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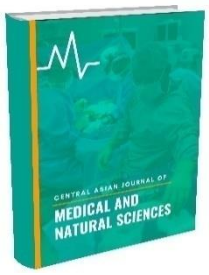

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Complex Surgical Treatment of Non-United Fractures and False Joints of the Femur

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Abstract: Despite greater understanding of biomechanics and improvements in implant design, nonunion of femoral shaft fractures continues to be a major challenge in the treatment of such injuries (Bishop JA, Palanca AA). Femoral nonunion presents a challenge for the surgeon and entails significant personal and economic burden for the patient. In most cases of femoral fractures treated with intramedullary osteosynthesis, the incidence of this complication is estimated at approximately 1% (Zura et al., 2016; Santolini et al., 2015). Recent reports suggest an increase in this incidence due to advances in trauma medicine, resulting in increased survival of patients with severe trauma and expanded indications for the use of intramedullary nails. Although the treatment of femoral shaft fractures is well described in the orthopedic literature, information on the treatment of nonunions of this part of the bone is limited and controversial, due to the small number of cases in most of the reported series. Despite this, a careful analysis of the existing literature provides some answers regarding the choice between conservative and surgical treatment. The gold standard in the treatment of nonunions of the femoral diaphysis remains surgical intervention in the form of intramedullary osteosynthesis with closed reaming or exchange osteosynthesis. However, several alternative techniques have been noted, including the use of electromagnetic fields, low-intensity ultrasound, extracorporeal shock wave therapy, external fixators, and exchange or indirect plate osteosynthesis techniques. This article provides a comprehensive review of current treatments for aseptic midshaft nonunion, preceded by a brief review of the incidence, definition, classification, and risk factors of this complication.

Key words: Femur fractures, revision surgery,

osteosynthesis, intramedullary nailing, fracture healing.

Introduction

Diaphyseal fractures of long bones are usually accompanied by a characteristic morphological picture characterized by displacement and comminution. These phenomena are considered to contribute to unfavorable bone contact and compromised blood supply, which negatively affects the healing process. In addition, various additional aspects such as severe bony defects, soft tissue injuries, open fractures, and patient-related risk factors may result in delayed or complete failure of union. These cases are estimated to occur in 1.9% and 10% of all diaphyseal fractures (Mills et al., 2017; Nandra et al., 2016). Modern research in the field of orthopedics is aimed at increasing the formation of callus. This process is carried out using various strategies, including surgical, pharmacological, cellular and biophysical methods (Djouad et al., 2009; Mark Fisher et al., 2013; Hannemann et al., 2014). The purpose of this article is to review the biomechanical basis of failed reparative osteogenesis in diaphyseal fractures. In addition, surgical, biological, physical, and pharmacological treatment options will be reviewed to improve bone healing in acute fractures and delayed unions. The article will also consider the biological and biomechanical basis of surgical treatment of diaphyseal fractures. Healing of diaphyseal fractures of long bones can occur through direct or indirect healing, depending on the nature of the fracture (simple or multi-fragment), the state of the blood supply and the biomechanical environment at the fracture site after operative or conservative treatment.

The history of orthopedics is rooted in Wolf's Law (Wolf, 1986), who in 1982 first described the physiological response of normal bone to its mechanical environment during bone healing and remodeling. Frost's concept of the “mechanostat” then defined bone homeostasis as an independent unit that responds to changes in the mechanical environment (Frost, 1987). One of the most accepted theories is Perren's "strain theory" (Perren, 1989), which states that the formation of a bone bridge between distal and proximal callus can only occur when local strain is less than the tolerance of the forming fibrous bone (Perren, 1989) . Therefore, when interfragmentary strain (IFS), expressed as a function of motion and fracture width, is less than 2%, bone healing occurs in a direct manner, whereas when IDF is intermediate (5–10%), the fracture heals in an indirect manner. If stresses exceed the strain tolerance of the fracture, creating a high-stress environment (IFD >10%), the fracture will eventually result in malunion (Perren, 2003). The same deforming force produces more strain at the site of a simple fracture than at the site of a multifragment fracture, which tolerates more motion between the two major fragments because the total motion is shared by multiple fracture planes.

Klas et al have demonstrated that in simple shaft fractures, direct healing can only occur when the cortical integrity of the fractured fragments is restored and rigid fixation is achieved, resulting in low interfragmentary motion (Klas and Heigele, 1999; Shapiro, 1988; Klas and Heigele, 1999; al., 1997). Particularly important is a fragment gap of less than 0.01 mm and interfragmentary strain of less than 2% for the fracture to heal in an intramembranous manner (Shapiro, 1988). Therefore, surgical methods with absolute stability, such as internal plate fixation, are mandatory. In the case of complex, multi-part, diaphyseal fractures, the indirect healing process is enhanced by micromotion and body weight support, and therefore anatomical repair and absolute stability are not required. Fixation techniques with relative stability, such as external fixation, intramedullary nailing (IMN), and bridging, are preferred because they better tolerate deformational forces. If the interfragmentary deformation is excessive or the fracture gap is too large, bone bridging by hard callus is not achieved

despite good callus formation and may result in varus, delayed healing, or hypertrophic nonproliferative fusion. On the other hand, if the fixation device is too rigid and the gap is too wide, a low-strain environment is created, resulting in delayed healing and nonproliferative fusion (Klas et al. 1997). Therefore, the choice of treatment influences stability and determines the specific path of bone repair. An ideal fixation system should provide temporary support that protects callus formation and lead to fracture healing in the shortest possible time, allowing restoration of anatomy and early mobilization.

Later developments of these concepts emphasized the importance of "biological fixation" (Perren, 2003). The principle of "biological" internal fixation prefers to avoid anatomical reduction, especially for intermediate fragments, and emphasizes indirect reduction. The main goal of indirect reduction is only to align the fragments and limit bone exposure, which in turn reduces surgical trauma (Baumgaertel et al., 2002). This principle holds true for a variety of osteosynthesis techniques, including interlocking intramedullary nails (IMN), bridging plates such as minimally invasive percutaneous osteosynthesis (MIPO) and less invasive stabilization systems (LISS), and devices similar to internal fixators (Bong et al. , 2007; Saini et al., 2013; Zhang et al., 2017). Thus, callus formation is achieved through flexible fixation that utilizes wide fracture coverage and prevents excessive implant-bone contact. This creates optimal biological conditions for healing, rather than striving for absolute stability. The results of this approach have demonstrated excellent clinical results, making it the preferred method of fixation, especially in cases of unstable, complex, multi-part diaphyseal fractures (Piétu and Ehlinger, 2017; Celebi et al., 2006; Kesemenli et al., 2002; El-Desouky et al. ., 2016). On the other hand, for simple diaphyseal fractures, rigid fixation with absolute stability remains the treatment of choice (Wenger et al., 2017; van de Wall et al., 2019). Although the correct surgical indications generally lead to favorable clinical outcomes, the incidence of delayed unions and nonunions remains a significant concern.

In 2016, Elliott et al presented their theory of bone healing and aseptic nonunion (BHN) with the goal of creating a unified theory that integrates established facts about bone physiology and homeostasis with those related to fracture healing and the development of aseptic nonunion. The basic idea is that, according to Wolff and Frost's theories, a long-term increase in stress will lead to increased bone formation, while a long-term decrease in stress will lead to bone loss. The state of homeostasis is represented by the balance of osteoblast and osteoclast functions, followed by slow bone turnover. In the event of a fracture, the so-called bone healing unit acts as a specific functional unit that produces a physiological response to the biological and mechanical environment, leading to normal bone healing. The bone healing unit evolves through various stages of reparative osteogenesis, producing different tissues (hematoma, connective tissue, cartilage, and bone) capable of withstanding different levels of stress. The theory identifies three different mechanisms for bone healing. The normal response to a fracture is in which tension is initially high, connective tissue is formed, and the healing process gradually strengthens the area until stress decreases and bone forms and then remodels through normal homeostasis. This type corresponds to bone healing after conservative treatment of fractures and surgical fixation with relative stability. Callus-type healing occurs when higher stresses are within acceptable levels, maximizing bone formation with large volumes of callus. This is usually associated with relative stability surgical techniques such as intramedullary onlaying. Primary bone healing then occurs as the fracture is treated with anatomical reduction and absolute stability. In this low-stress environment, bone healing results from normal homeostatic remodeling of local bone, so the healing process is slow and is not accompanied by callus formation. According to the BHN theory, aseptic nonunion is mainly due to mechanical or biological origin, representing two main pathways that can lead to impaired bone healing. Mechanical instability is regaining a dominant role in clinical practice, and in most cases of nonunion there is an intact bone healing unit that retains its biological healing potential. When very high loads are maintained, movement at the fracture site destroys the bone

healing mechanism. Thus, the primary strategy to improve bone healing is to restore mechanical stability and reduce deformation. In addition, biological factors may positively or negatively modulate the response of the bone healing apparatus to stress and the mechanical environment.

Biological Factors Influencing Bone Healing

The healing process of a fracture can be affected by many biological factors that can interfere with its progression. Biological factors are classified into patient-related factors (i.e., lifestyle and comorbidities), and fracture-related factors (i.e., topography, soft tissue injuries) (Zura et al., 2016; Santolini et al. , 2015)

Age is the key patient-related factor with the greatest influence. In children and young adults, the periosteum is rich in osteoblasts and is characterized by strong blood flow. In the case of older adults, on the contrary, the periosteum is partially fibrous and therefore contributes to slower callus formation (Cheung et al., 2016). In patients with osteoporosis, including type I (postmenopausal estrogen deficiency) and type II (aging), the healing process is characterized by delayed expression of estrogen receptors, which correlates with impaired callus formation. Various factors such as recruitment, differentiation and proliferation of progenitor cells are reduced in the early stages of fracture healing due to low production of growth factors (BMPs) and deficiency of mesenchymal cells both qualitatively and quantitatively (Cheung et al., 2016). Nikolaou et al noted that the mean time to consolidation of femoral shaft fractures treated with intramedullary nails in patients with osteoporosis was 3 weeks longer compared with healthy controls (Nikolaou et al., 2009). Additionally, in patients with osteoporosis, surgical fracture fixation procedures are typically associated with poorer outcomes and higher rates of complications, such as loss of reduction, implant failure, and delayed union or nonunion (Marongiu et al., 2013). Genetic factors also influence the activity of osteoprogenitor cells. Recent studies in rats by Ma and O'Connor have identified a number of genes (C57BL/6, DBA/2, C3H9) that influence the process of fracture consolidation (Manigrasso and O'Connor, 2008). Fracture consolidation in C57BL/6 mice occurred in a shorter time. Hofmann et al. demonstrated altered cell viability and decreased gene expression of signaling molecules (Wnt-, IGF-, TGF-β-, and FGF) in osteoblasts from patients with hypertrophic nonunion of long bones (Hofmann et al., 2008). It has also been noted that various molecular polymorphisms and genetic profiles influence cell differentiation and the process of enchondral callus formation (Jepsen et al., 2008). Over the past several decades, several clinical and cohort studies have been conducted to quantify the impact of all of these factors on the healing potential of diaphyseal fractures. In the recent multicenter observational study FRACTING, these global and local factors were combined into a score that was calculated immediately after treatment and used to predict healing time for tibial shaft fractures (Massari et al., 2013). The authors concluded that patients with higher scores were more likely to experience nonunion problems and had longer healing times (Massari et al., 2018). The resulting score can be used to identify patients who may require therapeutic interventions to improve fracture healing, such as surgical techniques, cell therapy, growth factors, drugs, or physical stimuli.

Surgical Strategies to Improve Bone Healing

As mentioned earlier, the normal bone regeneration process can be disrupted or simply insufficient due to both mechanical and biological factors. Giannoudis et al., in their Diamond Concept theory, emphasized the role of the mechanical environment as a critical factor in improving bone healing, in addition to other cell- and tissue-based engineering strategies (Giannoudis et al., 2007). Surgical approaches aim to restore mechanical stability of the fracture site and stimulate or increase bone clearance through fracture fixation and bone grafting techniques, either alone or in combination.

Dynamization of nails

The nail dynamization procedure aims to create fracture compression by removing screws that block the nail proximal or distal to the fracture site. The biomechanical effect supported by dynamization is an increase in micromovements at the fracture site, which helps stimulate osteogenesis (Glatt et al., 2017). However, excessive movement can lead to loss of reduction, uneven limb length, or rotation, especially in highly comminuted fractures with significant gaps between fragments. Therefore, dynamization is considered appropriate only when sufficient stability has been achieved at the fracture site. Risk factors for failure of dynamization include open fractures and unstable atrophic nonunions, while for unstable hypertrophic nonunions, dynamization is considered an appropriate treatment option (Papakostidis et al., 2011). Previously, dynamization of the nail was recommended as a standard procedure after locked intramedullary nails for long bone fractures 2–4 months after surgery, while its current indications are mainly associated with delayed union or nonunion (Egger et al., 1993). . There is controversy regarding the optimal timing of the procedure, but available evidence suggests that dynamization of delayed union is more promising than dynamization of diaphyseal nonunions of the femur and tibia (Vauhn et al., 2016). In a study by Vicenti et al. dynamization has been suggested to be performed three to six months post-injury for femoral shaft fractures, demonstrating an overall healing rate of 94.1% for both delayed and nonunion femoral unions (Vicenti et al., 2019). Litrenta et al, in their large series of dynamization of intramedullary nails for tibial shaft fractures, noted that the procedure was performed at an average of 5.2 months after injury, with an 83% success rate of union, with the worst results observed in patients with a wide fracture gap (Litrenta et al., 2015). The application of this method is complicated after intramuscular fixation of humeral shaft fractures until the humerus becomes the main support (Congia et al., 2019).

Exchange of nails

Nail replacement involves removing the IM nail, drilling it out, and replacing it with a larger nail that is at least one millimeter thicker. The main advantage of this method is the additional mechanical stability provided by the larger diameter nail (Court-Brown et al., 2018). Mechanical rigidity is often improved by a design with multiple locking screws. Moreover, the reaming procedure followed by transport of mesenchymal stem cells to the nonunion site acts as an “internal autologous bone graft,” enhancing the healing process (Ghiasi et al., 2017). Several studies have reported successful results after nail replacement, with healing rates ranging from 72% to 96% (Brinker and O'Connor, 2007). Recently, results from a large series of delayed tibial unions showed a higher success rate after nail exchange compared with nail dynamization (90% vs. 83%; $p = 0.02$) (Litrenta et al., 2015). Some studies reported lower rates of nonunion healing after replacement nailing for femoral nonunions (Weresh et al., 2000) and were therefore then recommended as second-line therapy.

Magnification plate

Augmentation plate over a preserved intramedullary nail has been reported to be a viable treatment option for nonunion of long bone fractures. Applying the coating to the preserved nail increases the rigidity of the structure, reducing micro-movements. Additionally, non-combined section compression can be achieved using LC–DCP. Results in the literature are generally satisfactory, even when small series have been reported. Chiang et al obtained a 96.6% healing rate of 30 femoral fractures using an augmentation plate after a failed IMN procedure as the index procedure (Chiang et al., 2016). Excellent fusion rates have been reported for both the tibia (94.6%) (Ateschrang et al., 2013) and humerus (97%) in which IMN nails have failed (Gessmann et al., 2016).

External fixation methods

Several external fixation techniques using both uniaxial and ring fixators have been proposed for delayed union and nonunion of long bone diaphyseal fractures. Ilizarov fixators (circular) provide

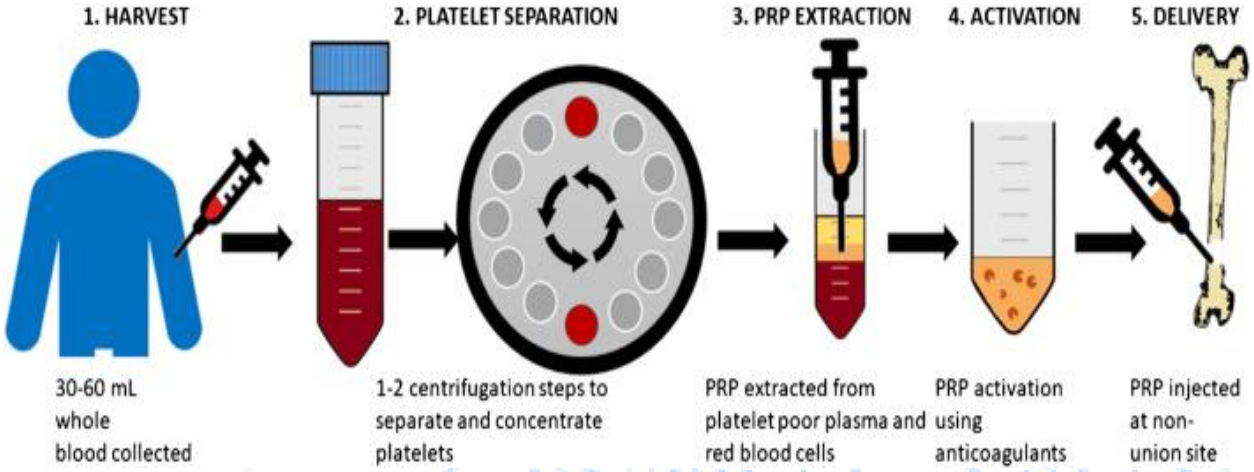
compression at the fracture site (axial dynamization and active compression), which restores cortical contact, imparts stability to the fracture and neutralizes interfragmentary deformation, promoting bone healing through enchondral remodeling (Ilizarov, 1989). Aro described this process as “second contact healing” (Aro et al., 2006). In cases of persistent nonunion, the fibrous fracture site can be resected, leaving a bone gap that can be filled by cortical compression. Daily gradual (1 mm/day) distraction with fixators enhances the transport of bone tissue through “distraction osteogenesis,” which involves intramembranous ossification pathways (direct healing) (Ilizarov, 2006). High union rates (up to 97%) have been reported in patients suffering from femoral or tibial nonunions treated with a monolateral or circular external fixator. External fixation has been shown to be superior to other techniques, especially in the treatment of humeral nonunions (98% union rate) and in the treatment of infected nonunions (Yin et al., 2015).

Current use of PRP for nonunion fractures

The use of platelet-rich plasma (PRP) in tissue regeneration is a rapidly developing area that is attracting the attention of both clinicians and researchers. Its use is found in a variety of areas, including treating osteoarthritis, rotator cuff repair, and promoting bone regeneration. This is because high concentrations of specific growth factors, such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF-β1 and TGF-β2) and insulin-like growth factor (IGF-1), necessary for tissue healing and regeneration can be easily obtained from concentrated platelets. The initial number of platelets in the blood of a healthy person varies from 1.5 to 4.5 × 10^5/μl. For therapeutic use, the platelet concentration should be 4–5 times the baseline level. The process of preparing PRP may vary slightly in the literature, but typically involves drawing blood into a tube, often pretreated with an anticoagulant. The platelets are then centrifuged and activated using chemical agents such as calcium chloride, bovine or autologous thrombin. Thrombin forms a gel-like substance from which the PRP is extracted and injected directly into the patient's body. Inside platelets are granules containing many growth factors and cytokines that play a key role in the early stages of bone repair. Once activated, as a result of blood clotting, these platelets release growth factors essential for the production of proteins necessary for tissue regeneration, such as cell proliferation, matrix formation, osteoid formation and collagen synthesis. Clinical studies have analyzed the effects of platelet rehabilitation (PRP) on nonunion healing, either alone or in combination with other treatment modalities such as mesenchymal stem cells (MSCs) [26, 27], internal fixation and/or nailing. nails When PRP is used in isolation to treat nonunions, therapeutic efficacy is shared, with some cases of PRP achieving successful bony union at the fracture site within 11 months of the initial injury or surgery [17]. In addition, studies have shown that PRP improves the healing of nonunions when combined with other treatment modalities, such as the gold standard autologous bone graft, as well as MSCs and internal fixation. Although many sources report PRP's success in promoting healing, it has been found to have less effect compared to other treatments, especially those using bone morphogenetic proteins (BMPs) such as rhBMP-7. This is likely due to the lower concentration of growth factors available for extraction using PRP compared to BMP. There are currently no prospective randomized clinical trials specifically examining the use of PRP for the treatment of nonunion fractures, and therefore there is limited literature with levels of evidence I–III. Existing studies are mainly represented by case series or preliminary studies (level IV evidence). Case series have the advantage of being relatively easy to conduct, requiring less time and financial resources than randomized clinical trials, cohort studies, or case-control studies. However, limitations include the lack of control subjects, which makes the interpretation of the results subject to bias. Although most published studies of PRP are case series, such studies are also largely preclinical in focus. However, recent work summarized by Roffi et al suggests that research is beginning to move in a more clinical direction, an important step for the successful application of this therapy.

Preparation and Application of PRP

Although PRP is widely used for several musculoskeletal conditions, there is currently a lack of standardization regarding how PRP is prepared and used to treat nonunion fractures. In general, the process of preparing PRP involves the processes of collection, centrifugation to separate platelets, extraction of platelet-rich plasma from red blood cells and platelet-poor plasma, and activation using an anticoagulant agent (although this is not always the case). followed by injection into the site of injury (Fig. 1).



Throughout the literature, a centrifugation process is used during preparation to concentrate platelets. However, centrifugation speeds vary between studies and range from 3200 to 5200 rpm, resulting in different relative forces depending on rotor length, while other studies do not specify speed. Moreover, centrifugation could potentially lead to platelet fragmentation and early release of growth factors, which would ultimately reduce the biological activity of PRP. Thus, PRP activation may be influenced by relative centrifugal forces between studies, causing undesirable changes. It is therefore recommended that future studies consider ultrafiltration, which potentially offers a more standardized PRP extraction process. Activation of PRP using chemical anticoagulants is an important step in the preparation process. A variety of activators are described in the literature, the most common being thrombin, calcium chloride and calcium gluconate. Thrombin is often combined with calcium chloride (CaCl2) or calcium gluconate to enhance platelet activation. Some sources do not provide details on the use of activators, and in other studies they were not used at all. Different reagents have different half-lives, which affects how long it takes for the anticoagulant to clear the system. This in turn influences the activation of PRP and therefore the rate of bone regeneration and the effectiveness of PRP. In addition, the use of anticoagulants, especially those with long half-lives, may limit the usefulness of PRP as a therapy for some patient groups, including those with anemia and kidney disease. When analyzing PRP delivery methods, there is significant variation in the volume of PRP administered across studies, with single injection doses ranging from 2.5 mL to 20 mL. Typically the total dose is given to the patient as a single injection, although it may also be divided into several injections over subsequent weeks. It is likely that this may result in different effectiveness of different administration methods, as administering a single dose versus the same dose divided over several weeks may affect the rate of bone regeneration. Splitting the prescribed dose over several weeks will likely delay the expected effect of the injection, resulting in a slower rate of healing of nonunions. In contrast, using multiple equivalent doses of PRP over an extended period of time may speed up the rate of healing, although this remains an issue requiring more research, including randomized clinical trials.

Effect of PRP activation on bone tissue regeneration

Most published studies currently do not report key aspects such as platelet concentration, leukocyte components, and modes of activation. This is despite the fact that Chen et al demonstrated how a mean concentration of PRP (2.65 ± 0.2 × 109/ml) induces estrogenic differentiation of bone marrow stem cells (BMSC/BM-MSC), improving fracture healing, whereas high concentrations of PRP (8.21 ± 0.4 × 109/ml) induce estrogenic differentiation of bone marrow stem cells (BMSC/BM-MSC), improving fracture healing. /ml) may inhibit osteogenic differentiation and delay callus remodeling. Labibzadeh et al reported that leukocyte-rich PRP induces higher BMSC proliferation, while others have found an effect of activation modality on molecules released by PRP. This highlights that different concentrations and ultimately activation levels will influence the effectiveness of therapy.

Isolated use of PRP for the treatment of nonunion fractures

Once PRP is prepared, anticoagulated, and activated, it is often used alone as a treatment. Only one study reported that PRP failed to achieve fusion when used in isolation. The study included 20 patients, 12 of whom were diagnosed with nonunion fractures. These subjects were treated weekly for 6 months. No patient experienced union within 10 months after treatment. Therefore, the authors concluded that PRP is not effective in the treatment of nonunions. However, the administration of PRP was a limitation of the study. A total of 2.5 ml of calcium chloride activated PRP was administered every week for 3 weeks. The 2.5 ml dose of PRP is relatively small compared to other studies; however, it is not possible to determine how the volume of blood drawn and/or the volume of delivery used in any study relates to the number of isolated platelets and/or white blood cells, since this value is very rarely reported in published studies. In addition, the size of nonunion varies widely when patients in study groups and individual studies are compared with each other. Moreover, the size/volume of nonunion is not always reported in published studies. PRP was reported to be successful at a dose of at least 5 ml per injection, often applied at least three times. In addition to this, PRP was activated by calcium chloride. In most of the published literature where PRP was successful in inducing union, bovine/autologous thrombin was used in the activation process, implying that activation is accomplished using calcium chloride alone and a lower dose of PRP could potentially be a key factor in the failure of fracture union in these patients. Despite the widespread use of bovine thrombin as an activator, its clinical use has been questioned as disease transmission, possible carcinogenesis, availability and cost are all issues associated with bovine thrombin. Moreover, Malhotra argued that sufficient thrombin is produced as a result of local trauma when the fracture site is pierced with a needle. To test this hypothesis, a large volume of 20 ml PRP was injected once without thrombin and with a high platelet concentration (approximately 5 times normal values). Eighty-seven percent of patients achieved union at the end of the 4-month follow-up period. In all cases, the average time between injury and PRP injection was 9.1 months. In 2008, Beletsky et al concluded that PRP is a sufficient method to achieve union if treated within ≤11 months of initial surgery. In a study by Malhotra et al. 13% of patients with no previous fusion were treated with PRP within 12 months of initial diagnosis. However, according to the findings of Bielecki et al, due to the delay in PRP treatment from the time of diagnosis, the fracture gap has likely become too large for PRP to have a regenerative effect. Limitations that were acknowledged in the study were that it was not an RCT and only included nonunions that had greater than 90% contact between the fracture fragments. Therefore, the results of this study may not be applicable to more severe nonunions. A more recent study by Tawfik et al. had similar inclusion criteria (more than 90% contact between fracture fragments) and PRP dose (20 ml) and found very similar rates (85%) of union among patients compared to Malhotra et al. (87%).

PRP as a hybrid treatment

PRP may also be used in combination with other forms of treatment for nonunion fractures, including autografts, compression plates, and/or fixation devices. Some studies have examined the effect of combining PRP with iliac crest autograft and concluded that the addition of PRP could potentially improve healing. However, in these studies, the authors were unable to attribute fracture healing to isolated PRP addition due to the lack of randomized control groups. Therefore, no information can be provided about the effectiveness of one specific method. This is evident in the case of Tarallo et al. where patients were treated using bone graft, dynamic compression plate and PRP. Despite this, fusion was achieved in 90% of cases, the average fusion time was 4 months. Gaffarpasand et al conducted the only randomized, double-blind, placebo-controlled clinical trial examining the effect of PRP on the rate of healing of nonunion fractures treated with autologous bone graft and internal fixation. During surgery, patients received either 5 ml PRP or 5 ml saline (placebo). The healing rate was significantly higher in the PRP group compared with the control group (81.1% vs. 55.3%, $p = 0.025$). Reports on the effectiveness of PRP and autograft fixation as treatments for nonunion fractures are mixed. The results of the case series were generally positive in terms of improved nonunion healing rates. However, the rate of healing cannot be related to the use of PRP due to the lack of effective control. However, in a unique case series by Mariconda et al, the fusion healing rate of patients treated with PRP and external fixation (90%) was compared with the fusion healing rate of a historical control group (85%), without any data. Significant clinical benefits of PRP have been reported. However, caution should be used when interpreting this result as the sample size was relatively small ($n = 20$), limiting the statistical power of the data. A recent randomized controlled clinical trial of the combined use of PRP and internal fixation found that the addition of PRP to internal fixation significantly increased the healing rate (94% vs. 78%, $p < 0.05$) while reducing healing time. (91.6 ± 6.9 vs. 115.2 ± 8.4 days, $p < 0.05$) compared to the control group. The study used not only the primary outcome measure of healing rate, but also secondary outcome measures assessed using a visual analogue scale (VAS). The VAS was used to measure subjective characteristics that cannot be measured directly, such as pain intensity, cost of treatment, and adverse reactions; these are all important aspects of the treatment modality, especially when considering clinical acceptance and transfer. Because PRP increased the rate of healing, it shortened treatment time while reducing pain and costs. Two case studies were conducted to investigate whether the combination of PRP and MSC could facilitate healing of nonunion fractures, and both reported success. Labibzadeh et al stated that when combined with MSC, PRP is successful in patients who previously failed to achieve fusion with the gold standard iliac bone graft. This highlights how effective PRP can be in improving bone regeneration in difficult nonunions. However, Centeno et al identified limitations of the method, including the fact that MSCs isolated from bone marrow aspirate obtained from the iliac crest required repeated invasive surgery. This increases the potential risk of infection and causes additional pain to the patient. Going forward, double-blind controlled studies are still needed to evaluate the clinical effectiveness of this treatment.

Conclusion.

1. The main complication after treatment of diaphyseal fractures continues to be delayed union and nonunion. To avoid these threatening events, the surgical and nonsurgical approach must be tailored differently for each fracture and each patient according to the biological and biomechanical basis of bone healing. In the last decade, the “diamond concept” of fracture healing has given equal importance to mechanical stability and the biological environment and has offered a new paradigm for the treatment of complex fractures and malunions. In this polytherapeutic approach, modern bioengineering technologies play a crucial role, improving traditional fixation methods with other surgical and non-surgical approaches (Calcei and Rodeo, 2019). Additional local biological

improvement through the addition of scaffold, growth factors and cell therapy while maintaining local blood supply. Currently available evidence has shown strong results supporting the use of "polytherapy" with the diamond concept compared with "monotherapy", although some studies have used all aspects of the diamond concept only for high-risk patients, which may have biased the results (Andrzejowski & Yiannoudis, 2019).

2. The literature suggests that PRP is effective in promoting healing of nonunion fractures. The success it has demonstrated when used in isolation ranges from 2.5 to 20 ml doses, meaning it has the potential to become a mainstream form of treatment. However, nonunion must be initially stable, and ideally PRP should be performed within 11 months of injury or initial surgery, although further studies are needed to confirm this barrier. It is further recommended that RCTs focus on the effect of injections of at least 5 ml PRP, as lower doses have not been reported to be successful in stimulating bone regeneration. The study by Malhotra et al., which is an important contribution to the research, showed that a common bovine thrombin activator may not be necessary and this should be further explored in future studies to determine whether sufficient thrombin is produced as a result of local trauma at the site the fracture is infiltrated with a needle to activate platelets. Other important contributions include the work of Ghaffarpasand et al. and Zhao et al., demonstrating the success of PRP and internal fixation as a combination treatment. However, additional RCTS are needed to determine whether PRP is a more effective bone-stimulating agent for promoting fusion compared with MSCs and BMPs. Finally, to further develop therapy, it is necessary to systematically investigate and standardize the most effective method of PRP preparation (centrifugation/ultrafiltration speed, activator, dose, etc.) and administration (single or multiple injection).

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