Indian Journal of Orthopaedics (2024) 58:835–844
https://doi.org/10.1007/s43465-024-01183-7

REVIEW ARTICLE

Safety and Efficacy of Bone-Marrow Aspirate Concentrate in Hip Osteoarthritis: A Systematic Review of Current Clinical Evidence

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Received: 30 March 2024 / Accepted: 4 May 2024 / Published online: 17 May 2024
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Abstract

Introduction Hip osteoarthritis (OA) is one of the leading causes of disability and morbidity worldwide. It is estimated to affect 9.2% individuals globally with age over 45 years. Conventional treatment modalities have limitations and side-effects. To overcome these limitations, over the last decade, there has been an increased interest in the use of orthobiologics derived from autologous sources including platelet-rich plasma (PRP), bone-marrow aspirate concentrate (BMAC) and adipose tissue derived formulations. This review qualitatively presents the in-vitro, pre-clinical, clinical and on-going clinical studies exploring the safety and efficacy of BMAC for management of hip OA.

Materials and methods The electronic database search was done through PubMed, Embase, Web of Science, Scopus, ProQuest and Google Scholar till February 2024. The search terms used were "osteoarthritis" OR "hip osteoarthritis" OR "orthobiologics" OR "efficacy or use of orthobiologic treatment" OR "bone-marrow concentrate" OR "bone-marrow aspirate concentrate", AND "BMAC". The inclusion criteria were clinical studies of any level of evidence written in the English language, published till February 2024, evaluating the safety and efficacy of intra-articular administration of BMAC for the management of hip OA.

Results A total of 5 studies were included in this review for qualitative data synthesis. The total number of patients who participated in the study was 182, ranging from 4 to 112 in a single study. No adverse events were reported throughout the duration of the study. In addition, intra-articular administration of BMAC led to reduced pain, and improved function and overall quality of life (QoL).

Conclusion The results from this review demonstrated that administration of BMAC is safe and potentially efficacious in terms of reducing pain, improving function and overall QoL of patients with hip OA in short- and mid-term average follow-up based on the included studies. Nonetheless, more adequately powered, multi-center, prospective, double-blind, non-randomized and randomized controlled trials with long-term follow-up are warranted to establish long-term safety and efficacy of BMAC for management of hip OA and justify its routine clinical use.

Keywords Orthobiologics · Hip osteoarthritis · Bone-marrow aspirate concentrate · BMAC · Regenerative medicine

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Introduction

A leading global cause of disability and morbidity is osteoarthritis (OA) [1–3]. According to Global Burden of Disease study 2021, 7.6% [595 million] of global population are affected by OA in 2020 which is expected to increase by 74.9% for knee OA, 48.6% for hand OA, 78.6% for OA hip, and 95.1% for other types of OA by 2050 [4]. Perhaps one of the most commonly affected joint is the hip, and it is estimated that 9.2% of people over 45 years of age have symptomatic hip OA, which is marked by pain, stiffness, and mobility loss, usually accompanied by reduced activity of daily living (ADL) and overall quality of life (QoL) [5, 6]. Such rise of OA cases over globe leads to increased economic healthcare burden throughout the world [7].

To manage hip OA, several conservative methods are currently available. These include weight loss, activity modification, physical therapy, oral medications, and intra-articular injections of corticosteroids or hyaluronic acid (HA) [8–11] with arthroplasty as a last resort for treating end-stage OA [12]. The above-mentioned conventional treatment modalities have limitations, continually focusing on decreasing pain rather than targeting the underlying pathology. To overcome these short-comings, the field of regenerative medicine has evolved [13–15]. Several orthobiologics including autologous peripheral blood derived orthobiologics, BMAC and SVF have seen significant increase in their utilization for musculoskeletal regenerative medicine applications. Despite this, there are limited studies assessing the safety and efficacy of BMAC for treatment of hip OA.

Orthobiologic treatments have gained attention as a more sustainable approach to tackling the increasing problem of OA. [16] The introduction of bone-marrow aspirate concentrate (BMAC) has resulted in greater ease of use and better acceptance by clinicians and patients [17]. Various techniques for concentrating bone-marrow aspirate to form BMAC have been proposed. Ficoll density gradients are used in the laboratory, and automated, closed centrifugation systems are used in the clinical setting [18]. The BMAC, which can be obtained directly on-site in a single treatment step using the minimal cell manipulation approach, has recently been proposed as a promising injective treatment for degenerative orthopaedic conditions [19, 20]. The precise mechanism of action of BMAC is currently unknown. The MSCs contained within BMAC will provide a direct cell source for repair of the host tissue. Alternatively, the nucleated cells may also have a significant paracrine effect, delivering various cytokines and growth factors to orchestrate and direct host repair [21–23]. Growth factors found in BMAC have been linked to chondrocyte proliferation, mesenchymal stem cell (MSC) differentiation, wound healing, and the reduction of pro-inflammatory cytokines [24, 25]. BMAC could possibly have both anti-inflammatory and anabolic effects after being injected into an OA joint. Apart from this rationale, the increased use of BMAC is also due to the severe restrictions and regulatory issues associated with other strategies that require extended cell manipulation and in vitro cultivation [26–29].

The primary objective of this study is to summarize the outcomes of clinical studies involving BMAC for hip OA management. The secondary objective is to document the ongoing clinical studies listed on various clinical trial protocol repositories involving BMAC for the treatment of hip OA.

Materials and Methods

The electronic database search were done through PubMed, Embase, Web of Science, Scopus, ProQuest and Google Scholar for manuscripts published till February 2024, in English language, while adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search terms used were “osteoarthritis” OR “hip osteoarthritis” OR “orthobiologics” OR “efficacy or use of orthobiologic treatment” OR “bone-marrow concentrate” OR “bone-marrow aspirate concentrate”, AND “BMAC”. A systematic literature review was carried out using aforementioned search terms for BMAC as an intervention for the treatment of hip OA. Studies not published in English, review articles, in vitro and pre-clinical studies, and congress abstracts were excluded. Studies not using BMAC alone or not targeting treatment of hip OA or treating other hip pathologies were excluded. Each article was reviewed independently by the two authors, and any discrepancies between their reviews were reconciled through discussion and consensus. For the included studies, relevant data were extracted from article texts, tables, and figures and then summarized and analyzed according to the purpose of the present review. In particular, data such as author, study title, year of publication, place of a study conducted, study design, tools and technique used, intervention and outcome measures, follow-up lengths and significant findings were analyzed. The flow diagram of the article selection process is presented in Fig. 1.

Results

A preliminary search of abstracts and titles yielded 2245 articles. There were duplicate articles removed, and 1221 studies were screened, with 1193 studies excluded due to

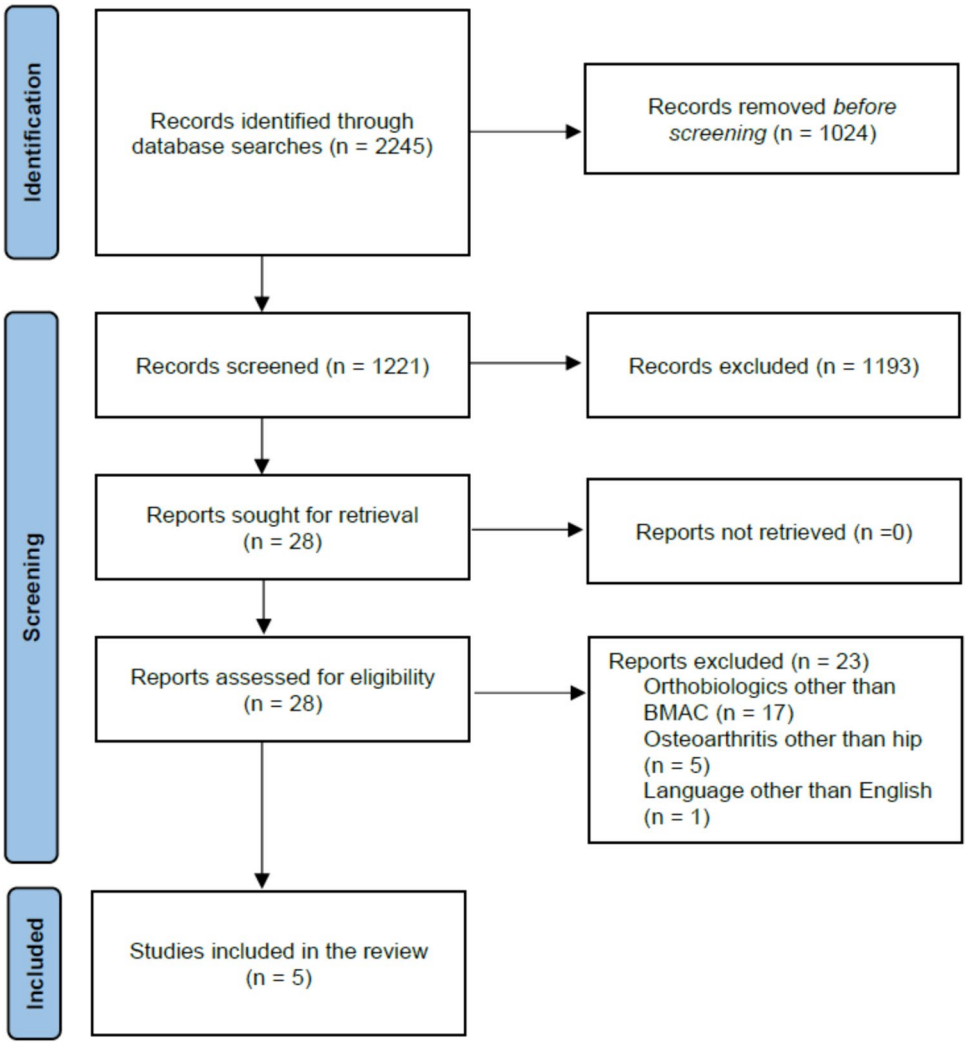


Fig. 1 PRISMA flow diagram of included studies

title and abstract issues. The most common reasons for exclusion were that the study was not on orthobiologic intervention but not on intervention for osteoarthritis, concept articles, conference proceedings, unrelated topics, and 28 full-text articles assessed for eligibility. However, 23 studies excluded BMAC not for hip osteoarthritis, reviews, studies assessed other forms of orthobiologics for hip and other arthritis and preclinical research studies. Thus, a total of 5 studies are included in this review.

Description of Studies and Study Participants

The review included five studies in total. Four studies were conducted in the USA and one in Canada. For the current review, studies published from 2018 to September 2023 were included. One study was done in 2022, one in 2021, one in 2020 and two in 2018. Of the total reviewed studies, one was retrospective, and one was prospective. Most of the studies were case series. All the analyses were done in a single setting with one group except one study where the findings were compared with a previous study on knee arthritis. Out of five studies, The total number of patients who participated was 182, ranging from 4 to 112 in a single study. The age of the patients was from 18 to 83. Patients included in the study had the diagnosis of unilateral or bilateral hip arthritis, with few patients having both hip and knee arthritis.

Techniques and Intervention

Approximately 6–120 ml of bone-marrow was aspirated from the anterior or posterior iliac crest guided by ultrasound and centrifuged to have final bone-marrow concentrate except in one study where BMA was injected. The different techniques and tools used to collect the bone-marrow aspirate were The Marrow Cellution Bone-marrow Harvesting Device (Ranfac Corp., Avon, MA), BMA kit (Arrow On Control; Teleflex) and bone-marrow aspiration needle of various sizes/gauges. The 60–120 ml of BMA was centrifuged to get the final BMC of different volumes in these studies ranging from 6 to 12 ml using an IEC Centra-CL2 benchtop centrifuge

(Bio CUE Platelet Concentration System; Zimmer Biomet, Warsaw, IN) (Thermo IEC) as well as manual method.

Using an ultrasound-guided image, the final bone-marrow aspirate concentrate varying from 6 to 12 ml was injected into the intraarticular space. In one study, 4 BMC treatments were in succession, with follow-up injections given on average 45 days, 12.75 days, and 13 days after the first treatment. Post-procedure, patients in all studies were asked to avoid taking NSAIDs, have gradual exercises and weight bearing as tolerated, and refrain from high-impact sports for six weeks.

Outcome Measures

The primary outcome measured was pain reduction and functioning. The scales Hip Disability and Osteoarthritis Outcome Score Jr (HOOS-Jr) for function and the Numerical Rating Scale (NRS) for pain were used. The other scales used include the 12-Item Short Form Health Survey (SF-12), modified Harris hip score (mHHS), hip outcome score-activities of daily living (HOS-ADL), Western Ontario and McMaster University arthritis index (WOMAC) and Quality of Life. The satisfaction with the treatment was also assessed. Some studies used all these scales before and after the procedure and in follow-up. The follow-up period they were ranged from three months to 12 months. The major findings of the reviewed studies have shown significant results with interventions compared to baseline scores. A summary of the included studies is given in Table 1.

Discussion

BMAC is increasingly being used as an injectable treatment for OA, with the rationale focusing on the transplantation of the entire bone-marrow niche, which contains MSCs, haematopoietic precursors, monocytes, and endothelial cells, as well as a wide range of soluble factors [11, 35–37]. In this review, the efficacy of intra articular injection of bone-marrow aspirate concentrate was assessed. The main finding of this systematic review is that the available clinical studies indicate the effective use and overall positive results of injective treatment with BMAC in OA hip joints.

The posterior superior iliac crest is the most common site for BMA harvesting as it is safe, easy to approach, and produces more mesenchymal stromal cells than other sites [38–40]. The present review also showed that BMA harvest was done from the posterior iliac crest, which further supports the benefit of BMAC. Two studies in the current review used The Marrow Cellution Bone-marrow Harvesting Device, BMA kit, and the manual method. Hernigou et al. [41]. popularised the concept of "safety zones" by developing the sector rule for BMA from the iliac crest. The researchers investigated the anatomy of the iliac bone and the adjacent neurovascular elements that can be damaged by the trocar when inserted into the iliac crest. They looked at 480 trocar entry points performed by six surgeons on 120 patients. They discovered that the sector system accurately predicted safe and unsafe zones for inserting the trocar into the iliac crest—a further investigation by Hernigou et al. [42]. Another study discovered that using 10 mL syringes to harvest BMA was superior to using 50 mL syringes. The 10 mL syringe aspirations resulted in progenitor cell concentrations that were 300% higher in 30 patients.

Various protocols have been developed to concentrate the nucleated cell numbers to produce BMAC. Therefore, increasing the amount of MSCs is an attempt to provide an effective environment for healing and regeneration [19, 40, 43]. In the present review, the harvested bone-marrow was centrifuged at 3400 rpm and 1400 g for 15 min to get final BMC varying from 6 to 12 ml. The study was conducted by Themistocleous et al. [44] used a single-spin centrifuge (Hettich Rotofix 32A centrifuge for 15 min at 2800 RPMs) and produced about 20 ml of BMAC.

The combination of cells and bioactive proteins distinguishes BMAC from other orthobiologics currently on the market, and it may have the potential to change the course of disease rather than alleviate pain [45]. This research highlighted many clinical studies published in the last five years. Nevertheless, the review analysis also highlighted the limits of this new field, with only a few studies supporting the rationale of BMAC injections and an overall low quality of evidence, as some of the studies are case series. Regardless of several still-controversial aspects, BMAC is technically simple and offers the benefits of eliminating the need for culture expansion, lowering the risk of infection and avoiding the risk of allogeneic diseases [46]. Though studies using BMAC were done mainly for knee arthritis [44, 47–49] and few on the shoulder [50, 51] earlier studies done by Sampson S et al. [52], 2016, Centeno C et al., 2014 [53] showed the efficacy of BMAC for patients suffering from HOA.

Potential complications of iliac crest bone-marrow aspiration are rare (0.05%), with bleeding being the most common, while others include infection, donor site morbidity, and persistent pain [54]. In this review, the procedure had a favourable outcome and improved pain and function in most patients after short- and long-term follow-up. No serious adverse events or failed aspirations were reported due to the BM harvest or injection procedure. However, in one study, few patients said pain for the first two weeks after BMC injection and swelling [33]. A few patients were unsatisfied, and 2 of them converted to THA, which one had multiple comorbidities: diabetes, obesity, and osteoporosis. The same findings were noted in a previous study by Centeno C et al. 2014 [53].

Table 1 Summary of the studies included in the systematic review

Author (year)	Design	Participants/setting/ sample size	Tools and techniques	Intervention	Outcome measures	Major findings
Tsitsilianos et al. (2022) [30]	Retrospective study	31 patients with a Kellgren- Lawrence (KL) Hip OA grading of 2–4 (mean 2.9 ± 0.7), ranging in age from 32 to 83 (62.4 ± 16.5), who underwent intra-articular bone-marrow aspirate injection into the hip at outpatient rehabilitation centre at tertiary care hospital	Marrow Cellution Bone-marrow Harvesting Device (Ranfac Corp., Avon, MA) was used with the guidelines, and expert consensus technique to aspirate bone-marrow from the posterior iliac crest after achieving optimal fluoroscopic positioning.About 6–8 mL of BMA harvested close to the cortex were obtained by rotation/aspiration technique	Using antero-posterior fluoroscopic imaging, approximately 6–8 cc of bonemarrow aspirate was injected into the into the intra-articular and subcapsular space. Patients followed the recommended post-procedure protocol, which includes daily home exercises from Day 1 through Day 28 after the procedure, following therapy goals, and progressive and evolving precautions	Using the Hip Disability and Osteoarthritis Outcome Score Jr (HOOS-Jr) for function and the Numerical Rating Scale (NRS) for pain, evaluations were performed at baseline, 12 weeks, 6 months, and 12 months	A statistically significant improvement in NRS scores was observed at the 6 and 12-month follow-ups ($P < 0.05$). when groups were separated by KL grade, subjects with KL grades 2 and 3 showed statistically significant increases in NRS scores at 6 and 12 months. KL grade 4 patients had significantly less pain at 12 months
Burnham et al. (2021) [31]	Prospective Case Series	A total of 112 patients with refractory OA of knee(s) and/or hip(s)		A single intra-articular injection of 8–10 mL BMC into their knee(s) and/or hip(s)	Pain, disability and quality of life were prospectively assessed prior to and 3, 6 and 12 months post-injection	Outcome scores were significantly improved at all time points post-BMC injection with maximal improvement observed at 3–6 months. Improvements were unrelated to patient age, sex or radiographic OA severity

Table 1 (continued)

Author (year)	Design	Participants/setting/ sample size	Tools and techniques	Intervention	Outcome measures	Major findings
Whitney et al. (2020) [32]	Case series;	At the time of their evaluation, a total of 24 patients between the ages of 18 and 80 were identified as having unilateral or bilateral hip OA. Among them a final sample of 16 patients included for analysis	From all BMA samples and final BMC products, a complete blood count (CBC) was obtained using a CellDyn Ruby (multiparameter automated haematology analyzer, Abbott Diagnostic Division). A BMA kit (Arrow OnControl; Teleflex) was opened, and a battery-powered aspiration drill, approximately 60–120 mL of BMA was collected in 30-mL syringes preloaded with 5 mL of ACD-A, BMC was produced using a centrifugation and manual extraction technique. A total of 6–12 mL of BMC has been extracted and 0.8 mL of that volume were used for haematology testing to evaluate the final BMC product	Using the 22-gauge needle, 6–12 mL of BMC was injected into the intra-articular space under ultrasound guidance. Patients were asked to refrain from high-impact sports for six weeks following the procedure and were allowed to bear weight as tolerated. Patients were also advised to ice the joint for at least two weeks and refrain from taking nonsteroidal anti-inflammatory drugs	The 12-Item Short Form Health Survey (SF-12), NRS pain scores, modified Harris hip score (mHHS), hip outcome score-activities of daily living (HOS-ADL), Western Ontario and McMaster Universities arthritis index (WOMAC), and pain scores were gathered before and after the procedure (6 weeks, 3 months, and 6 months). Pre injection antero posterior pelvis radiographs were used to score joint space and Tonnis OA grade	Over the course of six months, there were significant improvements in the NRS pain scores with (from8 to 4.5) and without activity (from 5 to 1); $P < .001$), WOMAC (from 31 to 16; $P = .006$), mHHS (from 63 to 80; $P = .004$), and HOS-ADL (from 71 to 85; $P = .014$). All patients sustained their improvements at 6 months and did not revert to their pre-procedure conditions. No adverse sideefeects reported

Table 1 (continued)

Author (year)	Design	Participants/setting/ sample size	Tools and techniques	Intervention	Outcome measures	Major findings
Fontan F et al. (2018) [33]	Prospectivecohort study	19 patients (16 female and 3 male), 25 joints (10 knees, 15 hips) treated with intra-articular BMC for early OA between 2014 and 2016	A bone-marrow aspiration needle was used to take 2- to 4-mL bone-marrow aspiration samples from the anterior iliac crest, moving forward every 5–10 mm. To produce a final BMC volume of 12 mL, 120 mL of bone-marrow were collected and centrifuged at 1400 g for 15 min using BioCUE Platelet Concentration System; Zimmer Biomet, Warsaw, IN	Under radiographic or ultrasound guidance, 12 ml of BMC was injected intraarticularly into the knee or hip joint. All patients were given immediate full weightbearing permission and urged to engage in gradual exercise. For three weeks following surgery, nonsteroidal anti-inflammatory drug use was prohibited for the patients	Outcomes were measured using Western Ontario and McMaster Universities Arthritis Index (WOMAC) at baseline and at 6, 12, 18 and 24 months. Satisfaction of treatment was assessed by asking yes or no question	WOMAC score improved from a baseline of $40.8 \pm 18.3\%$ to $20.6 \pm 17\%$ ($P < .001$) at final follow-up. The satisfaction level was 63.2%. 64% of the patients met the minimal clinically significant difference threshold of 9.15 points. No adverse complications reported except pain and swelling in few patients. Two patients were converted to total hip arthroplasty at 8 months after BMC injection due to not having satisfaction and comorbidities in one patients
Darrow et al. (2018) [34]	Case series	A total of 4 patients who went to private practice for the treatment of OA hip	A fenestrated 11-gauge, 4-in disposable needle was drilled to enter the PSIS and extract BMC after a sufficient level of local anaesthesia had been achieved. BMC was extracted using a 20-cc syringe pre-prepared with 1 cc of heparin (1000 USP units/mL), yielding a total of 19 cc	Patients received a total of 4 BMC treatments in succession, with follow-up injections given on average 45 days, 12.75 days, and 13 days after the first treatment. The final follow-up questionnaire was administered 22.75 days after the final injection. Patients were told not to take NSAIDs while receiving treatment	Changes to resting pain and active pain (numerical pain scale), overall improvement (percentage scale), and joint function (scored questionnaire). Variables were chosen for ease of comparison with similar variables reported by other studies of BMC for knee OA treatment	According to the findings, patients' resting and active pain levels were lower than they had been at baseline, with a mean overall improvement of 72.4%. Following the procedure, patients said they had less trouble going about their daily lives

Limitations

This systematic review has several limitations that reflect the limitations of the available studies. First, the level of evidence was low as the reviewed studies were prospective cohorts and case series, not RCTs. The second one is that no control group was used to compare the findings. Thirdly, only some of the studies used the same assessment tools, making it difficult to compare the results. The fourth limitation was that the follow-up period differed with 12 months after the procedure was the last follow-up. Only some studies in the review had a very small sample size.

Future Directives

Though this review had promising results regarding safety and effectiveness, the current knowledge is still preliminary. Hence, studies with large sample sizes with RCT could be done in future. The studies can be done by adding other orthobiologics to check the efficacy of BMAC and confirm it as a stand-alone procedure. Additionally, studies with long-term follow-up are required to prove its sustainability of effectiveness. Also, further evaluation of post-procedure physical activity should be considered in future studies.

Conclusion

In conclusion, this systematic review indicated an increasing interest in the clinical application of BMAC injections to treat Hip OA. Many aspects, including harvesting, centrifugation, and application methods, need to be clarified to maximise the potential of BMAC and provide a standardised method targeted for HOA treatment. The BMAC has excellent potential, and large-scale, placebo-controlled RCTs can pave the way for a futuristic regenerative treatment approach for hip OA.

Data Availability All data is contained within the manuscript.

Declarations

Conflict of interest No conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study informed consent is not required.

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