank-Sum test, Kaplan-Meier Survival Curves, Univariate Cox Proportional-Hazards Models, Multivariate Cox Proportional-Hazards Models	N/A	NS
Anz, 2020	Moderate	WOMAC Pain	1 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.1 (-1.34, 1.54)	NS
Anz, 2020	Moderate	WOMAC Pain	3 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-0.3 (-1.63, 1.03)	NS
Anz, 2020	Moderate	WOMAC Pain	6 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	1.5 (0.06, 2.94)	PRP
Anz, 2020	Moderate	WOMAC Pain	9 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	-0.3 (-1.76, 1.16)	NS
Anz, 2020	Moderate	WOMAC Pain	12 mos	concentrated bone marrow aspirate: 1x, 7ml	PRP: 1x, 7ml	Mean Difference	0.6 (-0.73, 1.93)	NS
Li, 2020	Low	VAS Pain	6 mos	BMMSCs: 3ml platelet lysate on 1st day of surgery, 3ml of BMSC suspension on 4th day of surgery	Arthroscopic Debridement and Sodium Hyaluronate: 2ml, 1x/wk for 5wks	Mean Difference	-1.33 (-1.68, -0.98)	BMMSCs

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Li, 2020	Low	VAS Pain	12 mos	BMMSCs: 3ml platelet lysate on 1st day of surgery, 3ml of BMSC suspension on 4th day of surgery	Arthroscopic Debridement and Sodium Hyaluronate: 2ml, 1x/wk for 5wks	Mean Difference	-1.64 (-2.05, -1.23)	BMMSCs
Mautner, 2019	Low	VAS Pain	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.3 (-1.31, 0.71)	NS
Mautner, 2019	Low	Emory Quality of Life - Pain/Discomfort	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.064 (-0.32, 0.19)	NS
Mautner, 2019	Low	KOOS Pain	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	0.2 (-9.52, 9.92)	NS
Centeno, 2018	Moderate	VAS Pain	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	NS
Goncars, 2017	Moderate	KOOS Pain	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Pain	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Pain	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS Pain	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Table 11: concentrated bone marrow aspirate vs. Other Tx- QOL

Reference Title	Quality	Outcome Details	Duration	Treatment 1 (Details)	Treatment 2 (Details)	Effect Measure	Result (95% CI)	Favored Treatment
Mautner, 2019	Low	Emory Quality of Life - Anxiety	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	-0.107 (-0.33, 0.12)	NS
Mautner, 2019	Low	KOOS QOL	Postop	concentrated bone marrow aspirate: 1x, 8cc	MFAT: 1x, 9cc	Mean Difference	4 (-7.33, 15.33)	NS
Centeno, 2018	Moderate	SF-12 Mental Component Summary	3 mos	concentrated bone marrow aspirate w/ Platelet Products: 5-7cc, 75% concentrated bone marrow aspirate, 12.5% PRP, 12.5% Platelet Lysate	Physical Therapy: n/a	Author Reported - Linear Mixed-Effects Models w/ Post hoc Tukey, ANOVA, Post-hoc t-tests, Paired t-tests	N/A	NS
Goncars, 2017	Moderate	KOOS QOL	1 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS QOL	3 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS QOL	6 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS
Goncars, 2017	Moderate	KOOS QOL	12 mos	BMDMC: 1x	Sodium Hyaluronate: 25mg/2.5ml, 1% gel, 800-1500kDa, 1x/wk for 3wks	Author Reported - Student t-test, Levene's test, Independent Student t-test, Mann-Whitney U test	N/A	NS

Quality Appraisal

All studies which are considered for inclusion are evaluated using a standardized quality appraisal form and scoring key. In the quality evaluation report, domains with no flaws or a low risk of bias will be represented as a full black circle ●. Domains with a high risk of bias will be represented as a circle with a white center ○, and domains which are uncertain or not clearly stated in the study's methodology will be represented as a half black/half white circle ◐.

Randomized Study Appraisal Form

Resources used to develop the Randomized Trial Quality Appraisal System:

- GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; (328): 1490-1494.
- Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. The following domains are evaluated to determine the study quality of randomized study designs.
- Guyatt, G. H., Oxman, A. D., Sultan, S., et al. (2011). GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology*, 64(12), 1311–1316.

The following domains are evaluated to determine the study quality of randomized study designs.

- Random Sequence Generation
- Allocation Concealment
- Blinding of Participants and Personnel
- Incomplete Outcome Data
- Selective Reporting
- Other Bias

Randomized Study Design Quality Key:

High Quality Study	<2 Flaw
Moderate Quality Study	≥2 and <4 Flaws
Low Quality Study	≥4 and <6 Flaws
Very Low Quality Study	≥6 Flaws

Observational Study Appraisal Form

Resources used to develop the Observational Intervention Study Quality Appraisal System:

- Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the Development group for ROBINS-I. Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. Available from <http://www.riskofbias.info> [accessed July 2018]
- Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011;64:407–15.
- Guyatt, G. H., Oxman, A. D., Sultan, S., et al. (2011). GRADE guidelines: 9. Rating up the quality of evidence. *Journal of Clinical Epidemiology*, 64(12), 1311–1316.

Observational Study Design Quality Appraisal Questions

The following questions are used to evaluate the study quality of observational study designs. Note that all non-randomized intervention studies begin the appraisal process at “low quality” due to design flaws inherent in observational studies. They can only be upgraded to moderate quality in rare cases if they meet one of the criteria for upgrading listed below.

- Does the strategy for recruiting participants into the study differ across groups?
 - Enrolled new users of a treatment rather than current users of a treatment
 - Patients were not excluded for outcomes that occurred after the start of the study.

- Is treatment status measured/recorded accurately?
 - measured at the same time treatment started and did not rely on patient recall.

- Did the authors fail to take important confounding variables into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?

- Is there a high risk that outcomes were measured inaccurately?
 - Measured the same way in all patients
 - Blinded outcome evaluation or outcome was objective and couldn't be influenced by lack of blinding

- Are there low rates of missing outcome, treatment status, and confounder variable data OR were the rates and/or reasons for missing data similar between groups?

- Were results for all outcomes, statistical analyses and patient populations specified in the methods section, also reported in the results section?
 - No selective reporting of outcomes
 - Results from all statistical models described in methods section are reported
 - Study was not a subgroup analysis of a previously published study
 - No conflict of interest

Upgrading Observational Study Quality Questions

- Is there a large magnitude of effect?
- Influence of All Plausible Residual Confounding
- Dose-Response Gradient

Observational Study Design Quality Key

Moderate Quality Study	Only if upgrade criteria met
Low Quality Study	< 3 flaws
Very Low Quality Study	≥3 flaws

Quality Appraisal for studies included in this report:

**Intervention -
Randomized**

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias	Strength
Centeno, C., 2018	●	●		●	●	○	Moderate Quality
Hernigou, P., 2018	●	●	●	●	●	●	High Quality
Shapiro, S. A., 2017	●	●	◐	●	●	◐	High Quality
Shapiro, S. A., 2019	◐	◐	◐	●	●	●	High Quality
Anz, A. W., 2020	◐	◐	○	●	●	◐	Moderate Quality
Goncars, V., 2017	◐	◐	○	●	●	●	Moderate Quality
Hernigou, P., 2020	●	●	○	○	●	●	Moderate Quality

Intervention - Observational ROBINS 1

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Study	Is this an observational study? (If no, exit form)	Participant Recruitment	Treatment recording	Confounding Variables	Outcome measurement bias	Incomplete Outcome Data	Adequate Reporting	Strength
Estrada, E., 2020	○	●	●	◐	◐	●	●	Low Quality
Jin, Q. H., 2020	○	●	●	◐	○	●	●	Low Quality
Kim, H. J., 2020	○	●	●	◐	◐	●	●	Low Quality
Mautner, K., 2019	○	◐	●	◐	◐	●	●	Low Quality
Yang, H. Y., 2021	○	●	●	◐	◐	●	●	Low Quality

PICO Question

This technology overview is based on the following PICO question, which was developed prior to the literature search. This question specifies the patient population of interest (P), the intervention of interest (I), the comparisons of interest (C), and the patient-oriented outcomes of interest (O). They function as questions for the systematic review, not as conclusions. Once established, these a priori PICO questions cannot be modified.

Question Components	Constructing Your Question
P – Patient or Population	Patients treated for osteoarthritis of the knee
I – Intervention; Prognostic Factor; Exposure	Any Bone Marrow Aspirate Concentrate (concentrated bone marrow aspirate)
C – Comparison (if appropriate)	Any comparison treatment groups, placebo, or no treatment
O – Outcome	Any reported outcome
For patients treated for osteoarthritis of the knee, does Bone Marrow Aspirate Concentrate (concentrated bone marrow aspirate) result in significant differences in outcome, as compared to those who undergo other treatments, placebo, or no treatment?	

Literature Search Strategy

Database :	MEDLINE			
Interface :	Ovid (Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to November 04, 2020)			
Date:	11/5/2020			
Search	Biologics PICO: For patients treated for osteoarthritis of the knee, does , does Bone Marrow Aspirate Concentrate (concentrated bone marrow aspirate) result in significant differences in outcome, as compared to those who undergo other treatments, placebo, or no treatment?			
Line	Search Strategy	Results	Notes	Discarded Terms
1	exp Osteoarthritis-Knee/ OR (gonitis OR gonarthritis OR gonarthros*).ti,ab,kf.	21497		
2	exp Knee-Joint/ OR exp Knee/ OR (knee OR knees OR femorotibial OR tibial OR patella?).ti,ab,kf.	207649		
3	Osteoarthritis/ OR Arthritis/ OR (osteoarthriti* OR osteo-arthritis* OR osteo-arthros* OR osteoarthros*).ti,ab,kf. OR ((non-inflamm* OR noninflamm* OR degenerat* OR hypertropic) AND (arthriti* OR joint* OR disease*)).ti,ab,kf.	205750		
4	1 OR (2 AND 3)	45507	Knee OA Concept	
5	(exp "Animals"/ NOT Humans/) OR exp "Cadaver"/ OR (animal? OR dog OR dogs OR canine OR cat OR cats OR feline OR horse? OR equine OR mouse OR mice OR rat OR rats OR rabbit? OR sheep OR porcine OR pig OR pigs OR rodent? OR monkey?).ti. OR (cadaver* OR in vitro).ti,ab. OR ((comment OR editorial OR letter OR historical article) NOT clinical trial).pt. OR address.pt. OR news.pt. OR newspaper article.pt. OR pmcbook.af. OR case reports.pt. OR (case report?	1033941 4	Humans & Relevant Publication Types Only	

	OR abstracts OR editorial OR reply OR comment? OR commentary OR letter OR biomechanic*).ti.			
6	(4 NOT 5) AND English.lg.	31503	English Limit	
7	Bone-Marrow-Transplantation/ OR ((marrow AND (aspirat* OR concentrat* OR inject*)) OR concentrated bone marrow aspirate?).mp.	26479	concentrated bone marrow aspirate Concept	biological-therapy/de OR regenerative-medicine/de OR (biologic\$ OR orthobiologic* OR biotherap*OR autologous-blood OR (biologic* NEAR/3 therap*) OR thrombocyte-rich):ti,ab,kw
8	6 AND 7	177	Final Results	
		175	De-duplicated Results	

Database :	Embase			
Interface :	Elsevier			
Date:	11/5/2020			
Search	Biologics PICO: For patients treated for osteoarthritis of the knee, does , does Bone Marrow Aspirate Concentrate (concentrated bone marrow aspirate) result in significant differences in outcome, as compared to those who undergo other treatments, placebo, or no treatment?			
Line	Search Strategy	Results	Notes	Discarded Terms
1	knee-osteoarthritis/exp OR (gonitis OR gonarthriti OR gonarthros*):ti,ab,kw	35611		
2	knee/exp OR (knee OR knees OR femorotibial OR tibial OR patella\$):ti,ab,kw	262061		
3	osteoarthritis/exp OR (osteoarthriti* OR osteo-arthritis* OR osteoarthros* OR osteoarthros* OR OA):ti,ab,kw OR ((non-inflamm*	294965		

	OR noninflamm* OR degenerat* OR hypertropic) AND (arthriti* OR joint* OR disease*)):ti,ab,kw			
4	#1 OR (#2 AND #3)	64857	Knee OA Concept	
5	abstract-report/de OR book/de OR editorial/de OR editorial:it OR note/de OR note:it OR letter/de OR letter:it OR case-study/de OR case- report/de OR chapter:it OR conference-paper/exp OR conference-paper:it OR conference- abstract:it OR conference-review:it OR (abstracts OR editorial OR reply OR comment\$ OR commentary OR letter OR biomechanic*):ti OR cadaver/de OR in-vitro-study/exp OR (cadaver* OR in-vitro):ti,ab OR animal-experiment/exp OR (animal\$ OR dog OR dogs OR canine OR cat OR cats OR feline OR horse\$ OR equine OR mouse OR mice OR rat OR rats OR rabbit\$ OR sheep OR porcine OR pig OR pigs OR rodent\$ OR monkey\$):ti	1665296 0	Humans & Relevant Publicatio n Types Only	
6	#4 NOT #5 AND [english]/lim	29376	English Limit	
7	bone-marrow-transplantation/exp OR ((marrow AND (aspirat* OR concentrat* OR inject*)) OR concentrated bone marrow aspirate\$):ti,ab,kw	125855	Platelet- Rich Plasma Concept	biological- therapy/de OR regenerative- medicine/de OR (biologic\$ OR orthobiologic* OR biotherap*OR autologous-blood OR (biologic* NEAR/3 therap*) OR thrombocyte- rich):ti,ab,kw
8	#6 AND #7	122	Final Results	
		32	De- duplicated Results	

Database :	CENTRAL			
Interface:	Cochrane Library			
Date:	11/5/2020			
Search	Biologics PICO: For patients treated for osteoarthritis of the knee, does , does Bone Marrow Aspirate Concentrate (concentrated bone marrow aspirate) result in significant differences in outcome, as compared to those who undergo other treatments, placebo, or no treatment?			
Line	Search Strategy	Results	Notes	Discarded Terms
1	[mh "Osteoarthritis, Knee"] OR (gonitis OR gonarthritis OR gonarthros*):ti,ab,kw	4786		
2	[mh "Knee Joint"] OR [mh "Knee"] OR (knee OR knees OR femorotibial OR tibial OR patella?):ti,ab,kw	32549		
3	[mh ^Osteoarthritis] OR [mh ^Arthritis] OR (osteoarthriti* OR osteo-arthritis* OR osteo-arthros* OR osteoarthros*):ti,ab,kw OR ((non-inflamm* OR noninflamm* OR degenerat* OR hypertropic) AND (arthriti* OR joint* OR disease*)):ti,ab,kw	29053		
4	#1 OR (#2 AND #3)	12868	Knee OA Concept	
5	"conference abstract":pt OR (abstracts OR editorial OR reply OR comment? OR commentary OR letter OR biomechanic*):ti OR (cadaver* OR "in vitro"):ti,ab OR (animal? OR dog OR dogs OR canine OR cat OR cats OR feline OR horse? OR equine OR mouse OR mice OR rat OR rats OR rabbit? OR sheep OR porcine OR pig OR pigs OR rodent? OR monkey?):ti	191866	Humans & Relevant Publication Types Only	
6	#4 NOT #5	11145	English Limit	
7	[mh "Bone Marrow Transplantation"] OR ((marrow AND (aspirat* OR concentrat* OR inject*)) OR concentrated bone marrow aspirate?):ti,ab,kw	4670	Platelet-Rich Plasma Concept	biological-therapy/de OR regenerative-medicine/de OR (biologic\$ OR orthobiologic* OR biotherap*OR autologous-blood

				OR (biologic* NEAR/3 therap*) OR thrombocyte- rich):ti,ab,kw
8	#6 AND #7	87	Final Results	
		1	De- duplicate d Results	

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