

Effectiveness of Platelet-Rich Plasma as an Adjunct to Core Decompression to Treatment Outcomes and Femoral Head Preservation in Avascular Necrosis of the Hip: A Meta-Analysis of Randomized Controlled Trials



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ABSTRACT

Background Avascular necrosis (AVN) of the femoral head results from intraosseous pathology causing functional impairment. Early diagnosis allows conservative treatment like core decompression, delaying total hip arthroplasty.

Objective This meta-analysis aims to summarize platelet-rich plasma's (PRP) impact as an adjunct to core decompression (CD) on treatment outcomes and femoral head preservation in hip AVN.

Methods The study conducted a comprehensive literature search using PubMed, Cochrane Library, Science Direct, Google Scholar and Med Line, including randomized controlled trials (RCTs) and previous meta-analyses from various databases. Using a random effects model, it compared PRP+CD with bone grafting to CD with bone grafting alone

in AVN patients, evaluating function, pain scores, disease progression and the need for hip surgery.

Results The meta-analysis examined 1041 records and included three studies. The primary outcomes were function and pain scores using Harris Hip Scoring (HHS) and Visual Analog Scale (VAS). Postoperative HHS scores at final follow-up favored the PRP+CD group significantly over CD alone. Postoperative VAS scores showed a trend towards higher scores in the CD alone group. The PRP+CD group demonstrated higher survival from disease progression compared to CD alone. Overall, the study suggests that PRP+CD led to better functional outcomes and disease progression outcomes than CD alone in AVN of the hip.

Conclusion The PRP+CD treatment group showed significant benefits in AVN patients compared to CD alone, including higher HHS scores, improved disease progression survival and reduced need for hip surgery. Although PRP+CD resulted in decreased VAS scores, the difference was not statistically significant.

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INTRODUCTION

Avascular necrosis (AVN) of the femoral head is a progressive, debilitating and multifactorial disease due to an intraosseous pathology leading to a decrease in functional outcomes hindering patients to perform daily activities.[1] It occurs in patients in the most productive age group of 25-50 years old in the male population with bilateral involvement in 59% of cases.[2,3] Patients with AVN reported symptoms of localized groin pain which can limit the range of motion (ROM), especially during passive internal rotation, and is associated with a decrease in the quality of life among patients usually presenting within two years from the onset of disease and in the absence of treatment.[2,4] Affected femoral heads would present with head distortion or collapse with arthritis. The pathology is based on multiple etiologies associated with a reduction in vascular supply to the subchondral bone of the femoral head leading to osteocyte death and eventual progressive collapse in the structure of the femoral head leading to arthritis of the hip joint.[2,3] When the articular surface has already collapsed, the disease usually does not regress which often leads to subsequent total hip arthroplasty (THA) at a young age.[2]

AVN can occur due to an atraumatic or traumatic cause. Majority of the patients present with a non-traumatic cause of AVN of the femoral head which is usually associated with the use of alcohol, glucocorticoids, hematologic disorders, pregnancy, chronic renal failure and other metabolic disorders. In 30% of non-traumatic AVN, the etiology of the disease is unknown and hence called idiopathic.[2,3] On the other hand, post-traumatic osteonecrosis of the femoral head is also a possibility with an incidence of around 20%-40% following femoral neck fractures and is typically related to the fracture pattern and involvement of the medial femoral circumflex artery (MFCA).[5]. Traumatic AVN occurs due to disruption of the vascularity to the femoral head, specifically the MFCA which is the major blood supply to the femoral head during adulthood.

The gold standard of treatment for late-stage Osteonecrosis of the Femoral Head (ONFH) is a total hip replacement which showed significant clinical success in this population. However, there are concerns with regard to its outcomes among young adults aged 25-50 years old undergoing joint arthroplasty. On the other hand, conservative methods

such as physical therapy for the management of ONFH usually lead to poor outcomes with failure to provide long-lasting improvement. Early recognition and surgical treatment for patients with pre-collapse or early stages of ONFH are necessary for good clinical outcomes.[6,7] If diagnosed in the early stages of the disease, a more conservative surgical technique like core decompression may be done which is aimed to delay and prevent the need for future total hip arthroplasty. However, the efficacy of this procedure still remains to be controversial as failure of a single core decompression may not provide adequate bone healing in the necrotic area.[7]

Platelet rich plasma (PRP) is an autologous blood plasma that contains a concentrated and supraphysiological level amount of platelets and growth factors such as platelet-derived growth factors (PDGF), transforming growth factor beta 1 and 2 (TGF- β 1, TGF- β 2), IGFs and epidermal growth factors (EGF).[8-11] The use of PRP is considered safe and has shown positive effects on the stimulation of tissue healing with a rationale that additional platelets will exponentially increase the number of multiple growth factors mentioned above at the site of injury.[2,8,9] Aside from this, PRP used in conjunction with autologous bone graft is postulated to synergistically augment the growth and formation of bone.[5,10,11] In another study by Houdek, et al., they concluded that bone marrow-derived mesenchymal stem cells possess the capacity to transform into different mesenchymal cell types like osteoblasts, chondrocytes and adipocytes, thereby aiding tissue regeneration. When used alongside PRP in ONFH treatment, the growth factors in PRP enhance Multipotent Stem Cells' ability to differentiate into new bone and blood vessels. This collaboration between PRP and MSCs fosters osteogenesis and leads to improved healing process for early-stage ONFH leading to good clinical outcomes with 93% showing no progression of disease on MRI after 12 months.[11]

Core decompression is the most widely accepted hip-preserving treatment for early-stage osteonecrosis of the femoral head. Its main function is to reduce intramedullary pressure to allow adequate blood flow and promote new bone formation to reduce pathogenesis of the disease process.[2] It is known that core decompression relieves pain and helps in delaying or preventing disease progression by allowing creeping substitution of the necrotic area

by bringing blood supply through drill tunnels.[2] The use of an autologous bone graft placed through the track of core decompression has evolved to be an appealing option for orthopedic surgeons.[7] In recent years, studies have been made regarding the use of biological adjuvants incorporated in autologous bone grafts to improve the outcomes of patients treated with Core Decompression (CD). However, findings were inconclusive and had heterogenous results with limited evidence.[2,10,11]

MATERIALS AND METHODS

This study was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items from Systematic Reviews and Meta-Analyses statement.

Eligibility Criteria and Study Inclusion

This meta-analysis included all RCTs comparing the use of PRP as an adjunct to core decompression and bone grafting vs core decompression alone to patients with AVN of the hip with the following characteristics: The population in the study included adult patients of both sexes diagnosed with AVN or ONFH. The intervention assessed for the study was the use of PRP as an adjunct to standard core decompression with bone grafting compared to the control which is core decompression with bone grafting alone as treatment. The primary outcome of the study was functional and pain levels before and at the final follow-up measured using the Harris Hip Scores (HHS) and the Visual Analog Scale (VAS), respectively. The secondary outcomes were treatment failure assessed by the number of hips with survival from disease progression, which were patients with no signs of further worsening of the AVN based on serial radiographs until final follow-up, and the number of those patients needing further hip surgeries for the same problem. All outcomes assessed in the study included preoperative and post-treatment scores assessed with a minimum of 24 months follow-up. Only full-text and published RCTs from 2000 up to the year prior to the commencement of review (2021). The search was performed and not limited by language. Duplicates were removed and retrieved references were screened in two steps: the first step was to screen titles/abstracts for

matching our inclusion criteria and the second step was to screen retrieved full-text articles for eligibility to meta-analysis.

Exclusion Criteria

The exclusion criteria included the following: (1) Unpublished studies; (2) Case reports, cohort, reviews, other study methodologies other than RCTs; (3) Animal experiments; (4) Full-text journals which are not available; (5) Application of other biologic agents other than PRP as an adjunct to CD for treatment of ONFH; (6) Diseases other than ONFH.

Search Methods for Identification of Studies

The study was based on a comprehensive literature search using PubMed, Cochrane Library, Science Direct, Google Scholar and Med Line including RCTs as well as previous meta-analyses published from 2000 up to prior to the commencement of the review (2021). Studies that compared the use of PRP as an adjunct to CD and bone grafting versus CD alone to patients with AVN of the hip in terms of function and pain scores as well as disease progression and the need for further hip surgery for the same condition were identified.

The main key search terms used were (((Avascular Necrosis) OR (AVN) OR (Osteonecrosis)) AND (Femoral Head)) OR (((Platelet Rich Plasma) or (PRP)) OR (Core Decompression))) and (Randomized Controlled Trial). The articles gathered are not limited to the English language. Three independent reviewers first screened the search results from each of the databases by title and abstract alone. Studies that do not satisfy the inclusion criteria or include any of the exclusion as well were not included in the meta-analysis. This screening included removing duplicated studies. Studies should have the same population, intervention, control and outcome. Potentially relevant articles were then reviewed and subsequently screened by way of full-text eligibility. Any discrepancies were resolved between the authors as to whether the study will be excluded or removed.

Data Extraction

The researchers gathered all available data from the literature collected that have passed the initial

screening. Information from the original studies was extracted based on their relevance to the topic regarding the “Effectiveness of Platelet Rich Plasma for Bone Graft Incorporation as an Adjunct to Core Decompression to Treatment Outcomes and Delay Progression of Avascular Necrosis of the Femoral Head”. Non-relevant studies or data such as those patients undergoing surgeries other than core decompression were disregarded. Parameters collected for comparison between the two techniques included assessment of functional score using HHS and pain score using VAS. Other outcomes evaluated included the presence of disease progression by radiography and the need for further hip surgery for the same pathology.

Risk of Bias Assessment

The researchers appraised the risk of bias for all studies collated based on guidelines in the Cochrane Handbook. This involved proper randomization and blinding of participants, surgeons and outcome evaluators. Data extracted and methods were reviewed by two main authors. The presence of bias was further subdivided into low-risk, unclear risk or high-risk. Any study with high-risk bias in even one category was categorized as high risk of having bias. Studies in the low-risk group are studies that had a low-risk bias for all categories. Otherwise, they were classified to the unclear risk group. Disagreements on the classification of bias scoring or data were discussed with a third author.

Statistical Analysis

Statistical analyses were performed using Review Manager Statistical Software, Version 5.4. A p -value ≤ 0.05 was considered statistically significant. A random effects model (REM), using the Mantel-Haenszel model, was employed in the analysis since the study did not assume one effect size among all the studies. This type of model in meta-analysis takes within-study and between-study variations into account. The means and standard deviations of the study's outcome variables were utilized to compute the standardized mean difference (SMD). Statistical heterogeneity between studies was scrutinized using the Q statistics test, I^2 statistics and tau squared (τ^2) statistics (Higgins & Thompsons, 2002).

RESULTS

Results of the literature search: a total of 1041 potential records as seen in Figure 1 were identified from the databases. After the removal of duplicate studies, 948 studies were further screened. 928 studies were excluded for not meeting the PICOM requirements after screening the title and abstract. In all, seven full-text articles were assessed for eligibility, of which four trials were excluded due to the modified intervention group with the use of other ortho-biologic agents other than PRP instilled through the core decompression site. The remaining three studies were included in this meta-analysis.

Of the three studies, all were RCTs. Two studies were conducted in China while one study was conducted in India. Two articles (Aggarwal and Xian) [2,7] were published in English, while one study (Yang) [12] was in Chinese language with publication time from 2019-2020. The study done by Yang, et al. [12] was translated into the English language to gain full assessment of the study methodology and data.

Evaluation of Treatment Outcomes

The study's primary outcomes include an assessment of the function and pain scores of patients using the HHS and VAS system, respectively, for both the treatment and control groups. Data gathered for assessment included preoperative baseline scores and postoperative scores at the final follow-up (at least 24 months) to assess the effectiveness of treatment. HHS is a widely known scoring system that is considered to be reproducible and objective for hip pathologies with a maximum score of 100 as the best outcome. [13] VAS score is an essentially quantitative method of pain assessment with a horizontal 0-10 point scale with 10 being the most intense pain.[14]

On the other hand, secondary outcomes included treatment failure until the date of final follow-up (at least 24 months). This was assessed with the presence or absence of disease progression with serial radiography and the number of patients that need further hip surgery due to the same condition.[15]

Risk of Bias Assessment

Figure 2 and Figure 3 show the risk of bias graph and summary, respectively. It is noted that the study

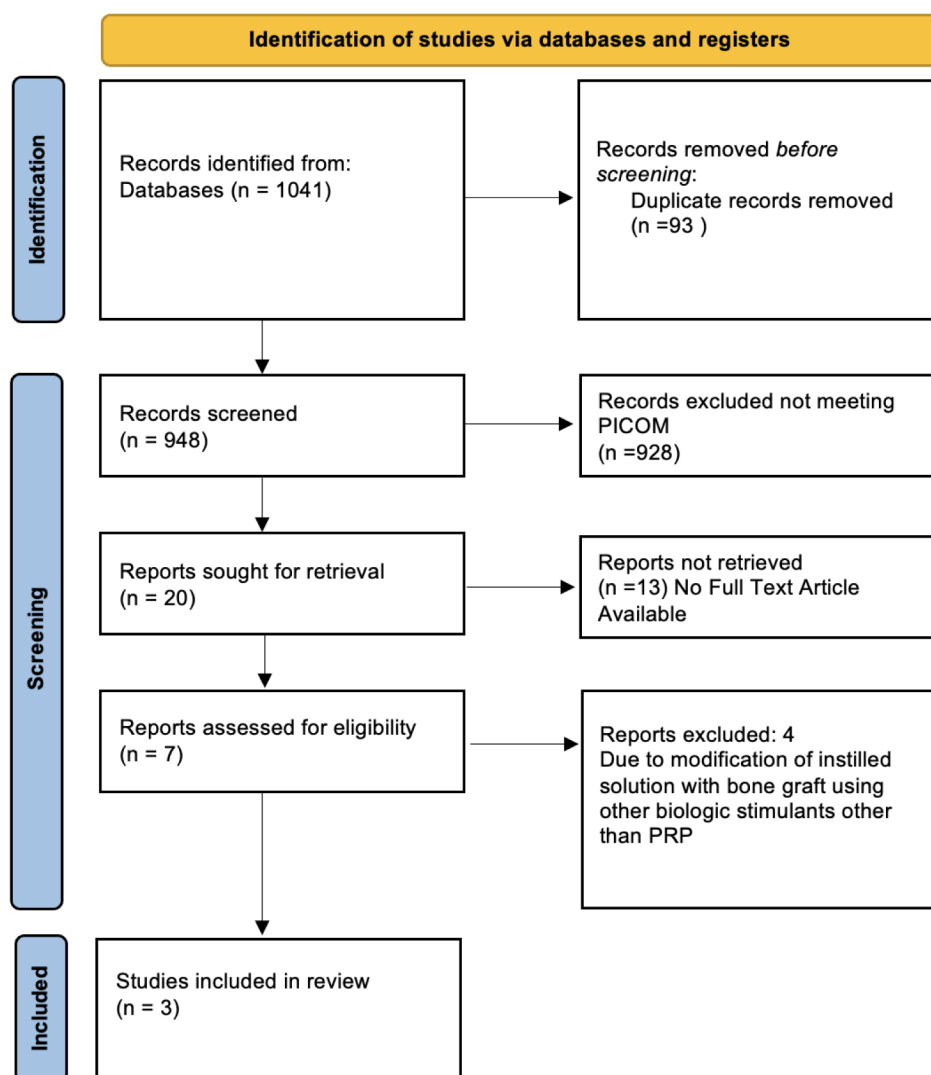


Figure 1 Flow diagram for selecting studies.

of Yang, et al. 2019,[12] showed a high risk of bias for selective reporting due to a shorter time of final follow-up with only 24 months compared to 36 months by Xian, et al. 2019,[7] and Aggarwal, et al. 2020 [2] with 64 months. It was also seen that the study of Yang, et al. 2019 [12] showed the presence of a high degree of bias as it also used oral alendronate as an adjunct to the PRP+CD group.

I. HHS Preoperative (Baseline) and Postoperative (at Final Follow-up)

It can be gleaned from Figure 4a-b, that analysis of the pooled data of preoperative baseline HHS showed a non-significant standardized mean difference (SMD)

between PRP+CD versus CD alone using the random effects model (SMD = 0.32, $z = 1.62$, $p = 0.11$, 95% CI = -0.71 to 0.07). This finding denotes that the preoperative baseline HHS were not statistically different between the two groups. On the other hand, the postoperative HHS (at final follow-up) showed a statistically significant difference favoring higher HHS for the PRP+CD group compared to the CD alone group (SMD = 2.04, $z = 3.80$, $p = 0.0001$, 95% CI = 0.99 to 3.09). This denotes that patients who received PRP+CD had significantly higher functional scores compared to the control group as assessed with a higher HHS score upon final follow-up (at least 24 months).

Analysis of the functional outcome included all the three studies as seen in Figure 4a-b, using the HHS system which included pain, function, range

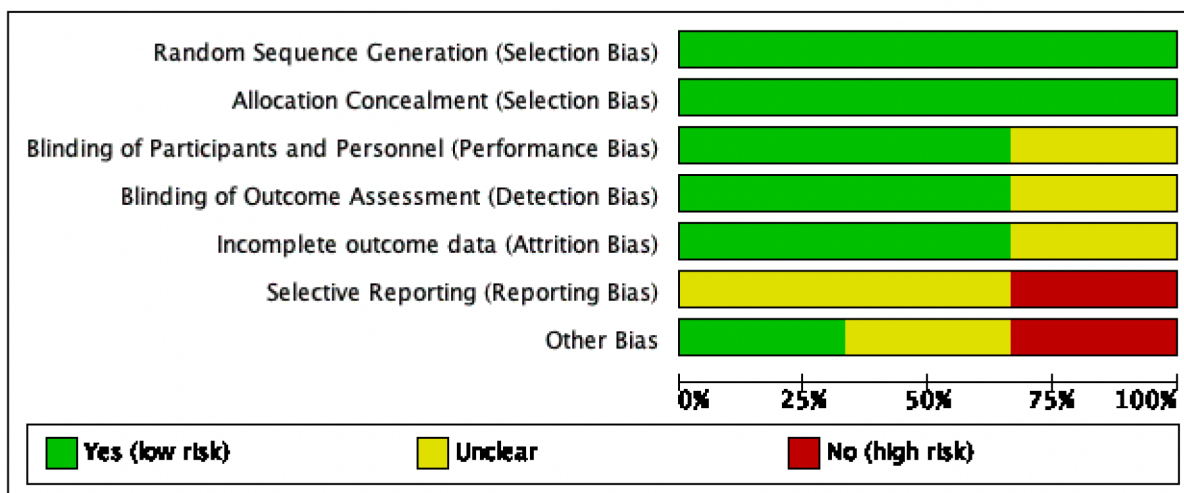


Figure 2 Risk of bias graph presented as percentages across all included studies.

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete outcome data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Aggarwal 2020	+	+	+	+	+	?	+
Xian 2019	+	+	+	+	?	?	?
Yang 2019	+	+	?	?	+	-	-

Figure 3 Risk of bias summary for each risk of bias items in all included studies.

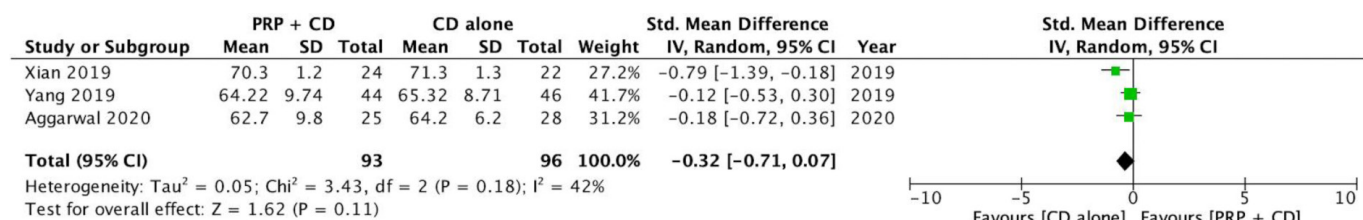


Figure 4a Preoperative (Baseline) Harris Hip Score comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

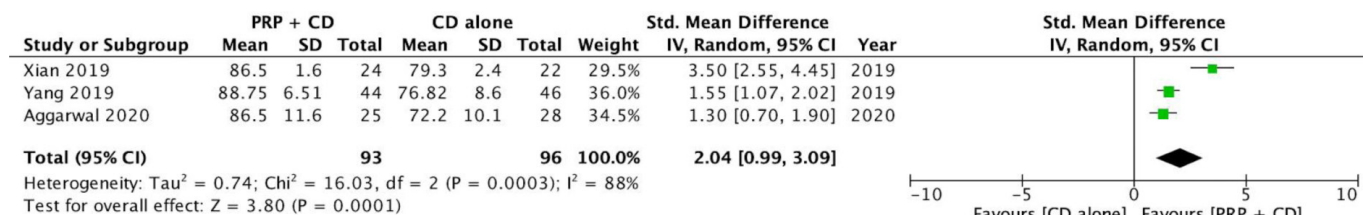


Figure 4b Postoperative (at Final Follow Up) Harris Hip Score comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

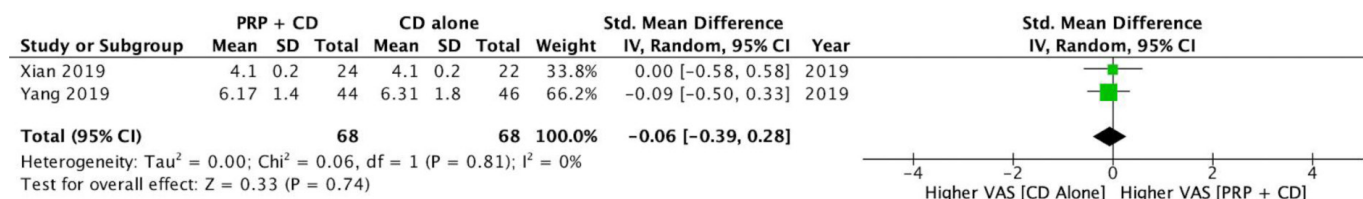


Figure 5a Preoperative (Baseline) VAS score comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

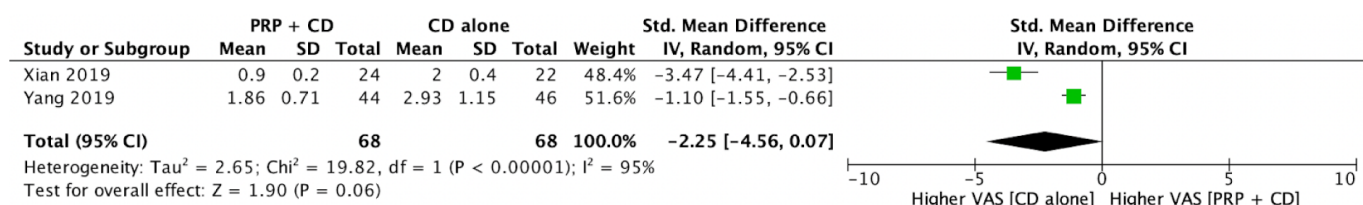


Figure 5b Postoperative (at Final Follow-up) VAS score comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

of motion and presence or absence of deformity with 100 having the best score. All patients for both groups underwent this scoring system. However, HHS results in three studies between the preoperative baseline scores prior to the HHS score at the final outcome were not specifically mentioned in the study.

II. VAS score Preoperative (Baseline) and Postoperative (At Final Follow up)

The analysis of pooled data of preoperative baseline VAS score, as seen in Figure 5a-b, showed a non-significant standardized mean difference (SMD)

between PRP+CD vs CD alone using the random effects model (SMD = -0.06, z = 0.33, p = 0.74, 95% CI = -0.39 to 0.28). This finding denotes that the preoperative baseline VAS scores were not statistically different between the two groups. On the other hand, the postoperative VAS scores (at final follow-up) showed a trend towards higher VAS scores for the CD alone group compared to the PRP+CD group (SMD = -2.25, z = 1.90, p = 0.0001, 95% CI = -4.56 to 0.07), however, this finding was not statistically significant. This denotes that patients who received PRP+CD had similar pain scores compared to the control group upon final follow-up (at least 24 months).

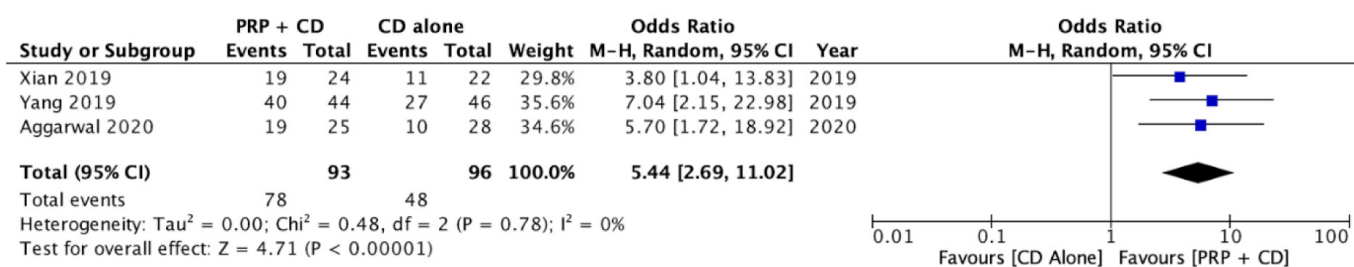


Figure 6a Survival from disease progression comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

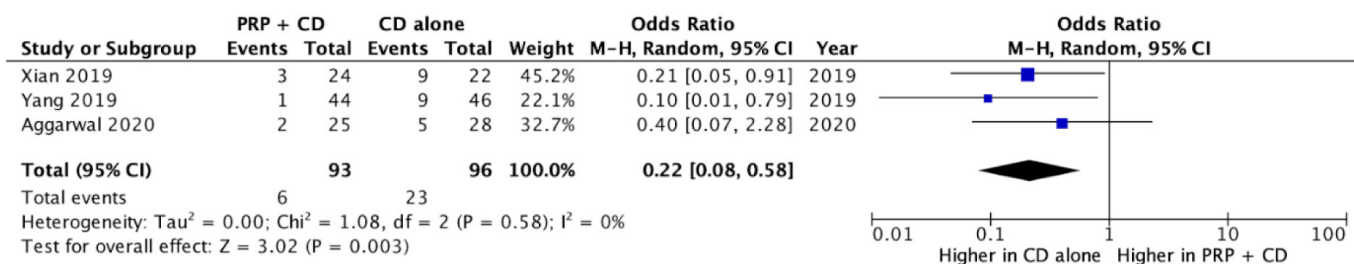


Figure 7a Needing further treatment comparison between Platelet Rich Plasma + Core Decompression vs Core Decompression alone

Analysis of the pain outcome included the two studies as seen in Figure 5a-b, using the VAS score with 10 having the worst pain to 0 with no pain. All patients in these two studies for both groups underwent this scoring system. VAS scores at final follow-up were measured at 24 months for the study of Yang, et al., [12] while the study of Xian, et al. [7] was measured at 36 months.

III. Survival from Disease Progression

The study of pooled data of disease progression after receiving treatment, as seen in Figure 6a, showed a statistically significant SMD between the two groups, favoring the PRP+CD group (SMD 5.44, z = 4.71, p <0.00001, 95% CI = 2.69 to 11.02). This finding denotes that there is a higher survival from disease progression in the PRP+CD group compared to the CD alone group. All three studies were assessed based on final follow up which accounted for all patients per group in each study that had progression of femoral head deformity which was evidenced by serial radiography (CT, MRI or X-ray).

IV. Need for Further Treatment

Based on the analysis of pooled data for the need for further hip surgery for progression of the same pathology, as seen in Figure 7a, the CD alone group

showed a statistically significant higher incidence with a SMD compared to the PRP+CD group (SMD 0.22, z = 3.02, p = 0.003, 95% CI = 0.08 to 0.58). This finding denotes that there is a higher rate of patients needing further hip surgeries such as hip arthroplasties or rotational trochanteric osteotomies due to severe disease progression at final follow-up in the CD alone group. All three studies were assessed based on final follow-up which accounted for all patients per group in each study that had progression of femoral head deformity which was evidenced by serial radiography (CT, MRI or X-ray).

DISCUSSION

In the current literature, there is still no consensus regarding the usefulness of PRP as an adjunct to core decompression in treating AVN of the hip. In a previous meta-analysis of Han, et al., (2020) they concluded that PRP primarily addresses ONFH through three key mechanisms. Firstly, it promotes the growth of fresh blood vessels (angiogenesis) and formation of new bone tissue (osteogenesis), thereby expediting the bone healing process. Secondly, it suppresses inflammatory reactions in the necrotic regions. Lastly, it safeguards against cell death triggered by glucocorticoids. Additionally, when used as an adjunct therapy along with core decompression, PRP is recommended to enhance the

treatment of early-stage ONFH patients, particularly when combined with stem cells and bone grafts. This combination stimulates bone regeneration and encourages the differentiation of stem cells in necrotic lesions. However, the evidence was not highly conclusive due to limitations in the quality of studies included in the review which were mostly prospective cohorts.[16]

With the use of three new RCTs not present in the previous review, our meta-analysis was able to support the findings of Hao, et al. [16] and synthesize findings for preoperative (baseline) and postoperative (final follow-up) HHS and VAS scores. The PRP+CD group reported significantly higher functional postoperative scores based on HHS scoring compared to the conventional CD alone group. On the other hand, the postoperative pain score showed a trend toward clinical significance favoring PRP+CD with a lower VAS score compared to the conventional CD alone group. The PRP+CD group also showed less occurrence of treatment failure with a significantly decreased rate of disease progression and need for further hip surgery due to the same disease.

The preoperative baseline HHS difference for both pooled groups was not statistically significant

indicating comparable patient status prior to undergoing surgery. On the other hand, based on the postoperative (at final follow-up) scores, all patients for both groups in each study had significantly higher scores compared to their preoperative baseline scores. However, on comparing the two groups, there was a statistically significant difference that favored the PRP+CD group. These findings show that both methods are effective in increasing the functional status of patients with ONFH, however, using PRP as an adjunct to conventional CD with bone grafting could potentially increase the effectiveness of treatment.

The VAS score for both groups for preoperative (baseline) scoring was likewise similar indicating comparable baseline pain levels for both groups in two studies by Xian, et al. (2019) [7] and Yang, et al., (2019).[12] Individually, these studies indicated significantly lower pain scores at final follow-up with the use of PRP as an adjunct to core decompression versus core decompression alone. However, upon pooled data in this study, we can see that at final follow-up VAS scores, there is a trend towards significance that favors the intervention group versus the control group with P-value = 0.06. This could be explained by high heterogeneity ($I^2 = 95\%$) of the

Table 1 Characteristics of the Included Studies

Characteristics of Included Studies								
Author (Year)	Group	Study design	Population	Intervention	Outcome			
					Functional Score (HHS)	Pain Score (VAS)	Disease Progression	Need for further Surgery
Aggarwal (2020)	Total [n=43]	RCT	Early stage (stage I and II) of ANFH as diagnosed by magnetic resonance imaging (MRI) and staged by Ficat and Arlet staging		Pre-operative, 63-65 months	No	Yes	Yes
	PRP+CD [n=25]							
	NSS + CD [n=28]							
Xian (2019)	Total [n=46]	RCT; single-blinded	Post-traumatic ONFH of Association of Research Circulation Osseous (ARCO) stages II to III		Pre-operative, 36 months		Yes	Yes
	PRP+CD [n=24]							
	CD [n=22]							
Yang (2019)	Total [n=90]		Early ONFH. ARCO I AND II		Pre-operative, 24 months		Yes	Yes
	PRP+CD + Oral Alendronate sodium [n=44]							
	CD [n=46]							

analysis due to high subjectivity of the VAS scoring and the difference in time of administration of tests per study as seen in Table 1.

The study also showed that the PRP+CD group had significant treatment failure as denoted by higher survival from disease progression and lower rates of need for further hip surgery. These could potentially indicate that the addition of PRP to conventional core decompression adds to the effectiveness of treatment by delaying disease progression for better clinical outcomes.

Strengths of the study

The generated evidence from this meta-analysis is credible, particularly in terms because the results showed statistical homogeneity despite some clinical heterogeneity. This implies that the use of PRP as an adjunct treatment to core decompression in patients with AVN provides better functional and treatment success compared to core decompression alone.

Limitations of the study

There are several limitations that are worthy to mention in our meta-analysis. There was considerable heterogeneity in the VAS score outcome at the final follow-up due to the difference in the time of administration of tests at the final follow-up. Aside from that, the study of Xian, et al.,[7] also used patients with ARCO stage III aside from those diagnosed with ARCO stage II or an early stage ONFH. Also, more studies to be included with more study populations would be recommended. Longer follow-up RCT study designs could also be helpful in determining long-term outcomes. Studies with more outcome measures between baseline and final follow-up results would be helpful in determining short-term, medium-term and long-term clinical effects.

CONCLUSION

In the treatment of patients with AVN, there is a statistically significant difference between the PRP+CD treatment group versus CD alone group in terms of HHS, increased survival from disease progression and decreased rate of need for further hip surgery at final follow-up favoring the use of PRP as an adjunct to core decompression. PRP+CD shows decreased VAS score at final follow-up compared to CD alone, however, this is not statistically significant.

DECLARATION STATEMENT

Ethics Approval and Consent to Participate

Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies.

Consent for publication

The authors confirm that this research has not been published prior to this submission and is not under consideration for publication for other journals. This is a meta-analysis and patient consent for publication is not required.

Availability of data and material

Not applicable

Competing Interests

The authors have no financial, commercial, legal, or professional relationship with other organizations that could influence the research or interpretation of results.

Funding

The authors declare that the study is self-funded and would not receive monetary gains from any company or organization.

Authors' Contributions

CF served as the main author of the study, which includes formulation of the population, intervention, control and methodology. The main author did the main research data collection as well as data analysis. BA served as the validator of the data collected as well as the data analysis.

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APPENDIX

Disclosure

The authors of this paper/research declare that they have no known competing financial interests, consultancies, honoraria, paid expert testimonies, grants, or personal relationships that could have appeared to influence the work reported in this paper.

Ethics

Ethical approval and patient consent are not required since this study is a meta-analysis based on published studies.

Authors' Contributions:

1. Research Project:
 - A. Conception – C.F.F, B.S.A and C.L.B.
 - B. Organization - C.F.F, B.S.A and C.L.B.
 - C. Execution - C.F.F.
2. Statistical Analysis:
 - A. Design - C.F.F. and B.S.A.
 - B. Execution - C.F.F.
 - C. Review, and Critique - B.S.A and C.L.B.
3. Manuscript Preparation
 - A. Writing the First Draft - C.F.F.
 - B. Review and Critique - B.S.A and C.L.B.