Review Article

Role Of Orthobiologics In Core Decompression For Femoral Head Preservation In Early Avascular Necrosis Of Hip

Abstract-
Head preserving procedures for early Avascular Necrosis of hip are invariably effective in early stage. Core decompression (CD) is mostly performed modality for early stages of AVN having different success rates. Current review aims at determining efficiency of Bone marrow aspirate concentrate , Platelet rich Plasma, Bone morphogenic proteins and combining it with Core Decompression for early AVN stage, before femoral head collapse. To preserve a femur head damaged by osteonecrosis, treatment options should be applied early in the disease process for best results. When the articular cartilage becomes deficient to nutrients, it become more difficult to save a particular femur head, and eventually bone destruction occur, affecting hip biomechanics; articular changes eventually develop, necessitating arthroplasty or arthrodesis. Other early treatment techniques has been identified & improved to improve femur head survival & delay replacement. Analysis of 20 studies published between 2011 and 2020 was done of which 6 were retrospective & 14 were prospective. PRP showed better survival and functional outcome, however 3 studies showed inconclusive evidence for its regular usage. BMAC enhanced efficiency of CD & cell increment or combination of PRP for growth stimulation. Concluding, CD and BMAC worked effectively before femoral head collapse. But, PRP need more evidences for extensive utilization. Adding PRP to BMAC or culturing it would increase potency of CD with BMAC. Less data is available to assess efficiency of BMP-7 & role of Intraosseous bisphosphonate therapy could be studied for inexpensive & better alternate.
Keywords- Orthobiologics , AVN, Core Decompression, Femur, PRP.

Introduction-

Femur head AVN is progressive intraosseous condition leading to limitation of function as condition progress [1]. There is subchondral damage radiologically, which leads to support loss to femoral head joint surface, further leading to subchondral collapse & femoral head distortion [2-5].

The etiology of atraumatic osteonecrosis hip includes steroid, alcohol, coagulopathies, and others resulting in decreasing mesenchymal stem cells & increasing quantity of adipose cells & apoptotic cells, according to studies conducted over the last decade and a half [6-8]. It causes a mismatch between bone synthesis & osteolysis, resulting in loss of bony trabeculae. As a result, the articular cartilage's subchondral support is compromised, resulting in subchondral collapse, head deformation, altered hip biomechanics & arthritis.

The goal of core decompression is to relieve intraosseous pressure & enhance blood supply to femur head in order to slow/stop progression of osteonecrosis. It had shown promise for the

early phases of osteonecrosis, allowing for blood vessel growth & restoration of vascularity. CD only has shown promising outcomes in FICAT Stage 1, the success of similar technique in succeeding stages falls[9-11]. As a result, adjuvants are required to boost efficiency in further stages.

Transtrochanteric rotational and varus or valgus osteotomies transfer sick region of head away from weight bearing area in early stages of disease process, allowing unaffected portion to take its place; they have previously been reported to preserve the damaged head [12, 13]. The outcomes of these procedures have been mixed, and their use has fallen in recent years [13].

Fibular & vascular grafts have been added with CD with better results, however they're difficult operations to execute. Newer orthobiologics, are progressively investigated in last 10-12 years; CD has been augmented with BMAC, PRP, & BMP-7 to boost the success rates [14-17]. Less studies [18, 19] had looked at them in the later stages.

Goal of systematic review is to evaluate efficiency of current orthobiologics to core decompression for head preserving in early stages of osteonecrosis & to search literature for any new therapy that might improve their survival chances in new century. In order to improve the findings, we looked into other ways to administer these adjuvants.

Methodology-

Study design

According to the PRISMA standards [20], systematic evaluation of literature is conducted using specific search engine such as Pub-Med and scopus.

Inclusion & exclusion criteria

Surgical methods for preserving the femur head damaged by AVN were included in study. We focussed mostly on CD & adjuvants used in conjunction with CD that improve femoral head survival rates in pre-femur head collapse stages of AVN. PRP & BMAC orthobiologics were perfectly recognised & included in study describing their use. Excluded studies included patients with extensive head deformation & arthritis alterations. Any studies published before 2011 were eliminated, including cadaveric investigations. Articles written in other languages were also excluded.

Data collection and analysis

Data was plotted on a table that contained the authors' names, year of publication, pertinent demographic information, study type, & outcome measures of relevance.

Results-

Total hips in both databases using our chosen keywords were 569, of which 288 studies were identified for further investigation. 46 studies were chosen after a review of titles and abstracts, and complete texts were examined. Finally, 20 studies [21-40] were included (all published between 2011 and 2020).

Characteristics of studies

This review comprised a total of 20 studies, which were tabulated [21-40]. There were 14 prospective studies [33, 39, 21, 22, 23, 24, 27, 28, 29, 30, 31, 35, 36, 37] and six retrospective studies [25, 26, 32, 34, 38, 40]. Three investigations on the use of PRP with CD were published, one of which was a randomised study [21]. 14 studies looked at effectiveness of BMAC as a CD adjuvant [24-37], while one looked at the use of recombinant BMP-7 [40]. The results of employing both BMAC & PRP with CD were assessed in the remaining two investigations [38, 39].

In the studies covered, total 665 cases having 846 hips affected by AVN were included, with 295 cases being male & 195 being females. 3 studies [23, 31, 38] didn't divide patients by gender (n 1/4 93 patients), while three others [28, 29, 33] did so depending on number of hips performed (M 1/4 78; f 1/4 26). In general, there was a significant male preponderance in the research that were considered.

In individual research, lowest number of cases were four [23], but greatest were hundred [37]. Average age of patients in the study was 37 yrs, demonstrating frequency of early osteonecrosis in young people & need for procedures such as arthroplasties to prevent progression. The average age of the patients in two trials [23, 28] was not mentioned. In the trials, the average follow-up length ranged from 9 months to 6 years.

Core decompression + PRP

When compared to normal circulation, PRP is plasma with a higher number of platelets [41]. The platelets have many growth factors, that are released post treatment & aid in tissue growth and development. Theoretically, if CD lowers intraosseous pressure, growth factors may aid in growth & bone formation, reducing complains & potentially reversing/postponing disease progression. In current study, three studies looked at the impact of PRP with CD (Table I). While CD procedure differed from study to study, the therapy principle remained the same. In a randomised control experiment, Xian et al. used PRP with CD to treat 24 cases with early AVN. They compared them to 22 CD-only patients [21]. Both groups received autologous bone grafts, with a three-year minimum follow-up.

Table I-Literature sources

S. No.	Authors(year) (Study design)	AVN stages	Intervention	Number of patients,(Mean Age in years),(M:F)	Mean Follow up(months)	Final HHS, WOMAC scores	Final VAS score/pain	Survival/Arthroplasty conversion	Inference
1.	Guadilla et al.(23)	Steinberg IIa, IIb	Arthroscopic Core decompressio	4 (NA) (NA)	14	NA	>60% significant improvement	-	Procedure needs to

	(2012) (Prospective case series)		n + ABG + PRP				in all cases.		be explored further.
2.	Samy et al.(22) (2016) (Prospective case series)	Modified Ficat IIb, III	Anterior dislocation + Removal of Necrotic area + Multiple drill holes + ABG mixed with PRP; covered with collagen gel and fibrin glue.	30(40 hips) (36.7) (19:11)	41.4	HHS-90.28(p<0.0001) Excellent-27 Good-9	35(p<0.0001)	4 patients with fair HHS-prepared for THR	PRP increases reparable capacity after necrotic segment drilling.
3.	Xian et al.(21) (2019) (RCT)	Post traumatic:ARCO II, III	T/t:Core decompression (CD)+ PRP incorporated ABG. Control: CD + ABG	T/t: 24 Control:22 (T/t:28.3 Control:29.6) (T/t: 15:9 Control:10:12)	T/t-44.9 Control-46.2	HHS-T/t-86.5 Control-79.3 (p=0.0254)	Significantly better in T/t group(p=0.125)	T/t- 3 THR Control- 7 THR; 2 transtrochanteric osteotomies	PRP is an effective adjuvant to CD + ABG

Despite the fact that both groups improved their HHS, PRP group had higher clinically important increase. At last follow-up, the HHS and VAS scores too favoured PRP group (P

1/4 0.024 and 0.0125, respectively). 3 cases in PRP group required THR, whereas 7 individuals in another group had to undergo procedure owing to arthritis. PRP is a successful adjuvant to CD for early stages of AVN, according to the authors' findings.

In 40 hips of 30 patients, Samy et al. used another procedure for decompression: they did anterior dislocation, and drilled several holes [22]. To keep the adjuvant in place, they injected bone graft combined with PRP & coated area with fibrin glue. At follow up, HHS became 90.3 as compared to preoperative HHS, with 36 patients having better score. THR was presented to the remaining four. In addition, the VAS score improved dramatically (P 0.0001).

Guadilla et al. studied CD using arthroscopy & under C arm, as well as the effects of CD using graft & PRP in 4 cases with AVN hips [23]. By the fifth month after surgery, all 4 cases had a sixty percent improve in pain intensity and were able to resume normal lives. Authors described a procedure that involved accessing femur head from base when hip was flexed to 10 to 15 degrees and the hip was in a neutral coronal plane with mild traction. A Steinmann pin (3.2mm) was used to drill numerous holes through anterior/accessory port. PRP was infiltrated into channel that had been formed.

Core decompression + BMAC

Mono-nuclear stem cells, which are building blocks of hip's skeletal anatomy, are found in bone marrow aspiration concentrate (BMAC). They develop into bone-forming cells replacing old, faulty cells, preserving structural balance & integrity [16-19]. Introducing fresh pool of lineage cells capable of differentiating into cells required for hip's normal physiology appears to be promising therapy option for pre collapse phases of AVN. BMAC, MSCs, BMMCs had all be used to refer to the cells [24-28]. Several studies have looked into its use as a CD adjuvant, with great result (table II). Wang et al. used a combination of CD, curettage, bone transplant, and BMAC to treat 20 hips in 15 patients [24].

Table II-Literature review

S. No.	Authors(year) (Study design)	ARCO stage	Intervention	Number of patients,(Mean Age in years),(M:F)	Mean Follow up(months)	Final HHS, WOMAC scores	Final VAS score/ pain	Survival/ Arthroplasty conversion	Inference
1	Gangji *et al.* [30], (2011) (Prospective)	ARCO I, II	T/t: CD + BMAC Cntrl: CD	19 (24 hips) • 13 hips and 11	60	Overall WOMAC score did not differ (pain part was significantly worse	Lesser VAS in T/t group (*P* = 0.009)	Progression to Stage III more in cntrl group (*P* =	Long-term study suggests BMAC impla

				hips (42.2 45.7) (10:9)		in control group; $P < 0.05$)		0.038) Time to failure better in BMAC group. **THR:** T/t : 2 Cntrl: 3	ntation in early AVN is effective
2	Sen *et al*. [28], (2012) (RCT)	ARCO I, II	Gp A: CD; Gp B: CD + BMAC (mononuclear)	• 40 (51 hips) • A: 25 hips • B: 26 hips (-) (A-18:7 B-19:7)	24	• HHS • A: 77.39 ±16.98 • B: 82.4± 9.63	-	Better survival in B ($P < 0.0351$)	Marked improvement with CD+ BMAC specially in patients with poor prognostic features
3	Zhao *et al*. [37], (2012) (RCT)	ARCO I, II	CD versus CD with trephine + bore graft + BMAC (cultured & expanded)	• 100 (104 hips) • 50 patients in each gp (51 and	60	Significantly better HHS in second group	-	• 10 worsened (5 THR) • 2	Functional scores and necrotic volume of femoral head had better outcomes with

				53 hips) (33.8 32.7) (26:24 27:23)				worsened (noTHR) • *P* < 0.05	BMAC
4	Rastogi *et al*. [31], (2013) (Prospective clinical trial)	ARCO I, II, III	• Group 1: CD + BMAC (mononuclear cells) • Group 2: CD + unprocessed BMA	• 40 (60 hips) • 30 hips in each group (34.67 33) (NA)	24	• Improvement in HHS • Gp 1- 31.85 • Gp 2- 19.72 • (*P* = 0.03)	-	• NoTHR • 3 THR • ARCO I, II: showed improved ra	BMAC is safe and effective with better outcome than unprocessed aspirate in early AVN

								diology	
5	Liu *et al*. [32], (2013) (Retrospective series)	ARCO I, II, III A	• A: CD + BMMC + filler • B: CD + filler	• 34 (53 hips) • A: 26 hips • B: 27 (38 38.1) (13:4 14:3)	26.8 24.8	Group A had more increase in HHS (28.6; $P < 0.001$)	VAS decreased more in Group A ($P < 0.001$)	• Higher success rate in Group A ($P = 0.004$); 6 hips showed collapse (4 THR)	Addition of BMMC makes CD + Filler more effective

								• Group B: 16 collapses (5 THR)	
6	Wang *et al*. [24], (2014) (Prospective)	ARCO II, III	CD + curettage + ABG + BMAC (mononuclear cells)	15 (20 hips) (35) (10:5)	24	• HHS • 85 • Excellent : 7 • Good : 8 • Fair : 4 • Poor : 1	N/A	80% survival; 4 hip worsened but no THR	Effective procedure in early stages
7	Tabatabaee *et al*. [29], (2015) (Prospective	ARCO I, II, III	• A: CD + BM	• 18 (28 hips) • A:	24	Better WOMAC in Group A ($P < 0.001$)	Mean score significantly lower in	3 THR in group B; none in group A	Combination is more effective in early

	randomized trial)		AC • B: CD	14 • B: 14 (31 26.8) (9:5 10:4)			Group A		stages than only CD
8	Pepke *et al*. [33], (2016) (Randomized clinical trial)	ARCO II	CD versus CD + BMAC	• 24 (25 hips) • CD-14 • CD + BMAC-11 (44.5 44.3) (12:2 10:1)	24	Comparable HHS in both groups	VAS decreased in both groups ($P < 0.05$)	No difference in survival	No difference with BMAC as an adjuvant to CD in short term
9	Nally *et al*. [34], (2017) (Retrospective series)	Ficat I, II	1. CD 2. CD + BG 3. CD + BMAC	• 33 (47 hips) • 27 (34 hips) • 12 (16 hips)	72 48 72	-	-	• Survival- • 56% • 50% • 50	No difference in any of the groups

				(38 40 41) (24:9 21:6 8:4)				% • (no significant difference)	
10	Einhorn *et al*. [27], (2017) (Prospective series)	ARCO I, II	CD + BMAC	52 (66 hips) (40) (29:23)	24	• Total score improved 63% ($P < 0.001$) • SF-12 scores and EQ-5D improved ($P < 0.001$)	65 % improvement in pain(as per WOMAC subcategory score)	• 1 1 lost to follow up. • Survival of 75% (41/55 hips) • 14 ca	CD + BMAC is a promising option for early AVN hips.

								ses failed (needed THR)	
11	Tomaru *et al*. [25], (2017) (Retrospective)	JOA staging, I, II	CD + BMAC	31 (40) (19 12)	69.5	JOA walking & quality of life scores improved. ($P < 0.05$)	Pain scores decreased significantly ($P< 0.05$); 2 patients had pain on walking	3 THR; 11 hips showed secondary collapse when lesions were large	Long-term outcomes were good with disease progression rate less than natural course
12	Talathi *et al*. [26], (2018) (Retrospective)	ARCO I, II	CD + BMAC	28 (43 hips) (40.1) (13:5)	16	-	2.5 (significant decrease, $P < 0.0001$)	3 THR (after average of 17 months)	CD + BMAC provides significant pain relief and arrests progr

									essio n
13	Mardo nes *et al*. [36], (2019) (Prosp ective cohort)	Fic at II, III (*n* = 4 and 1); <50 % hea d inv olv ed	CD + BM AC (*ex vivo* expan sion)	5 (41.2) (4:1)	33.8	MHHS: from 73.6 to 98.2	From 4.6 to 0.4	No THR	MSC - based thera py is safe and effect ive in early stage s
14	Wu *et al*. [35], (2020) (Prosp ective series)	AR CO II	CD + BM AC (mononucl ear cells) in collagen sponge	30 (30.6) (19:11)	9	• H HS • 84. 66 ±6. 97 (*P* < 0.0 5)	1.91± 0.53 (*P* < 0.05)	Mean repair ratio better in patients receiving BMAC with better differenti ation	Quali ty of stem cells deter mine succe ss of the meth od

Tomaru et al. looked examined 31 AVN patients who were treated with CD and BMAC over the course of 5.8 years [25]. Eleven of the 31 hips having greater regions of damage collapsed, necessitating hip replacement in 3 cases. Authors claimed their collapse rate in hip having a larger region of damage was lower in other studies' course of identical AVN. Overall, the study found that CD and BMAC is less invasive technique having great results in early stages of Avascular necrosis.

At follow-up of 64 weeks, Talathi et al. used the approach for forty three hips of twenty eight cases & saw substantial drop in VAS score [26]. 78% of cases said their pain had decreased by more than half, and serial radiographs revealed that 40 hips had not progressed. At average of 17 mnths post surgery, three occurrences of femur head collapses necessitated arthroplasty. According to the authors, this technique could halt disease development and give significant symptom alleviation.

Einhorn et al. combined core decompression and BMAC in 66 hips from 52 patients & found a 63 percent improving overall WOMAC score [27]. Symptoms reduced dramatically, and quality of life scores (SF-12 and EQ-5D) increased significantly as well (P< 0.001). With exception of 11 hips lost to follow-up, hip survival was 75% (41/55), with only 14/55 hips requiring THR. Authors described core decompression with BMAC as a worthwhile method in Stage 1 & 2 AVN hips because of the overall positive outcome . However, whereas CD alone has been demonstrated to particularly effective in Stage 1 instances, BMAC should be utilised in following stages if possible.

Several Level 1 randomised clinical trials comparing CD & CD with BMAC in the early stages of AVN hip have also been undertaken. Sen et al. utilised BMAC as adjuvant in other 26 hip and performed CD in 25 of them [28]. The cases demonstrated significant improvement in HHS after a 2-year follow-up, with BMAC grp having better outcome at 1 yr follow-up (P <0.016). On two year follow-up, the BMAC group exhibited higher improvement in pain and deformity domains. The Kaplan Meier survival revealed that average survival rate in two groups were 46.72 and 51.85 weeks (P <0.0351). After two year of follow up, authors didn't disclose number of further failure or THR performed. Surprisingly, individuals with less HHS & bad radiological appearance pre-operatively had higher hip survival rate with BMAC, according to the investigators.

Tabatabaee et al. separated 18 cases (28 hip) in two group, each with 14 hips, & noted BMAC cases were having good WOMAC score (p <0.001) and VAS score at two years [29], CD only group had 3 cases which required THR. For early AVN hips, the authors claimed that the combination of CD and BMAC was superior to CD alone.

Gangji et al. earlier reported similar findings in ARCO 1 and 2 stage AVN hip, with average 5 year follow up, compairing CD with BMAC (13 hip) and CD only (11 hip) in ARCO 1 & 2 stage of AVN hip [30]. VAS score (P 1/4 0.009) and pain score of the WOMAC score (P <0.052) was considerably bad in the CD only group, despite the fact that the overall WOMAC scores were not different. With 8/11 hips in the CD alone group, disease progression to Stage III was more significant, compared to only 3 of 13 hip in BMAC group (p 1/4 0.038). BMAC infiltration as adjuvant to CD is also a more effective treatment modality than only CD, according to this long-term study.

Rastogi et al. [31] adjusted the CD only group as compared to prior research by adding un-processed BMAC with CD in 1 group & BMMCs with CD in other (n 1/4 30 hips in both group). Their results demonstrated improved HHS in both groups after a two-year follow-up, although it is significantly better in group of BMMC (P 1/4 0.03). The unprocessed bone marrow group had three THRs, while the BMMCs group had no hips that required THR. In the ARCO I and II cases, size of lesions in BMMC group dropped (P 1/4 0.03). Technique was described as safe and successful in the early stage of AVN.

Liu et al. divided AVN patients into two groups, treating one group (26 hips) with nano hydroxyapatite or polyamide filler and the other group (27 hips) with BMMC [32]. When two groups were compared, it was shown that patients who took BMMC had higher percentage gain in their score (28.660.5%) than the other group (18.461.7%), P< 0.001. Similarly, improvements were reported in overall VAS ratings, with the BMMCs group (66.361.4 percent) showing a greater reduction (p< 0.001) than the other group (51.762.9 percent). The authors defined clinical success as a proportion of patients in either group with an HHS of 80 or greater, which was similarly higher in the BMMCs group (75.4 percent versus 37 percent

). Furthermore, in this group, radiographic head collapse and the onset of the osteoarthritic stage were much lower (21.4 percent versus 59.3 percent failure). The authors suggested that using BMMCs as an adjuvant treatment for early AVN could be more successful than using CD alone.

There have also been reports that BMAC with CD has no further benefits. In a randomised clinical trial, Pepke et al. compared CD and CD with BMAC in 24 patients with 25 hips in ARCO I and II stages (14 and 11 hips in both groups, respectively) [33]. Patients in both groups had comparable HHS and considerably lower VAS ratings from pre-operative values at a 2 year follow up ($p < 0.05$). Survival rates did not differ in groups, with 8 & 7 instances in each group not advancing or requiring THR. Overall, the authors found no evidence of BMAC's enhanced efficacy as a CD adjuvant.

In Ficat phases I and II, Nally et al. compared 3 groups: CD (47 hips), CD with bone graft (34 hips), & CD with BMAC (16 hips) [34]. They looked examined the differences in converting THR & discovered that rates of conversion to THR didn't differ (p 1/4 0.2), with 48 instances (49.5 percent) requiring it after five year follow up. At a four-year follow-up, 50% of patients who got BMAC (MSC) required THR. Overall, adding MSC or a bone graft to CD had no effect on the survival of afflicted hips. The quality of BMAC/MSCs could be one explanation for these research producing contradictory result.

After average 9 month follow up, Wu et al. studied 30 cases with CD by 6.5 mm drill, curetting, & BMAC soaked in collagen gauze & found substantial progress in HHS & VAS (HHS- 84.66, VAS- 1.91; $p<0.05$) [35]. MRI used to assess the necrotic region, and the ratio of repair was computed by dividing difference between the area before & after nine months after surgery by area before operation, then multiply result by hundred. At 9 months, necrotic area ratio has decreased significantly from 35.51 - 13.74 percent. Mean ratio of repair was 62.263 %, & it was positively connected with improvement of HHS, implying that the more repair radiologically, the better is outcome functionally. Furthermore, BMAC cells from patients having a higher ratio of repair was showing stronger stain for osteogenic & chondrogenic development, which is likely what decides the final outcome of BMAC therapy in AVN hip.

Given the conflicting data on the utility of BMAC/MSC, treatments were created for improving content quality of these cells prior to infiltration to patient. In five cases, Mardones et al. enhanced volume of MSC in BMAC by growing & expanding them ex-vivo & injecting them through CD tract [36]. Modified HHS scores improved significantly (mean 1/4 was 98.3) and VAS score reduced (from 4.6 - 0.4) in all 5 patients during a follow-up period ranging from 19 - 54 month. Despite small number of patients, no arthroplasty was required. In their experience, when non expanded stem cell was employed with CD, eighty percent of cases eventually required Hip Replacement, according to the scientists. It's worth noting that expanding the stem cells boosted their numbers, which were measured prior to instillation. In each hip, a minimum of 40106 cells were implanted.

CD (50 patients) was compared to CD + cultured BMAC with expanded MSC (50 patient) by Zhao et al. [37]. They told considerably better HHS in BMAC group after a 5-year follow-up. In addition, ten hips in the CD-alone group deteriorated radiologically (necrotic volume), with five of them requiring arthroplasty; just two hips in the BMAC group deteriorated further. The scientists came to the conclusion that a larger BMAC delivers a better functional

outcome and slower disease development, as well as a higher chance of survival. As a result, cultured BMAC in combination with CD may be a viable alternative in the future.

When administered as an adjuvant, BMAC with MMNCs had shown to improve CD effectiveness. In the early stage of AVN, the vast majority of trials testing this combination showed excellent results, with symptomatic pain reduction & better functional outcome. Improving quality & quantity of these cells prior to infiltration could help achieve these therapeutic aims of hip survival even more.
By BMAC's mixed outcomes, the focus might be turning to increasing no. of bone formation cells. Aside from ex vivo cultivation of cells mentioned, adding growth agents to increase number of these cells could be viable option. Latter is accomplished by combining BMAC with PRP, which contain all of necessary growth factor (Table III).

Table III- growth factor

S. No.	Authors(year) (Study design)	AVN stage	Intervention	Number of patient,(Mean Age in years),(M:F)	Mean Follow up(months)	Final HHS, WOMAC scores	Final VAS score/ pain	Survival/Arthroplasty conversion	Inference
1	Martin *et al*. [38], (2013) (Retrospective)	Fic at I, II	CD + BMAC + PRP	49 (77 hips) (43) (-)	17	-	86% had significant pain relief	16 THR	Provides significant pain relief and halts disease progression in early AVN
2	Houdek *et al*. [39], (2018) (Prospective)	UOP Stage I, II	CD + BMAC + PRP	22 (35 hips) (43) (11:11)	36	HHS 85±15 (*P*< 0.0001) Excellent - good: 78%	-	84% survival; collapse in 7%; 4 THR; 2 bilateral patients needed repeat CD	Successful results of >90%; better when necrotic area was smaller at

						hips			early stages.

Martin et al. used a CD, BMAC, & PRP combinations in forty nine patient with seventy seven hips & observed considerable pain reduction in 86 percent of patients after average follow up of 17 months [38]. THR was necessary in 16 of the 77 hips.

Houdek et al. treated twenty two patients of thirty five AVN hips as a result of steroid use with CD with BMMSC with PRP [39]. The survivability free of THR at two and three year follow up was ninety seven percent & eighty four percent, according to the findings. Only 4 hips required THR, with 2 bilateral patients requiring additional CD.

CD + rh-BMP-7

MSCs are stimulated by bone morphogenetic proteins (BMPs), which help them proliferate and differentiate into bone-forming cells. BMP-7 is a available product that is tested in non-union situations. Papanagiotou et al. employed recombinant (rh) BMP-7 with CD & non-vascularized fibular graft in seven hip of six cases [40]. The authors documented THR in 2 hips of bilateral cases after one year operation following mean follow up of four year. Clinically, other patients shown remarkable improvement, with both VAS & HHS values improvement dramatically. Femoral heads revealed nil evidence of flattening or collapsing on X rays taken at final follow up. Presence of heterotrophic ossification in four hips had nil clinical implications. So, treatment combination proved to be beneficial in slowing disease development and improving clinical outcomes.

Overall, recombinant BMP-7 has been used sparingly as a CD adjuvant in the last decade, owing to its limited availability and expensive cost. Although the lone trial evaluating its efficacy found significant improvements in all seven hips, the data is insufficient to endorse it as a useful adjuvant. More research is required to determine the utility.

Other adjuvants—bisphosphonates

Such pricey therapies become inaccessible in countries with high percentage of the people living below poverty line & no comprehensive insurance coverage. As a result, there is demand for cheaper adjuvants that could be administered to large number of patients. Bisphosphonates prevent bone loss caused by osteoclasts by triggering osteoclast death [42]. In theory, their ability to prevent bone death in osteonecrosis may be critical, and studies utilising bisphosphonates with both subcutaneous & enteral routes have shown promising result in early AVN [43, 44]. Therefore, it is necessary for targetting action of drugs to exact location where it is required; intraosseous route can be a viable approach for improving bisphosphonate effect in the diseased part[45-47].

Some studies had combined BMP-2 locally and intraosseous bisphosphonates to boost bone-forming cell proliferation. Further local infiltration of ibandronate & BMP-2 improved

sphericity of femur head & accelerated healing of bone in piglets having ischemic osteonecrosis, according to Vandermeer et al. & Kim et al. [46, 47].

To summarise, it is likely that, in addition to CD, which stimulates new bone formation, a bisphosphonate such as ibandronate injected intraosseously, will limit bone resorption. They are substantially less expensive than the rest of adjuvants mentioned, so if they are proven to be beneficial in combination with CD, they can benefit a large number of patients. This therapy technique is already being tested by the authors of this review.

Miscellaneous-Combination and Routes of administration-

Aside from intraosseous administration, BMMCs can also be administered intra-arterially via the femoral artery. In thirty patients (24 male; 6 female) having AVN, Cai et al. instilled BMMC coupled with allogenic umbilical cord derived MSC [48]. This approach was used to treat 49 hips with AVN at ARCO 2 or 3 stage. Procedure included Digital Subtraction Angiography(DSA) and identifying one of 3 arteries: MCFA, LCFA, or obturator artery, with major one in femur head cannulated and cells injected within thirty minutes. Patient's pain and function of joint improved as a result of the treatment. The HHS healed dramatically after a year, and forty four bone lesions on CT improved. They came to the conclusion that such treatment was safe option for AVN patients.

Chen et al. used solely MSC from cord for intra-arterial injections in 9 ARCO II & III cases (4 male & 5 female). Their MRIs showed that between 1 & 2 years, necrotic volumes dropped dramatically (7.1660.73 to 5.8661.67 cm3); the approach was also effective in boosting the HHS as compared preoperatively at one year [49].

Daltro et al. proposed method for injecting BMAC into a femoral head lesion that involved a percutaneous technique and single puncture by a 3 mm trocar under fluoroscopic supervision [50]. 89 patients were observed for five years, & their complains and HHS improved significantly from 75.8 - 93.2 (p 1/4 0.0005). 3 patients didn't improve to their satisfaction, but their radiological phases did not progress.

Sun et al. studied use of recombinant BMP-2 with the 'Light bulb operation' [51]. The study included forty two patients with seventy nine hips in ARCO stages 1, 2, and 3A, with a follow up of 6 year. BMP-2 was given to 36 hips together with curettage and bone graft, while forty three hips got simply curettage & bone graft . HHS in the 1st group was 82.3613, while in the non-BMP group it was 78.9612. Stage 2 disease produced better results than Stage 3. 2 groups had survival rate of 81.9 and 71.9 percent, respectively, with Stage 3a having only 34.5 percent overall. Few of the related studies were reviewed[52-54].

CONCLUSION:

The high frequency of hip AVN in a younger group necessitates early intervention to save the affected hip & postpone THR as long as possible. Core Decompression, in combination with available adjuvants such as BMAC, PRP, or their combination, is better and effective than Core Decompression alone for getting this therapeutic goal; but, the associated cost

necessitate evaluation of other adjuvants & appropriate selection of patients in determining best routes of administration of the ortho-biologics, in order to improve the outcomes.

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