Effect of Platelet-rich Plasma Combined With Core Decompression Bone Grafting for Osteonecrosis of Femoral Head: A Meta-Analysis

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Research Article

Keywords: ONFH, core decompression bone grafting, PRP, meta-analysis

Posted Date: May 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-513630/v1>

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Abstract

Objective: Core decompression bone grafting usually is used hip-preserving approach for osteonecrosis of femoral head (ONFH). Platelet-rich plasma (PRP) is an adjuvant therapy, combined with core decompression bone grafting for ONFH. However, it remains controversial. Therefore, its efficacy was systematically evaluated and meta-analysis in this study.

Methods: Literature on core decompression bone grafting for ONFH was retrieved in CNKI, Wan Fang, PubMed, Embase, Cochrane Library and Web of Science from inception to March 2021. Review Manager 5.3 software and Stata 12.0 software were used for data synthesis.

Results: A total of 10 RCTs were included. The results showed at final follow-up that, Harris hip score was significantly difference in the treatment group, adjuvant therapy with PRP (group A) better than the control group (group B), MD=7.53 [95%CI (5.29,9.77)] $P < 0.00001$. There was MD=-0.71[95%CI (-0.96, -0.46)], $P < 0.00001$, of visual analog scale (VAS) of hip pain between the two groups. The excellent and good rate of function of hip was 1.42-fold higher in group A than that in group B, RR=1.42, 95%CI (1.25,1.62), $P < 0.00001$. The progression and total hip arthroplasty were showed improvements, RR=0.37,95%CI (0.21,0.65), $P=0.0006$ and RR=0.39,95%CI (0.18,0.85), $P=0.02$, respectively. Begg's and Egger's tests did not indicate publication bias.

Conclusion: It was shown that the use of PRP combined with core decompression bone grafting improved the symptoms better than core decompression bone grafting only, and might delay progression and total hip arthroplasty. However, as the study's limitations, it needed to be fully verified by more large-sample multicenter prospective clinical studies.

Introduction

Osteonecrosis of femoral head (ONFH), a refractory orthopedic disease that occurs most in 30–50 years old, usually progresses to collapse of the femoral head and causes hip pain and loss of function without treatment^[1–3]. It was reported that the annual new cases in the United States was 15,000–20,000. In some Asian countries, the prevalence was greater. The incidence rate in South Korea was 28.91/100,000^[4, 5]. 5–12% of cases that performed total hip arthroplasty (THA) each year was due to ONFH^[6]. THA is the most reliable option for the treatment of end-stage ONFH^[7, 8]. However, for early ONFH, especially in young patients, the long-term clinical and radiological results are still the focus. The results of THA in these young and more active patients were not perfect, mainly due to the limited life and durability of the prosthesis, and complications such as infection, prosthesis loosening and periprosthetic fracture^[9, 10]. These concerns have led to hip preservation treatments, such as physiotherapy and core decompression, which aimed at relieving symptoms, preserving their own hip, and delaying or preventing hip arthroplasty.

Core decompression, one of the most common methods for early ONFH, is used to reduce intraosseous pressure, promote vascular growth and the healing of necrotic areas^[11, 12]. ONFH treated with core decompression, the satisfactory clinical result was 63.5%, while that of conservative management was 22.7%, and for pre-collapse hips, there were 71% and 34.5%, respectively^[13]. In order to improve the efficacy of core decompression, there are some advanced versions, combined with (autologous or allogeneic) bone graft, mesenchymal stem cells, tantalum rod implantation, platelet-rich plasma et cetera^[14]. Some studies have reported good clinical results^[15–17]. Platelet-rich plasma (PRP), as one of them, isolated from autologous blood plasma, is a platelet concentrate, rich in autologous cell growth factor, and promotes the repair of injured tissue^[18]. PRP has been utilized for bone regeneration and cartilage repair^[19], and in recent years, platelet-rich plasma has been receiving increasing attention for the treatment of ONFH^[20, 21]. However, as a novel treatment for ONFH, its efficacy has been questioned. Therefore, we reviewed recent studies to assess its efficacy combined with core decompression bone grafting.

Materials And Methods

This study was executed in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^[22]. All the analysis were extracted relevant data from published studies, so ethical approval or patient informed consent was not required.

Search strategy

In the initial screening, 2 investigators systematically conducted the main search in the electronic databases of PubMed, Embase, Cochrane Library, Web of Science, CNKI (China National Knowledge Infrastructure) and Wang Fang to retrieve eligible articles from the inception of the databases to March 2021, without restrictions to languages, publication types or regions. The combined terms of Medical Subject Headings (MeSH) and non-MeSH were searched as follows: “osteonecrosis of femoral head” “osteonecrosis of the femoral head” “ONFH” “aseptic necrosis of femoral head” “avascular necrosis of femoral head” “platelet rich plasma” “PRP” “platelet-rich plasma” “core decompression” “CD” “drilling decompression” “femoral neck window” “femoral head decompression” “osteonecrosis bone scraping” etc..

Inclusion criteria

The inclusion criteria included the following: (1) The published studies: randomized controlled trial (RCT); (2) Subjects: patients diagnosed with ONFH; (3) Intervention: Core decompression bone grafting was conducted in the treatment group, adjuvant therapy with PRP (group A); and only Core decompression bone grafting in the control group (group B). (4) Clinical outcomes during follow-up included at least one of the following: Harris hip score (HHS), visual analog scale (VAS) of hip pain, excellent and good rate of function of hip, progression, total hip arthroplasty (THA) at the final follow-up.

Exclusion criteria

The exclusion criteria included the following: (1) cases report, conference abstracts, letters and review articles; (2) duplicate or overlapping data; (3) animal experiments; (4) full-text that cannot be downloaded; (5) improper statistical methods, data defect literature.

Data extraction

Two investigators independently reviewed the titles and abstracts of the articles to verify their relevance with the topic of core decompression bone grafting in the treatment of ONFH, exclude significantly unrelated studies and select the possible included articles. For the selected articles, read the full text carefully and then marked as the included articles. Finally, they extracted the data according to the inclusion criteria. We extracted the general details from the included articles, including the first author, time of publication, number of cases, follow-up, intervention, stages of ONFH, Harris hip score (HHS), visual analog scale (VAS) of hip pain, excellent and good rate of function of hip, progression, total hip arthroplasty (THA) during follow-up and other related information. In case of any disagreement, the results were discussed and unified by a third investigator.

Quality assessment

The methodological quality and risk of bias of the included RCTs was evaluated by 2 independent reviewers based on the items of the Cochrane Collaboration's risk of bias tool^[23], including comprising random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcomes assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.

Statistical analysis

The *I*-square (I^2) test was adopted to evaluate the influence of heterogeneity on the output of meta-analysis. I^2 values of 0%, 25%, 50% and 75% represented no, low, medium and high heterogeneity, respectively. According to the Cochrane review guidelines, severe heterogeneity of $I^2 \geq 50\%$ required the utilization of random-effect models. If substantial heterogeneity did not exist ($I^2 < 50\%$ and $P > 0.1$), a fixed effect model was implemented; Otherwise, the random effect model was approved. Sensitivity analysis was conducted by Stata 12.0 software. Funnel plots were visually checked, and Begg and Egger linear regression tests of potential publication bias were carried out by Stata 12.0 software. *P* value less than 0.05 was accepted as statistical significance, and the confidence interval (CI) was 95%.

Results

Search results

As a result, 167 references were initially obtained, 101 left after eliminating duplicate literature, then 81 without high-relevant to our topic were discarded by reading titles and abstracts, and 20 studies remained. Finally, by reading the full text, 10 articles that did not meet the inclusion criteria were

abandoned. Therefore, 10 studies^[20, 21, 24–31] were included in the meta-analysis. The flow chart of the selection process for the study was shown in Fig. 1.

Characteristics and quality assessment

The 10 included references were published differing from 2016 to 2021. Nine were conducted in China, 1 in India. In the selected RCTs, the sample sizes varied between 35 and 105 participants. After reading the articles, there were 547 patients (593 hips), including 275 patients (298 hips) in the combined group and 272 patients (295 hips) in the control group for analysis. There was one reference^[26] that reported the case of loss to follow-up. The stages of ONFH of the patients were ARCO I–II and Ficat–Arlet I–II. More details of the included studies were presented in Table 1.

According to the Cochrane Collaboration's risk of bias tool, quality assessment of the articles was shown in Fig. 2 and Fig. 3. As shown in the figure, the risks of bias for selection were low in the most studies, so was the attrition bias and reporting bias. Because participant must provide written informed consent before their inclusion in the included study, the performance bias was high in the most studies.

Table 1
General characteristic of the included studies

The study	Median age (year)	Group A/Group B Patients (hips)	Follow-up (months)	Stages	Outcomes
Aggarwal 2021 ^[20]	36.6	19 (25)/21 (28)	64.0	ARCO _a - _b	1,4,5
Dai 2019 ^[24]	46.5	26 (26)/26 (26)	6.0	Ficat _a - _b	1,2,3
Jiang 2018 ^[25]	37.1	26 (35)/24 (32)	6.0	ARCO _a - _b c	1,2,3,4
Li A 2020 ^[26]	38.2	35 (35)/35 (35)	12.0	ARCO _a - _b	1,2,3,4
Li R 2020 ^[27]	47.1	27 (28)/20 (25)	15.8	ARCO _a - _b c	1,2,3
Xian H 2020 ^[21]	28.9	24 (24)/22 (22)	45.5	ARCO _a - _b c	1,2,3,4
Yang 2016 ^[28]	36.5	15 (20)/20 (20)	12.0	Ficat _a - _b	1,2,3,5
Zhang 2020 ^[29]	42.2	52 (52)/56 (56)	24.0	ARCO _a - _b	1,2,5
Zhao 2017 ^[30]	39.7	30 (32)/30 (33)	12.0	Ficat _a - _b	1,3
Zhu 2018 ^[31]	43.7	22 (22)/22 (22)	12.0	ARCO _c - _b	1,2
1.Harris hip score; 2.VAS of hip pain; 3. Excellent and good rate of function of hip; 4. Progression; 5.THA					

Harris hip score

Of the 10 included studies, all reported Harris hip score at the final follow-up between the two groups. Because of significant heterogeneity among the studies, the random effect model was utilized ($I^2 = 87\%$, $P < 0.00001$). The results showed that Harris hip score at final follow-up in the treatment group was significantly better than that of the control group, MD = 7.53 [95%CI (5.29,9.77)], $P < 0.00001$. (Fig. 4)

VAS of hip pain

Data on VAS of hip pain were available for the meta-analysis from 8 studies, and significant heterogeneity was presented among the studies ($I^2 = 83\%$, $P < 0.00001$). Therefore, the random effect

model was applied. The differences in VAS between the two groups were still significant, MD=-0.71[95%CI (-0.96,-0.46)], $P < 0.00001$. (Fig. 5)

Excellent and good rate of function of hip

7 articles have reported excellent and good function of hip based on Harris hip score. The fixed effect model was chosen due to nonsignificant heterogeneity in comparisons ($I^2 = 0\%$, $P = 0.74$). The outcome manifested a statistically significant difference in the item between the two groups (RR = 1.42, 95%CI:1.25,1.62, $P < 0.00001$). (Fig. 6)

Progression

Four references concerning the data on progression of ONFH were available for the analysis. The fixed effect model was used as nonsignificant heterogeneity was found in intra-study comparisons ($I^2 = 0\%$, $P = 0.45$). The statistically significant difference in this index was shown between the two groups (RR:0.37,95%CI:0.21–0.65, $P = 0.0006$). (Fig. 7)

THA

Information in 4 of the references recorded total hip arthroplasty at the final follow-up was included in meta-analysis by the fixed effect model due to a nonsignificant statistical heterogeneity ($I^2 = 0\%$, $P = 0.97$). However, it was shown that there was significant difference in THA between both groups (RR:0.39,95%CI:0.18–0.85, $P = 0.02$). (Fig. 8)

Sensitivity analysis

Harris hip score and VAS of hip pain were found significant heterogeneity. The sensitivity analysis was performed on the selected studies to assess whether individual studies would affect the overall results using Stata 12.0 software. The outcomes suggested that no data strongly affected the overall results (Fig. 9 and Fig. 10). The heterogeneity might be due to the subjectivity of HHS and VAS, to some extent.

Evaluation of publication bias

Visual inspection of funnel plots was adopted in the estimation of Harris hip score and VAS of hip pain. There was asymmetry in funnel plots, suggesting publication bias. But, Begg's and Egger's tests showed no publication bias in this study ($P = 0.118$). (Fig. 11, Fig. 12 and Fig. 13)

Discussion

The treatment for ONFH includes hip arthroplasty, hip preservation surgery and conservative management. THA has been considered as the ultimate option for end-stage osteoarthritis (OA) secondary to femoral head collapse^[32], which can relieve pain and get better function of hip. But, the age

of ONFH is mostly between 30 and 50 years old, and hip arthroplasty cannot meet some requirements for the young adults, such as service life of the prosthesis. On the other hand, hip arthroplasty may have complications that the surgeons concern mostly, such as infection, prosthesis loosening, periprosthetic fracture and so on, which are risks for revision. For early-stage ONFH, pain relief and preservation of the autologous hip are still an important choice, so there are a lot of hip salvage surgery^[14]. However, pain relief and hip survival remain a challenge for orthopedic surgeons. There is no consensus on the strategy for hip-preserving surgery in the current guidelines.

Core decompression, one of the most commonly surgery used for hip preservation of ONFH, is to reduce intramedullary pressure, thereby preventing neurovascular compression and promoting new bone formation^[33], and some studies^[11, 13], compared core decompression and conservative management, have proved its effective. In order to increase its efficacy, there are modified versions, including the improvement of methods and combined with bone graft (autologous or allogeneic), mesenchymal stem cells and so on. It was reported^[34, 35] that Arthroscopic management in the process of core decompression with additional treatments was viable and had significant advantages. Hu B et al^[36], in the study to investigate the efficacy of fibula fixation in the treatment of early-stage ONFH, found that fibula fixation could effectively relieve the joint pain in patients with early ONFH, but it was not superior to core decompression in preventing articular surface collapse. Martinot et al^[37] reported that augmented core decompression (combined with adjuvant therapy) was significantly better than core decompression alone in 2-year survival and the long-term survival (without arthroplasty). Similar results were reported treatment with modified core decompression^[15–17, 38]. Nonetheless the clinical outcomes have varied widely^[39]. However, other studies reported^[40–43] that core decompression combined with adjuvant therapy can improve the symptoms of pain, but it did not affect the progress and collapse of femoral head, especially in the late stage of ONFH. So, there is still controversial about core decompression (with or without adjuvant therapy) for ONFH.

As one of the adjuvant therapies, platelet-rich plasma, with the advantages of cheap, simple and less complications, is effective in the treatment of ONFH. Victor Ibrahim et al^[44] reported a case of ONFH with autologous PRP injection. The patient demonstrated significant functional improvements after 1-year follow-up. Some animal experiments^[45, 46] also confirmed the effects and illustrated the mechanism of PRP. PRP promoted beneficial effects by inducing angiogenesis and osteogenesis to accelerate bone healing, inhibiting inflammatory reactions in necrotic lesions, and preventing apoptosis^[18]. Samy et al.^[47] found that, with a mean follow-up of 41.4 ± 3.53 months in a prospective study, core decompression combined with PRP and collagen sheet in the treatment of ONFH, the Harris hip score increased from 46.0 ± 7.8 preoperatively to 90.28 ± 19 at final follow-up. The mean values of VAS decreased from 78 ± 21 to 35 ± 19 , with an average decrease of 43 points. Therefore, in patients with ONFH, the use of PRP with collagen after core decompression can relieve pain and improve function. It was reported that by Grassi et al^[48], with 22 patients (30 hips) of ONFH, including Ficat I – IIA – IIIB , Harris hip score improved from 64 points before operation to 84 points two years later. At the end points of THA, the hip survival rates were 100% in stage I , 67% in stage IIA and 0% in stage IIIB after follow-up for 5 years. Therefore, core

decompression combined with PRP in the treatment of ONFH, the earlier the treatment, the better the benefit may be. In addition, some studies^[49, 50], core decompression combined with mesenchymal stem cells, bone grafting, PRP in the treatment of early ONFH, reported good preliminary results.

In this study, we conducted a meta-analysis of 10 selected studies to corroborate the efficacy of PRP combined with core decompression bone grafting in the treatment of ONFH. To ensure a reliable conclusion, previously published studies were retrieved, reviewed and summarized to answer various clinical questions of this malady. Overall, our results show that the use of PRP combined with core decompression bone grafting can significantly improve the symptoms, may delay the progression (or collapse) of femoral head and THA. For the analysis of progression and THA, it should be noted that the articles included in the analysis were relatively few and the time of follow-up was insufficient, and on the other hand, the articles included in the analysis only described the number of progression and THA at the final follow-up, but did not specify the time of progression and THA, which might affect the result. So, it was not clear whether the use of PRP delayed progression and THA. In addition, the sensitivity analysis did not indicate significant influence on the overall results. The publication bias was found by the visual distribution of funnel plots, but it did not indicate publication bias by Begg's and Egger's tests ($P = 0.118$).

Limitations

The meta-analysis contains the following limitations. First, the studies included in this analysis is insufficient, and potential publication bias may exist. Second, this study just includes references in English and Chinese. Therefore, we may have lost data from those in other languages. Third, the references included have a lot confounding factors and we cannot adjust for the confounding factors, such as the etiology and stages of ONFH, different amounts of PRP et cetera. Forth, the time of follow-up is different in the included studies, so it cannot evaluate the long-term efficacy, and there is a high heterogeneity. Therefore, we should be cautious about the conclusions of the meta-analysis. In all, the quantity and quality of the included studies in this meta-analysis still need to be improved. So, the conclusions of this study need to be fully verified by more large-sample multicenter prospective clinical studies.

Conclusion

In summary, our meta-analysis suggested that the use of PRP combined with core decompression bone grafting in the treatment for early ONFH improved the symptoms better than core decompression bone grafting only, and might delay progression and THA. Because of the limitations, we should be cautious about this conclusion. In the future, more prospective, large sample, multicenter, randomized clinical trials are needed to provide more reliable evidence.

Abbreviations

ONFH: Osteonecrosis of femoral head; PRP: Platelet rich plasma; MeSH: Medical Subject Headings; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ARCO: Association research circulation osseous; Ficat-Arlet: Ficat and Arlet classification of femoral head osteonecrosis; THA: Total hip arthroplasty; RR: Risk ratio; CI: Confidence interval; MD: Mean difference.

Declarations

Acknowledgements

None.

Authors' contributions

Z-QW and C-ZQ conceived and designed the study. L-QZ completed the draft of the manuscript. L-TY and Y-P analyzed the data. X-BL, Z-QZ and C-KS contributed to data collection. Z-QW, H-W and L-ZQ revised the manuscript. All authors read and approved the manuscript.

Funding

National Natural Science Foundation of China (81873327), Youth Project of National Science Foundation of China (81904226).

Availability of data and materials

The present study was a review of previous published references.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow chart of studies selection

Figure 2

Quality assessment of the articles

	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 2021	+	+	+	+	+	+	+
Dai 2019	+	?	-	?	+	+	?
Jiang 2018	?	?	-	?	+	+	?
Li A 2020	+	?	-	?	-	+	?
Li R 2020	?	?	-	?	+	+	?
Xian H 2020	+	?	-	+	+	+	+
Yang 2016	+	?	-	+	+	+	?
Zhang 2020	+	?	-	?	+	+	?
Zhao 2017	?	?	-	?	+	+	?
Zhu 2018	+	?	-	?	+	+	?

Figure 3

Quality assessment of the articles

Figure 4

Forest plot for the comparison of Harris hip score between the two groups

Figure 5

Forest plot for the comparison of VAS between the two groups

Figure 6

Forest plot for the comparison of excellent and good rate of function of hip between the two groups

Figure 7

Forest plot for the comparison of progression between the two groups

Figure 8

Forest plot for the comparison of THA between the two groups

Figure 10

Sensitivity analysis for VAS between the two groups

Figure 11

Funnel plot of the Harris hip score

Figure 12

Begg's test for the Harris hip score

Figure 13

Egger's test for the Harris hip score