

The management of platelet-rich plasma in ONFH treatment: A systematic review

Jun Han

China-Japan Friendship Hospital <https://orcid.org/0000-0002-2750-3391>

Fuqiang Gao

china japan frienship hospital

Wei Sun (✉ 1316294568@qq.com)

Lijun Shi

China-Japan Friendship Hospital

Xinjie Wu

China-Japan Friendship Hospital

Tengqi Li

China-Japan Friendship Hospital

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Abstract

Background: Osteonecrosis of femoral head (ONFH) is a pathologic process characterized by the lacking vessel blood of femoral head leading to cellular death, fracture, and collapse of the articular surface. Currently, critical treatment for early stage ONFH is limited to core decompression. However, the efficacy of core decompression remains controversial. With the purpose to improve the core decompression efficacy, regenerative techniques like platelet-rich plasma (PRP) have been proposed to address early stage ONFH. PRP is defined as a sample of autologous blood with concentrations of platelets above baseline values, which have an important role in tissue repair, regeneration, and differentiation of mesenchymal stem cells (MSCs). Within this review, we will present a comprehensive overview of operation modes, mechanism and efficacy of PRP for early stage ONFH treatment.

Methods: We searched Pubmed, Embase, Web of Science databases for relevant studies. Any observational or experimental studies that evaluated PRP, MSC, core decompression and ONFH were our goal of searching the electric database.

Results: 17 studies that researched PRP and ONFH were identified in this review. We reviewed 10 studies related to the possible mechanism of PRP for treating ONFH. On the other hand, 7 studies were about to the operation modes of PRP in treating ONFH so far. We reviewed the efficacy of PRP in treating ONFH systematically, with an attempt to make a comparison of PRP operation modes of 7 studies and other operation modes of past studies in early stage ONFH treatment.

Conclusion: PRP works to treat ONFH mainly through three mechanisms: induce angiogenesis and osteogenesis to accelerating bone healing; inhibit inflammatory reaction in necrosis lesion; prevents apoptosis induced by glucocorticoid. In addition, PRP are recommended as an adjunctive therapy for core decompression to improve the treatment of early stage ONFH patients, especially combined with stem cells and bone graft to induce an osteogenic activity and stimulate differentiation of stem cell in necrosis lesion.

Introduction

Osteonecrosis of femoral head is a pathologic process characterized by the lacking vessel blood of femoral head leading to cellular death, fracture, and collapse of the articular surface[1–3]. Presently, the pathogenesis of the disease has not been elucidated clearly, but glucocorticoid use and alcohol abuse are recognized as the most common risk factors[4, 5].The ONFH prevalence of the world is unknown. In China, the overall amount of osteonecrosis cases have reached 7 million and 100,000 to 200,000 new patients are diagnosed continuously each year[6]. Meanwhile, it is estimated that 15,000–20,000 new cases are diagnosed in the US each year[7]. The incidence of ONFH is showing a tendency of rising and more and more patients with ONFH are now diagnosed in the clinic[8, 9].

At present, total hip arthroplasty(THA) remains the most widespread procedure used to treat end-stage ONFH[10]. However, THA is not the best choice for patients who are young or with early-stage ONFH, because THA reduces the life quality of patients by restricting the motion function of hip and brings about some complications. So that young patients who suffer early-stage ONFH tend to choose conservative treatment to avoid or at least delay THA. Core decompression of hip is currently the most common conservative treatment

for early-stage ONFH, but its cure rate is only 63.5% and its efficacy remains controversial[11–13]. It is because that core decompression is used to decompress the intraosseous pressure in the femoral head, but it doesn't have superiority in facilitating osteoanagenesis in the necrotic area[14, 15]. For this reason, with the purpose to improve the core decompression result, regenerative techniques like platelet-rich plasma (PRP) have been proposed to address early ONFH[16].

PRP is defined as a sample of autologous blood with concentrations of platelets above baseline values[17]. PRP contains additional growth factors as well as platelets, such as platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β), basic fibroblast growth factor (bFGF), endothelial growth factor (EGF), and vascular endothelial growth factor (VEGF), which have an important role in tissue repair, regeneration, and differentiation of mesenchymal stem cells (MSCs)[16, 18]. Its use in orthopaedics began early within decade as PRP was used with bone grafts to augment spinal fusion and fracture healing[19]. Van et al. reported that the use of PRP could relieve the pain and halted the disease progression of patients with ONFH[20]. Currently, increasing experimental and clinical evidences showed that PRP may play an effective role in ONFH treatment[21, 22].

Within this review, we will present a comprehensive overview of operation modes and mechanism of PRP for early stage ONFH treatment. And then, we will make a system review about the comparison of PRP and other therapies for treating early stage ONFH.

Materials And Methods

This system review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) reporting guidelines for the conduct of systematic review and meta analyses of intervention trials (Additional file1). The review was not prospectively registered as it did not meet the criteria for registration with PROSPERO. Ethical approval for this study was unnecessary because it was a review of existing literatures and did not involve any handling of individual patient data.

2.1 Search strategy

Three electronic databases (PubMed, EMBASE, and Web of Science) were searched and we used terms and Boolean operators as follows: "(platelet-rich plasma) AND (avascular necrosis OR aseptic necrosis OR osteonecrosis OR necrosis) AND (femoral head OR hip)". The search strategies are found in Additional files2. We did not limit the year of publication, publication status, or language, and there was also no limitation on any particular study design: randomized or nonrandomized clinical trials, cohort, and case-control studies. In addition, we also checked the references of the articles manually to identify other potentially relevant publications. We did not seek unpublished articles.

2.2 Eligibility criteria and study selection

The studies that met the following criterias were considered eligible: the study enrolled patients with ONFH; the study researched the PRP and ONFH. Letters, comments, editorials, and practice guidelines were excluded. The study selection was then independently performed by 2 of the authors, and any different opinions were

resolved through discussion, with mediation from a third peer if needed (LS, XW, and TL). All information of included studies are listed in Additional files2.

2.3 Data extraction and quality assessment

All potential data were extracted and assessed by two reviewers (LS, XW) independently. Discrepancies between the two collaborators were discussed to reach consensus. Data were extracted with respect to participant characteristics, authors, journal, publication date, study design, operation technique and outcomes for each study included in our review. Participant information included number, age and stage of participants. Information about outcomes were recorded including scores of pain and function, image of MRI and X-ray, conversion to THA, collapse of hip. The quality of each of the included articles was assessed using U.S. Preventive Services Task Force by two reviewers (LS, XW).

2.4 Statistical analysis

We will firstly make a comprehensive overview of the mechanism of the PRP in ONFH treatment in recent years. And then, the data of studies about PRP clinical application were collected, and we categorized the clinical operation modes of PRP into several groups and compared the therapeutic effects with other therapies for ONFH treatment systematically.

Results

A total of 69 articles were initially searched from the PubMed, EMBASE, and Web of Science databases (Figure 1). After duplicating, title screening, and abstract or full text screening, 17 studies that researched PRP and ONFH were identified in this review, 10 studies of which were for PRP mechanism and 7 studies of which were for PRP clinical application. We reviewed the mechanism of PRP in the treatment of ONFH. And then, we reviewed the efficacy of PRP in treating ONFH systematically, with an attempt to make a comparison of PRP operation modes and other operation modes of past studies in early stage ONFH treatment.

3.1 The mechanism of PRP in ONFH treatment

3.1.1 PRP accelerates angiogenesis and osteogenesis in ONFH

After PRP was verified as a useful management in ONFH treatment by Yokota et al.[23], massive clinical and epidemiological studies started to research the mechanism of PRP in ONFH treatment. Numerous studies have reported that enhancing osteogenesis and angiogenesis to reconstruct the bone structure of necrotic area are the main mechanism for early stage ONFH treatment[1, 24, 25]. And in light of above rationales, PRP could augment core decompression and bone graft substitutes to treat early stage ONFH through various cytokines that initiate and regulate the proliferation, differentiation and angiogenesis[16, 17, 26](Figure 2). The cytokines identified in PRP include platelet-derived growth factor (PDGF), transforming growth factor (TGF)- β , basic

fibroblast growth factor (bFGF), endothelial growth factor (EGF), insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF), some of which have been examined efficiently by many researchers. Nakamae et al. reported that the combination of vascular bundle implantation and FGF-2 administration may contribute to the treatment of ischemic osteonecrosis in rabbits[27]. Suzuki et al. reported that VEGF administration increased surgical angiogenesis and improved blood flow and neovascularization in necrotic bone during 1 week after arterovenous bundle implantation[28]. Yang et al. delivered that the management of VEGF gene transfection for ONFH of rabbits exhibits a higher bone formation than control group that didn't received VEGF transfection therapy[24]. Although several articles indicated that each growth factor individually induces angiogenesis and osteogenesis. On the contrary, some articles reported growth factors presenting a suppression of osteoanagenesis, such as a single administration of high doses of TGF β (335 μ g into humeral canine model) or high doses of VEGF (0.5 μ g into rat segmental defect) inhibited bone formation[29, 30]. Therefore, the angiogenesis is a complex process requiring a finely tuned balance between numerous growth factors. Brill et al. reported that a concomitant effect of bFGF and VEGF for the entire process of vessel formation seemed to be more essential than a single administration of bFGF or VEGF alone[31]. So that, PRP could create an optimal environment to increase the reparable capacity of ONFH by regulating the interactions of numerous growth factors with different systems.

Exception for PRP itself containing angiogenic factors, Tong et al. reported that the mRNA expression levels of VEGF, PDGF, IGF-1 and TGF- β in ONFH-mice model were significantly upregulated by PRP treatment compared with the control group (PBS-treated). PRP may increase the production of angiogenic factors via upregulation of angiogenic gene pathway, which may contribute to angiogenesis in femoral head osteonecrosis[32].

3.1.2 PRP treatment inhibits inflammatory reaction in ONFH

Osteonecrosis of the femoral head is associated with synovitis characterized by a series of inflammatory cells and proinflammatory cytokines in necrotic lesion and synovium[33, 34]. Previous research has found that the synovium is saturated by CD4+ T cells, macrophages, and some CD8+ T cells during the ONFH pathogenesis[35]. Some proinflammatory cytokines, such as Interleukin-1(IL-1) β , IL-6, TNF(Tumor Necrosis Factor) α , and IL-17, are also involved in the pathophysiology process of ONFH[36, 37]. Although the mechanism of ONFH induction are not fully understood, the inflammatory cytokines have been reported to be the critical mediators of ONFH pathogenesis according to previous studies[38, 39]. Zou et al. reported that a typical positive association between IL-17 and pain severity of ONFH[36].

Tong et al. reported that the mRNA and concentrations levels of inflammatory cytokines, such as IL-17A, TNF- α , IL-1 β and Receptor activator of nuclear factor- κ B ligand (RANKL), were significantly downregulated in the PRP treatment group compared with the control group in synovial cells of ONFH-mice model[32]. This result indicated that PRP treatment effectively suppressed the expression of IL-17A, IL-1 β , TNF- α and RANKL in ONFH. Interestingly, this study also suggested that PRP treatment upregulated the mRNA expression levels and concentrations of interferon (IFN)- γ and IL-6 compared with the control group in synovial cells. This result indicated that PRP treatment promoted IFN- γ and IL-6 in ONFH, which is in contradiction with the increasing of IL-6 in local synovium following ONFH and the negative effects of IL-6 on osteoblast differentiation[34, 40]. With regard to downregulation of IL-6 and IFN- γ , Tong et al. thought the PRP treatment could promote

chondrogenic proliferation and differentiation, which contribute to the production of IL-6 and IFN- γ when the articular cartilage perform maintenance[41, 42].

Totally, PRP treatment downregulates the inflammatory reaction, which may stop the ONFH progression and alleviate the pain by interrupting the circulation of inflammatory damage to joint.

3.1.3 PRP-exosomes treatment prevents apoptosis induced by glucocorticoid in ONFH

Glucocorticoids use could cause ONFH by inducing cell apoptosis which account for the bone loss and angiogenesis impairment[43, 44]. Glucocorticoids modulate endoplasmic reticulum (ER) stress to induce cell apoptosis. So that, if the treatment could prevent cell apoptosis by mediating ER apoptosis, it could reverse progression of ONFH.

Among the three main signal pathways in ER stress, Tao et al. found that the protein kinase R-like endoplasmic reticulum kinase (PERK) pathway is closely associated with apoptosis[45]. Glucocorticoids activate the PERK by phosphorylation of eukaryotic translation initiation factor 2 α (eIF2 α). As one downstream effector protein of PERK, CCAAT-enhancer-binding protein homologous protein (CHOP) inhibits B-cell lymphoma 2 (Bcl-2) protein expression, and then caspase-3 is cleaved, leading to cell apoptosis[46, 47].

Tao et al. reported that PRP-exosome could block ER stress-induced apoptosis without altering PERK activation and CHOP expression[45]. Adding PRP-exosome to BMSCs (bone mesenchymal stem cells) together with dexamethasone, the result exhibited that Akt (protein kinase B) and Bad (Bcl-2-associated death promoter) were phosphorylated, Bcl-2 expression increased, and then cleaved-caspase-3 could not be detected. so that, Bcl-2 might be the key protein in the anti-apoptotic effect of PRP-exosome. PRP-exosome inhibited cell apoptosis mainly through the activation of the Akt/Bad/Bcl-2 signal pathway.

In addition to inhibiting the apoptosis induced by dexamethasone, PRP treatment also could resist the toxic effect of dexamethasone directly. Tong et al. demonstrated that a significant decrease in the serological levels of anti-glucocorticoid IgG occurred in PRP-treated ONFH-mice compared with the control group, which indicated the humoral glucocorticoid concentration was decreased by PRP[32].

3.2 The applications of PRP in ONFH treatment

3.2.1 PRP combined stem cells treat ONFH

Houdek et al. conducted a prospective study basing on 22 early stage ONFH participants in Mayo Clinic who were treated by PRP combined bone marrow-derived mesenchymal stem cells (BmMSCs) after core decompression and observed that more than 93% of patients were free of femoral head collapse and 84% were free of conversion to THA at 3 years of follow up (Table 1). And also, that study exhibited that the mean modified Kerboul angle of necrotic lesion improved from $205^{\circ}\pm 47^{\circ}$ to $172^{\circ}\pm 48^{\circ}$ after 12-month postoperative MRI assessment, which indicated the risk of progressing to collapse reducing [48, 49]. MSC are capable of enhancing tissue regeneration by differentiating into multiple mesenchymal phenotypes, including osteoblasts, chondrocytes, and adipocytes[50]. When MSCs are combined with PRP to treat ONFH, necessary growth

factors of PRP could promote the potential of MSC differentiating into new bone and blood vessel. So that, PRP enhances the osteoanagenic effect of MSC to improve the healing of early stage ONFH.

In addition to BmMSCs, PRP combined with adipose derived MSCs (AdMSCs) also has been used for ONFH treatment. Due to the limited surgical cases receiving treatment of PRP and AdMSCs, none of articles containing large sample volumes has systematically evaluated its therapeutic effects so far. Pak et al. published two case reports about 4 patients with stage IV ONFH who received the treatment by injecting PRP/AdMSCs mixture into the femoral head under ultrasound guidance, suggesting a long-term improvement in pain and motion range and new regeneration of bone in MRI for 7 to 12 months at least [51, 52]. In another case report from Pak et al.[53], one patient with I stage ONFH received PRP/AdMSCs mixture treatment once and PRP treatment every week for 4 weeks in subsequent treatment. Eventually, the patient reported the complete resolution of hip pain and motion function abnormalities after 21 months followed-up, and the MRI presented a significant signal changes in both the T1 and T2 views of the femoral head before and after PRP/AdMSCs treatment. This is the first complete resolution of ONFH treated by percutaneous injection of PRP/AdMSCs.

The combination of AdMSCs and PRP may produce more therapeutic effect for ONFH than BmMSCs/PRP treatment. The concentration of AdMSCs(around 200 000/g) is higher than that of bmMSCs(around 6000–60 000/g) [53], and the source of BmMSCs is restricted by certain disease like osteoporosis and leucocythemia[54]. And the study from Wyles et al. also supported the AdMSCs, suggesting that AdMSCs show greater potency for proliferation and osteogenic differentiation superior to BmMSCs in the setting of osteonecrosis[53].

3.2.2 PRP combined with Synthetic or autologous bone graft treat ONFH after core decompression

Currently, there were only three articles reporting the PRP associated with bone graft to treat ONFH during core decompression surgery. Three articles all showed significant outcomes in the treatment of ONFH, particularly for early stage patients.

Guadilla et al. enrolled 1 patient with Grade IIA ONFH and 3 patients with Grade IIB ONFH who be treated with PRP and autologous bone grafting after core decompression through arthroscopy. The four patients all appeared significant reduction in visual analog score (VAS) and return to a normal state of life by the fifth month. While a significant improvement of symptoms was observed during the early follow-up process, the representative bone formation of MRI emerged soon afterwards. Considering the limit of patient number and the lack of advanced ONFH patients, this study cannot provide sufficient evidence to support the efficacy of PRP[55]. Samy et al. performed a prospective study of 40 hips in 30 patients with modified Ficat stages IIb and III ONFH, with an operation procedure of core decompression and a composite of iliac bone graft and PRP[56]. Significant pain relief was reported in 34 hips (85%), and Harris Hip Score (HHS) was improved from 46.0 ± 7.8 preoperatively to 90.28 ± 19 postoperatively after 4 years follow up. This result was much better than the study without PRP reported by Mont et al. who used the technique of core decompression and iliac bone graft[57]. D'Ambrosi et al. evaluated 24 hips in 16 patients including all the Ficat classification, treated by core decompression, injection of PRP and MSCs, and synthetic bone graft[58]. The clinical failure was defined as conversion to THA by 75 months of follow-up. The total survivorship of this operation is 50%. The survival rate

was 80% for patients in III stage and 28.6% for patients in III-IV stage. In comparison to patients at stage I and II, the patients with disease at stage III and IV suffered higher rate of failure of operation.

3.3 Effectivity of PRP in comparison to other treatments in treating ONFH

Currently, the method of applying PRP to treat ONFH is just beginning to take off, and There are barely articles to study the efficacy of PRP in treating ONFH. The amounts of articles could be retrieved only including 4 case reports and 3 self-controlled studies. Moreover, the main function of PRP is as an adjuvant substitute for core decompression to treat ONFH. For this reason, we reviewed articles to make a comparison between previous modes about core decompression and PRP in combination with core decompression.

To improve bone regenerative, the application of core decompression in association with stem cell is an appealing possibility. Hernigou and his colleagues are the pioneers in applying stem cell to ONFH treatment. They held a prospective study of 189 hips in 116 patients receiving core decompression and autologous BmMSCs grafting. After the follow-up of the 5- to 10-year, total hip replacement was necessary in 9 hips among the 145 hips with early stage ONFH(Steinberg Stage I and Stage II), presenting 95% high success rate[59]. But it should be note that Hernigou's study defined Steinberg Stage II as a hip with an abnormal MRI scan and an abnormal radiograph in a patient presenting with sclerotic or cystic changes in the femoral head but an absence of crescent line, which was equivalent of the stage in between actual Steinberg Stage I and actual Steinberg Stage II[60]. Thus, the rigid selection of early patient contributed to the high success rate. Actually, several studies discovered that the survivorship free from collapse for early-stage patients who received core decompression combined with MSC were 85%~90% after 24~60 months following-up[61, 62]. All the aforementioned literatures agree that core decompression associated with stem cell can improve the post-operative outcomes compared to core decompression alone. What if combining PRP on the basis of core decompression and stem cell? Houdek et al. applied PRP in combination with BmMSCs and core decompression to early stage ONFH of 22 patients with 31 hips (Steinberg Stage I and Stage II), which turned out that more than 93% and 84% of patients were free of femoral head collapse and free of THA after 3 years following-up[48]. Houdek et al. also analyzed BmMSC content of bone marrow concentrate (BMC) by test nucleated cell quantity and colony-forming unit (CFUs), presenting that patients who received lower mean concentration of nucleated cells per milliliter of BMC ($5.5 \times 10^6 \pm 2.8 \times 10^6$ cells/mL versus $2.3 \times 10^7 \pm 2.2 \times 10^7$ cells/mL, $p < 0.02$) and lower mean CFUs (13 ± 6 versus 19 ± 7 , $p < 0.04$) were more likely to undergo an additional surgical procedure (THA or repeat core decompression). In addition, this study showed that 80% of patients classified as high risk (modified Kerboul Grade 3 and 4) undergoing an additional surgical procedure (THA or repeat decompression), while no low-risk (modified Kerboul Grade 1 and 2) patients progressed to collapse[48, 49].

Through simply comparing the outcomes between Hernigou et al. and Houdek et al., it suggested that for preserving femoral head integrity, the curative effect of combining PRP with BmMSCs and core decompression was similar to that of combining BmMSCs and core decompression for treating early-stage ONFH. However, considering the rigid selection of patients in Hernigou et al. study excluding patients with crescent sign, PRP indeed could augment curative effect of combining BmMSCs and core decompression for early stage ONFH.

Considering the use of synthetic or autologous bone graft to augment core decompression, Rosenwaser et al. demonstrated a high clinical success rate (85%) for 15 hips of 13 patients with stages II and III ONFH at long-term follow-up (10–15 years)[63]. Wang et al. evaluated 110 patients (138 hips) with stage ARCO IIA–IIIA ONFH treated with core decompression combined with the mixture of autologous bone and demineralised bone matrix. The definition of clinical failure was a Harris hip score below 80 points or if the patients need further surgical procedure (THA or osteotomy). At the conclusion of the study, it reported 85% survivorship rates in stages IIA and IIB at 25 months following up[64]. However, some studies have come up with the exact opposite results for core decompression combined with bone graft. Yu et al. enrolled 18 patients (19 hips) with ONFH, 6 hips in stage IIC and 13 hips in stage IIIA, treated with core decompression combined with synthetic bone grafts (PRO-DENSE). The clinical failure was defined as conversion to THA or progression in head collapse. In the end, three hips of stage IIC and eight hips of stage IIIA were converted to THA in mean 8.5 months postoperatively. Advanced collapse of the femoral head was observed in the other six hips. Only 2 hips (10.5%) were free of further collapse during the 5-year follow-up[65]. The above results suggested that the efficacy of synthetic or autologous bone graft combined core decompression has been debated so far. According to published articles, filling mixture of PRP and autologous bone to core decompression track, the results were better than grafting bone alone. Samy et al. performed an operation procedure of core decompression and a composite of iliac bone graft and PRP on 30 patients, 16 hips (40%) on stage IIb and 24 hips (60%) on stage III ONFH, graded according to modified Ficat classification, presenting the rate of free from THA was 90% at 4 years follow-up[56]. Guadilla et al. treated 4 patients with Grade IIA and IIB ONFH with PRP and autologous bone grafting after core decompression, which showed cartilage integrity of 4 patients were preserved with average 14 months follow-up [55].

These results suggested that bone graft in association with PRP, and MSC, could have several theoretical advantages in enhancing the success rate of core decompression. The bone grafting provide provisional mechanical support after removing the necrosis lesion, while PRP stimulate the differentiation of MSCs and play a critical role in osteogenesis and angiogenesis to induce bone healing. But it was similar to other studies about core decompression[66–68], PRP is not an effective method of treatment in late stage ONFH. D'Ambrosi evaluated 24 hips in 16 patients of all stages Ficat classification, treated by core decompression, and backfilling of the core tract with mixture of synthetic bone graft, PRP and MSCs. The survival rate was 80% in early stage patients, however, 28.6% patients in advanced stage could survived the collapse[58]. So that, in the early stages of treatment, the outcomes of the core decompression may be improved by PRP with other regenerative therapy, but PRP is not suitable to advanced stage ONFH as well as necrotic lesion more than 50% [69]. This is verified by the research established by Yoon et al, which determined the importance of both Ficat stage and lesion size in ONFH treatment[70].

Conclusions

Currently, PRP is a possible treatment to meet various medical problems through the stimulation and acceleration of soft-tissue healing and regeneration[19, 71]. Especially in treatment of bone nonunion and diabetic neuropathic foot ulcers, many clinical studies represented satisfactory results, even be better than standard care[72–74]. However, for treatment of ONFH, PRP alone will not work very well to treat ONFH. Because ONFH is characterized by cellular death of bone due to interruption of the blood supply, the most important steps for treating ONFH are facilitating osteogenesis and angiogenesis and restoring bone formation

to reconstruct support to the joint surface. PRP must be in association with core decompression and other methods to play its role.

In summary, PRP couldn't reverse the pathophysiology course of ONFH, however, PRP are recommended as an adjunctive therapy for core decompression, combined with stem cells and bone graft (autologous or allogeneic) to induce an osteogenic activity and stimulate differentiation of stem cell for ARCO stage I and II patients(Association Research Circulation Osseous)[58]. PRP works mainly through three mechanisms: induce angiogenesis and osteogenesis to accelerating bone healing; inhibit inflammatory reaction in necrosis lesion; prevents apoptosis induced by glucocorticoid. Cotreatment with PRP may have a potent efficiency in ONFH, and its popularity would become higher and higher. But further prospective randomized clinical trials of PRP are needed to determine its efficacy; standardized preparation and the ratio to stem cells in the therapeutic algorithm must be investigated soon.

In general, our review also showed various limitations which shouldn't be ignored. First, the number of included studies that could be found were relative scarcity. Totally, 7 studies evaluated the efficacy of different operation modes of PRP, 3 articles for prospective descriptive study, and the other 4 studies for case report, all of which were low evidence-based medical classification. Second, there was not a uniform standard in operation procedure and curative effect evaluation of PRP among articles, in that there is a high heterogeneity in this study. In addition, there may be publication bias for every included article reporting good results.

Declarations

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Competing interest

The author(s) declare that they have no competing interests.

Authors' contribution

LS, XW, and TL searched the materials and analyzed the data. SW designed the study program. JH and FG wrote the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

List of abbreviations

PRP: platelet-rich plasma, ONFH: osteonecrosis of femoral head, MSCs: mesenchymal stem cells, BmMSCs: bone marrow-derived mesenchymal stem cells, AdMSCs: adipose-derived mesenchymal stem cells, HHS: Harris hip score, THA: total hip arthroplasty, PDGF: platelet-derived growth factor, TGF- β : transforming growth factor- β , bFGF: basic fibroblast growth factor, EGF: endothelial growth factor, IGF: insulin-like growth factor, VEGF: vascular endothelial growth factor, IL-17A: Interleukin-17A, IL-1 β : Interleukin-1 β , IL-6: Interleukin-6, TNF- α : Tumor Necrosis Factor- α , ER: endoplasmic reticulum, PERK: protein kinase R-like endoplasmic reticulum kinase, eIF2 α : eukaryotic translation initiation factor 2 α , RANKL: Receptor activator of nuclear factor- κ B ligand, Akt: protein kinase B, Bad: Bcl-2-associated death promoter, Bcl-2: B-cell lymphoma 2, CHOP: CCAAT-enhancer-binding protein homologous protein, VAS: visual analog score, BMC: bone marrow concentrate, CFUs: colony-forming unit, ARCO: Association Research Circulation Osseous.

Author's information

- Department of Orthopedic Surgery, Peking University China-Japan Friendship School of Clinical Medicine.
- Centre for Osteonecrosis and Joint-Preserving & Reconstruction, Department of Orthopedic Surgery, Beijing Key Laboratory of Arthritic and Rheumatic Diseases, China-Japan Friendship Hospital, Peking Union Medical College, National Health and Family Planning Commission of the People's Republic of China.
- Department of Orthopedic Surgery, China-Japan Friendship Institute of Clinical Medicine, Peking Union Medical College.

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Tables

Table 1. Detailed description of the 7 studies about PRP clinical application in the systematic review.

Author	Level of evidence	Patient/hip treated	Age(years)	Staging	Technique	Follow-up	Conclusion
Houdek et al.[48]	LevelII Prospective descriptive study	22/35	43	Steinberg stage I,II	PRP/BmMSCs/core decompression	36 months	93% of patients were free of femoral head collapse and 84% were free of conversion to THA.
Jaewoo Pak[52]	LevelIV case report	2/2	29,47	stage IV	PRP/AdMSCs mixture under ultrasound guidance	3 months	hip pain improved more than 70%, new regeneration of bone in MRI.
Jaewoo Pak[51]	LevelIV case report	2/2	34,39	stage IV	PRP/AdMSCs mixture under ultrasound guidance	16 months	a long-term improvement in pain and motion range and new regeneration of bone in MRI.
Jaewoo Pak et al. [53]	LevelIV case report	1/1	43	Ficat classification stage I	PRP/AdMSCs mixture under ultrasound guidance	21 months	no hip pain, and symptoms were completely resolved, MRI indicating the complete resolution of ONFH.
Guadilla et al.[55]	LevelIV case report	4/4	/	Steinberg stage IIa,IIb	PRP/autologous bone grafting/core decompression through arthroscopy	14 months	reduction in pain intensity (60%), new regeneration of bone in MRI.
Samy et al.[56]	LevelII Prospective descriptive study	30/40	36.7	modified Ficat classification stages IIb and III	PRP/autologous bone grafting/core decompression	41.4 months	HHS improved from 46.0 ± 7.8 preoperatively to 90.28 ± 19 (P < 0.0001). VAS were 78 ± 21 and 35 ± 19 at preoperatively period and final follow up.
D'Ambrosi et al.[58]	LevelII Prospective descriptive study	16/24	42	all the Ficat classification	PRP/MSCs/synthetic bone graft/core decompression	75 months	The conversion to THA rate was 80% for patients in III stage and 28.6% for patients in III-IV stage.

PRP: platelet-rich plasma, BmMSCs: bone marrow-derived mesenchymal stem cells, AdMSCs: adipose derived MSCs, HHS: Harris hip score, THA: total hip arthroplasty.

Figures

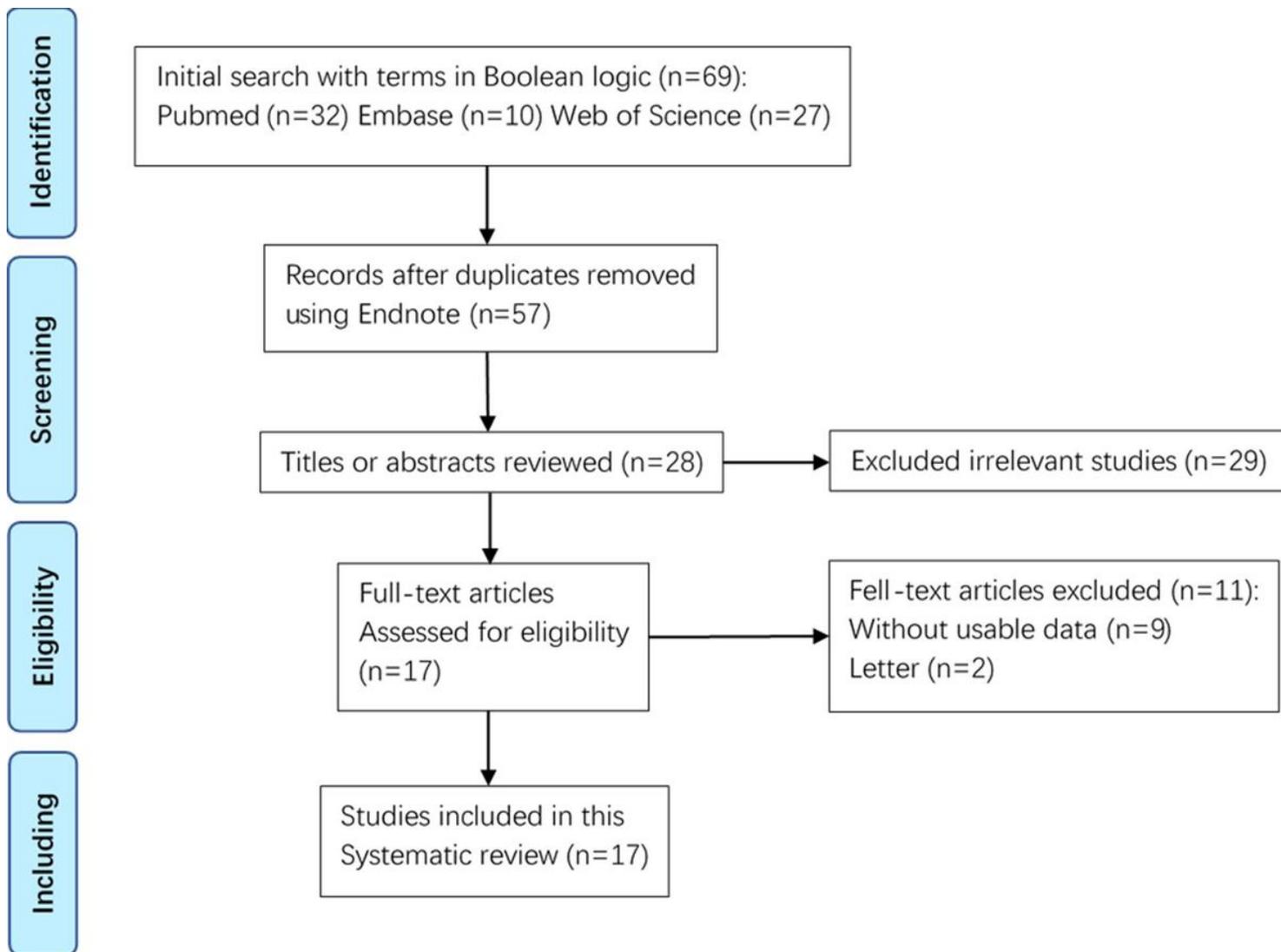


Figure 1

The selection process of this review.

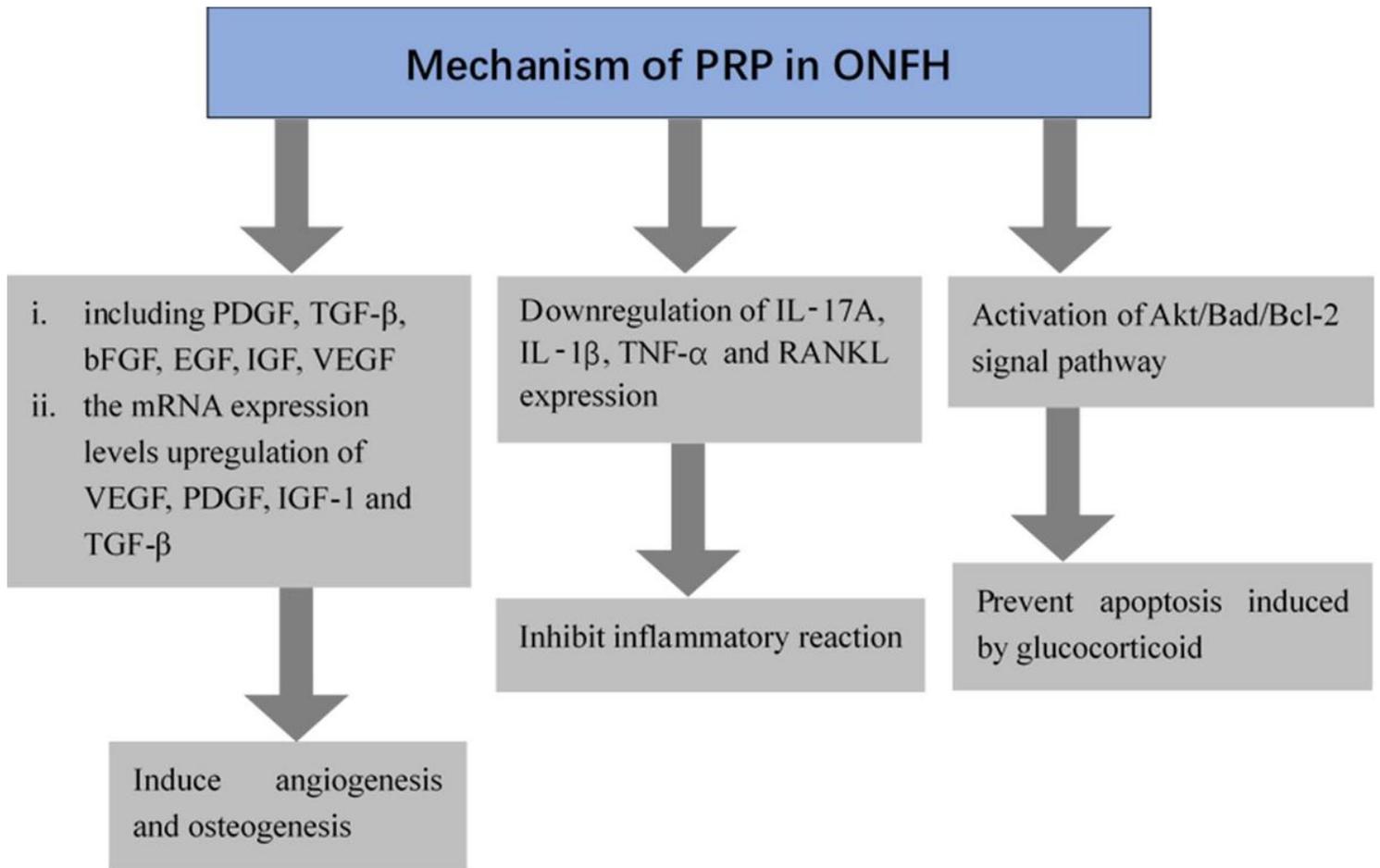


Figure 2

The mechanism of PRP in ONFH treatment. PRP: platelet-rich plasma, PDGF: platelet-derived growth factor, TGF- β : transforming growth factor- β , bFGF: basic fibroblast growth factor, EGF: endothelial growth factor, IGF: insulin-like growth factor, VEGF: vascular endothelial growth factor, IL-17A: Interleukin-17A, IL-1 β : Interleukin-1 β , IL-6: Interleukin-6, TNF- α : Tumor Necrosis Factor- α , RANKL: Receptor activator of nuclear factor- κ B ligand, Akt: protein kinase B, Bad: Bcl-2-associated death promoter, Bcl-2: B-cell lymphoma 2.

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