

SCOPING REVIEW

Osteoinductive Capacity of Platelet-Rich Fibrin vs. Biodentine for Mandible FractureMarda Agung Nugraha¹, Indra Mulyawan^{2*}, Ardian Jayakusuma Amran^{3,4}¹Resident of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.²Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine-Academic Dental Hospital, Universitas Airlangga, Surabaya, Indonesia.³Doctoral Program of Dentistry, Faculty of Dentistry, Universitas Hasanuddin, Makassar, Indonesia.⁴Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Universitas Muslim Indonesia, Makassar, Indonesia.**Article Info****Article history:**

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ABSTRACT

Background: Mandibular fracture is one of the most common fractures. The most common treatment for mandibular fractures is fixation. Therefore, xenogeneic agents such as platelet-rich fibrin (PRF) and Biodentine accelerate the reparative process. Biodentine is an interesting active ingredient that can induce bone regeneration. PRF and Biodentine can promote bone healing, but no literature discusses the differences between PRF and Biodentine osteoinduction mechanisms in treating mandibular fractures.

Objective: This article aimed to compare the effect of osteoinductive PRF with Biodentine for mandibular fractures.

Material and Method: The research was conducted as a scoping review by performing a thorough search of the PubMed, Scopus, ScienceDirect, Elsevier, and Google Scholar databases. The study was obtained based on literature studies in the form of journals and textbooks in the last ten years (2013-2023). **Result:** The osteoinductive effect and mechanism of Biodentine in enhancing bone repair are likely correlated with releasing biologically active ions from calcium silicate cement and stimulating gene expression Runx-2. PRF has an osteoinductive role, causing the mechanism of releasing growth factors such as PDGF, VEGF, TGF- β , and IGF that promote the osteogenic process. **Conclusion:** There was no significant difference in the osteoinduction effect of PRF and Biodentine because these materials have different mechanisms of action for bone repair.

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Highlights

1. Biodentine has undergone thorough research as a bone grafting substance due to its ability to promote bone regeneration and effectively treat root or tooth fractures.
2. PRF and Biodentine can stimulate osteogenesis, affecting bone repair, particularly in mandibular fractures.

BACKGROUND

Mandibular fracture is one of the most common fractures. The most common cause of mandibular fractures is traffic accidents. An impact that is too hard on the face can result in a mandibular fracture. According to its location, the mandible is more prominent and easier to receive impact. Mandibular fracture is a condition where the mandibular bone is broken, which can be caused by facial trauma or pathological conditions. Fracture lines in the mandible often occur in areas of weakness. The thin area on the mandible is the angle and sub-condyle, which becomes a weak mandible area. In addition, weak points are also found in the mental foramen, the mandibular angle where the third molar teeth are located, and the mandibular condylar neck (Dewi, et al., 2022).

Numerous studies demonstrate that patients with mandibular fractures require an individualized approach in the selection of a treatment strategy due to the potential concomitance of different types of bone diseases, odontogenic infections, fractures in various regions of the mandible or simple skeleton, etc. (Diachkova, et al., 2022). The most common treatment for mandibular fractures is fixation. There are two mandibular fixation techniques, the closed and open techniques. In the closed technique, maxillomandibular fixation devices can achieve fracture immobilization and reduction. In an open procedure, the fractured part is opened surgically, and the fracture segment is reduced and fixed directly using a wire or plate called wire or plate osteosynthesis. These two techniques are only done separately but are sometimes applied in combination, which is called combined procedures (Dewi, et al., 2022).

Despite the high efficiency of modern treatment methods, bone tissue cannot be restored at total volume in all cases. Therefore, xenogenic agents are used to accelerate the reparative process. The basis of the stimulation of regeneration lies in induction, conduction, and regeneration due to the introduction of estrogenic cellular elements (stimulation by substitution). Each potency can stimulate reparative osteogenesis, either independently or in combination. The bone deficiency was filled with a collagen osteotropic substance (Diachkova, et al., 2022). PRF (Platelet-rich fibrin) is a human blood biomaterial consisting of platelet concentrate, fibrin matrix, cytokines, growth factors, and cells. Biodentine is a calcium-silicate-based material that has drawn attention in recent years and has been advocated to be used in various clinical applications, such as root perforations, apexification, resorptions, retrograde fillings, pulp capping procedures, and dentine replacement. Platelet-rich fibrin and dentine can stimulate bone osteoinduction when combined with bone grafts.

OBJECTIVE

This article aimed to compare the effect of osteoinductive platelet-rich fibrin with Biodentine for mandible fractures.

MATERIAL AND METHOD

This study used electronic databases such as PubMed, Scopus, ScienceDirect, Elsevier, and Google Scholar for research screening. It used specific keywords: mandibular fracture, mandibular fracture and xenograft, jawbone regeneration, mandibular bone regeneration, platelet-rich fibrin and jawbone regeneration, and Biodentine and jawbone regeneration. The paper was then filtered through a qualitative and quantitative selection.

Inclusion Criteria

The study was obtained based on literature studies in journals and textbooks published in the last ten years (2013-2023). The inclusion criteria deliberated human studies, in vitro and in vivo research, and reports. Off-topic publications were excluded from the analysis. Afterwards, the publications were categorized according to the surgical process and the study design.

Selection of the Studies

Independently qualified and expert reviewers screened the study data and analysis. After a primary check on the research title, every abstract of the identified papers was assessed as the 1st screening level. The full text of the included papers was obtained. Furthermore, they were classified for qualitative synthesis. The electronic database research has identified a total of 156 manuscripts. Forty-eight

duplicates have been deleted from the screening, and 108 papers have been considered for the full-text evaluation. Eleven full texts were not found, and 87 were out of topic to be excluded. Finally, ten papers have been incorporated into the analytical synthesis.

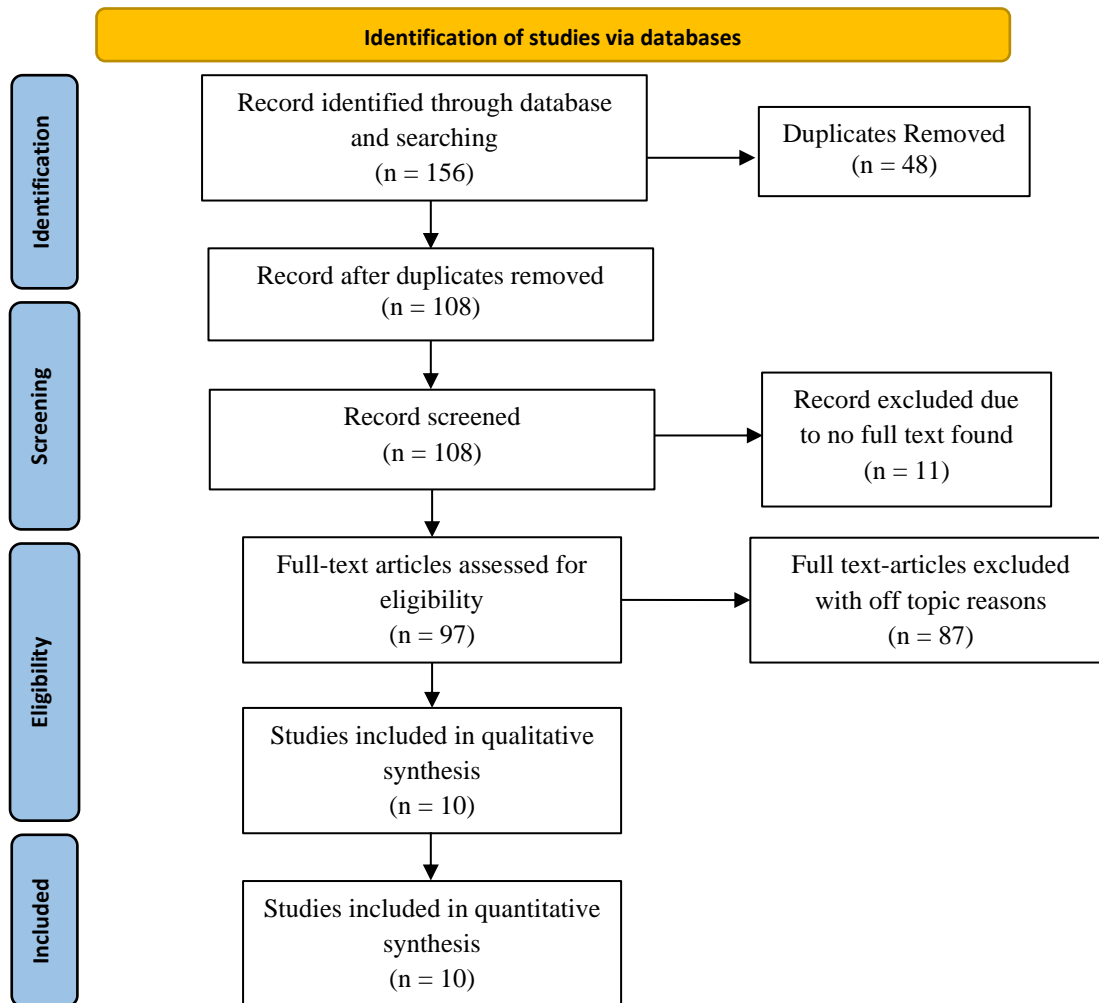


Figure 1. PRISMA flowchart of the study design and manuscript-selection process.

RESULT

Table 1 shows and summarizes the main effective results of the osteoinductive effect of platelet-rich fibrin and Biodentine.

Table 1. PICO Table of the osteoinductive mechanism of platelet-rich fibrin and Biodentine.

References	Population	Intervention	Comparison	Outcome
Hakam, et al., (2019)	Thirty adult male rabbits created bilateral bone defects in the right side of the mandibles as the experimental	The rabbits were divided into two groups. Group 1 was loaded with Biodentine on the experimental side.	Histological examination for bone defect specimens was prepared by light microscope and quantitative analysis of	Both Biodentine and nanobone had initiated osteogenesis. The Biodentine group showed spread-out braided bone trabeculae with entrapped osteocytes visible over one week. Several nuclei with different shapes and staining intensities were occasionally

	side and another side as the control.	Group 2 was packed with nanobones on the experimental side.	collagen one alpha and Runx-2 gene expression by real-time PCR.	detected in distinct lacunae. More bone spicules than in the preceding interval were visible after a two-month gap. Around the freshly produced trabeculae, it was clear that osteoblast-like cells were present to line their boundaries. However, Biodentine showed that the newly formed bone had apparently less quality than nanobone. It showed that nanobones had a more significant healing result.
Rajendran, et al., (2019)	Forty-five enamel specimens were extracted from human permanent premolars. It was free from defects, decay, and filling. All specimens were subjected to demineralization using McInnes demineralizing solution.	The specimens were divided into three groups. Group 1, as control, was treated with regular toothpaste. Group 2 was treated with toothpaste containing calcium sodium phosphosilicate. Group 3 was treated with a topical cream containing casein phosphopeptide—amorphous calcium phosphate.	The samples were then subjected to a scanning electron microscope to assess the topographical pictures and the surface changes seen on enamel; and energy dispersing X-ray analysis to estimate quantitatively the amounts of mineral in a given tooth sample after the remineralizing cycle.	Group I showed a mean calcium and phosphorus value of 65.32 ± 0.51 and 21.13 ± 0.75 , respectively, for sound enamel. After remineralization with regular toothpaste, the mean calcium and phosphorus values obtained were 55.24 ± 0.49 and 15.76 ± 0.54 , respectively, less than that of sound enamel and statistically significant ($p < 0.001$). The values obtained after remineralization were similar to the mean calcium and phosphorus content of demineralized samples.
Gandolfi, et al., (2017)	Six mature male rabbits with four surgical bone defects on each side of the tibia.	The control group was left empty from 4 surgical defects, and another bone defect was filled with Biodentine, MTA Plus, and ProRoot MTA.	After 30 days, tibiae were retrieved and submitted to histological analysis and microchemical characterization using Optical Microscopy (OM) and Environmental Scanning Electron Microscopy with Energy Dispersive X-ray analysis (ESEM-EDX).	ESEM observed the histological section of a surgical defect treated with Biodentine. According to the histology findings, the surgical defect was filled by freshly produced bone trabeculae. The resected walls of the old cortical bone were in close contact with the new bone. Wide gaps could be seen, and little remnants of material were found. The bone that had just developed displayed significant mineralization. The osteoid matrix is being mineralized in some places.
Kaskos & Ali (2020)	Twenty rabbits with three surgical created monocortical defects on the mandible.	One surgical defect was left unfilled and considered as control, and the other defects were	CT scan was used as a parameter for bone density on follow-up dates 7, 14, 21, and 28	The impact of adding Biodentine on a rabbit's mandible defect was examined. By the seventh day, there was no significant disparity in bone density between dentine-treated (116.17 ± 1.41) and

		implanted with MTA and Biodentine.	days after operative surgery.	control (112.3 ± 1.36) samples. Similarly, by day 14, there was no significant variation in bone density between the Biodentine (153.43 ± 1.86) and control (148.2 ± 1.78) groups. However, by day 21, a notable distinction in bone density emerged, with Biodentine (359.27 ± 3.56) surpassing control (344.07 ± 4.08) insignificance. By the 28th day, Biodentine demonstrated a mean of 1012.07 ± 11.95 .
Barczak, et al., (2020)	A literature review of 52 papers was selected, encompassing those directly focusing on Biodentine and other relevant papers not mentioning Biodentine but concerning dental materials in general.	No Intervention	No Comparison	Biodentine triggers the activation of cellular differentiation factors, such as osterix, which facilitates the differentiation of osteoblasts and thereby contributes to the generation of new bone. Biodentine also plays a role in regulating inflammatory responses and encourages the differentiation of both fibroblasts and osteoblasts. This process stimulates the creation of collagen bundles within the periodontal ligament and the matrix of bone.
Wang, et al., (2022)	Ten New Zealand white rabbits with separated SM-MSCs from the maxillary sinus.	The osteogenic differentiation ability of cells stimulated by PRF or osteoinductive medium was evaluated by alkaline phosphatase staining, alizarin red staining, PCR, and Western blot. As the bone graft materials for maxillary sinus floor elevation, an equivalent volume of Bio-oss and the mixture of Bio-oss and PRF were used.	To evaluate the the osteogenic effect, Micro-CT, bone double-staining, HE staining, Masson staining, and toluidine blue staining were used at 8 and 12 weeks post-surgery.	Due to the abundance of growth factors in PRF-conditioned medium, SM-MSC proliferation, migration, and osteogenic differentiation are all encouraged. Activating the ERK 1/2 signaling pathway, PRF-conditioned medium, OM, or the combination of the two above could enhance osteogenic differentiation. According to animal trials, using PRF significantly sped up the rate of new bone production in the maxillary sinus and increased the quantity and quality of newly created bone.
Augustina, et al., (2023)	Eighteen New Zealand rabbits with a critical bone defect surgery.	The rabbits were divided into three groups. Group 1 was treated by applying xenograft.	The results of the sample tissue were evaluated by immunohistochemical staining.	Lower MMP-13 expression was found in the PRF group. PRF possesses qualities that enhance graft position stability, bone regeneration, wound healing, and hemostasis. Controlled inflammation results in a drop in inflammatory mediators and a rise in osteoblast activity due to a

		<p>Group 2 was treated by applying PRF.</p> <p>Group 3 was treated by combining the application of xenograft and PRF.</p>		<p>reduction in MMP-13 production. Growth factors and other mediators that promote bone regeneration and faster wound healing are concentrated in PRF.</p>
<p>Neiva, et al., (2016)</p>	<p>Eight beagle dogs with first molars extracted on both sides of the mandibular.</p>	<p>On one side of the mandibular tooth sockets, L-PRF was filled, and then the implant, covered by L-PRF in a membrane shape, was placed.</p> <p>Conversely, the implants were placed on the socket without applying L-PRF.</p>	<p>The tissue samples were prepared and then subjected to Stevenel's Blue and Van Gieson staining technique.</p>	<p>General histomorphologic observations for the implants placed along with L-PRF in fresh extraction sockets differed from those where no L-PRF was utilized primarily due to the lack of soft tissue migration through the gap formed between implant and socket wall, suggesting L-PRF's efficiency as a barrier during healing. The osteogenic potential and adequacy of L-PRF substituting the blood clot during socket healing were confirmed since bone growth occurred from the socket walls towards the implant, leading to substantial bone formation.</p>
<p>Ocak, et al., (2017)</p>	<p>Twenty-four adult sheep</p>	<p>Two adult sheep were used as group control.</p> <p>Group 1 was treated with a bovine and autogenous bone mixture.</p> <p>Group 2 was treated with PRF.</p>	<p>The specimens were evaluated by histologic and histomorphologic examination.</p>	<p>In the ninth month, the PRF group continued to exhibit observable recent bone development, accompanied by remaining traces of PRF. The newly generated bone within the PRF group exhibited greater density and increased firmness.</p>
<p>Pripatnont, et al., (2015)</p>	<p>Twelve adult male New Zealand white rabbits on osteogenic periosteal distraction.</p>	<p>The rabbits were divided into four subgroups.</p> <p>A modified Hyrax device was performed in group 1.</p> <p>Group 2 was treated with a device and PRF.</p> <p>Group 3 was treated with PRF.</p> <p>Group 4 was treated with a sham.</p>	<p>The specimens were evaluated by performing analyses of radiographic, histological, histomorphometric, and micro-computed tomography (micro-CT).</p>	<p>During the 4-week and 8-week periods of bone consolidation, the PRF-treated group exhibited substantial healing of the defect, characterized by robust cortical and compact trabecular bone. Notably, the cortical bone in the 8-week group displayed greater thickness and density than the 4-week group. The highest percentages of bone volume and bone area were presented by group 2, which was treated with a device and PRF.</p>

DISCUSSION

Following the nasal bone, the mandible is the facial bone that commonly experiences fractures. The separation of the mandibular bone is termed a mandibular fracture. Consequences of such fractures include airway destabilization, teeth misalignment, impaired joint function, discomfort, infection, and nerve sensation abnormalities (Karthik & Sanjay, 2015). In some complex cases, bone grafts with osteoinduction effects are used because the atrophic mandible's dense cortical bone and poor vascularity and marrow supply make it difficult for the area to recover (Shokri, et al., 2019).

Osteoinduction refers to bone grafts' capacity to prompt bone tissue creation by activating inactive osteoblasts from undifferentiated cells. Grafting materials possessing osteoconductive and osteoinductive properties provide a structure for existing osteoblasts and stimulate fresh osteoblast generation, potentially expediting graft integration (Suprianto, et al., 2019).

Biodentine, as a bone grafting material, has been extensively studied for its ability to enhance bone healing and its utility in addressing root or tooth fractures. Tang, et al., (2019) study investigated the impact of MTA and Biodentine on periarticular bone healing, revealing that Biodentine can actively promote bone healing. Daltoé, et al., (2016) observed that MTA and Biodentine could enhance indicators of mineralization. Furthermore, Ho, et al., (2018) utilized three-dimensional printed Biodentine/polycaprolactone composite scaffolds to demonstrate the potential of Biodentine in dental and bone regeneration. These investigations collectively affirm Biodentine's role in facilitating bone repair. Gandolfi, et al., (2017) research established that implanted Biodentine in bone defects led to the formation of new bone due to its ability to stimulate bone neof ormation, differentiate osteoblasts, and promote angiogenesis.

The osteoinductive effect and mechanism of Biodentine in enhancing bone repair are likely correlated with the release of biologically active ions from calcium silicate cement (Gandolfi, et al., 2017). It was proposed that Biodentine would promote the proliferation and attachment of osteoblast-like cells, increasing their differentiation. These biological responses could be attributed to the material's topography and nano features, which provide a significant surface area for protein adsorption. Additionally, the production of bone matrix begins when osteogenic signals combine with soluble chemical cues, such as calcium, to cause a cascade of cellular development into osteoblast cell lines. According to a different theory, cements made of calcium silicate have an alkaline pH and can release calcium ions. These circumstances promote the activity of osteoblasts and the mineralization process by causing the nucleation of calcium phosphates and apatite (Hakam, et al., 2019). Calcium silicate cements release silicon, improving bone metabolism and speeding up new bone development. Also, calcium silicate cement is crucial in restoring bone by causing the calcium phosphate to precipitate at the periodontal tissue interface, causing a substantial rise in dentin gene expression for Runx-2. For osteoblastic development, matrix production, and mineralization during bone synthesis, Runx-2 is a key transcription factor (Rajasekharan, et al., 2018). This crucial gene is necessary for the production of osteoblasts and, as a result, the process of bone regeneration, as Runx-2 regulates osteoblast differentiation during the early stages of differentiation but suppresses it during the later stages (Kaskos & Ali, 2020).

On the contrary, platelet-rich fibrin (PRF) constitutes a composite comprising the cellular and molecular constituents essential for optimal healing. PRF represents the latest iteration of Platelet-rich plasma, a plasma from blood enriched with platelets housing a plethora of growth factors that encourage the mending of both bone and soft tissues (Augustina, et al., 2023). In some literature, it is stated that PRF can continuously increase the proliferation of all cell types, especially the proliferation of osteoblasts. This growth factor can regenerate bone tissue (Augustina, et al., 2023).

In in vivo or clinical studies, due to its abundant growth factors, PRF could be used as graft material. It can promote bone regeneration in extraction sockets, repair fractures, and improve gingival retreat. According to Neiva, et al., (2016), PRF can enhance bone formation within the socket arising from its compact fibrin network and cellular composition, which might enable a continuous discharge of growth factors. Furthermore, it can serve as a protective obstacle against soft-tissue growth. Growth factors generated by PRF significantly impact the volume and rate of new bone formation and the development of mature bone and thick bone trabeculae. In PRF, activated platelets may release various growth factors, including PDGF, VEGF, TGF- β , and IGF (Wang, et al., 2022). VEGF is the main factor that influences the differentiation of angiogenic cells and angiogenesis. It is the most powerful inducer of

angiogenesis, migration, and proliferation of endothelial cells. Controlling osteogenic growth factors through paracrine signals promotes osteogenesis and increases vascular permeability. VEGF can encourage bone regeneration in conditions such as radial segment defects in rabbits and femoral fractures in mice, resulting in good bone regeneration (Apte, et al., 2019). As the exclusive filling substance, the PRF membrane provides benefits such as simplified acquisition and application, the absence of supplementary grafting materials, immune responses, and stimulation of bone generation (Ocak, et al., 2017).

These two bone graft materials have their respective advantages and mechanisms when compared. PRF and Biodentine can induce osteogenesis, which impacts bone healing, especially mandibular fractures.

Strength and limitations

This study can be used as a reference point for further research endeavours. Studies have demonstrated that PRF and Biodentine can effectively promote bone regeneration. Currently, no research investigates the distinct osteoinduction mechanisms of PRF and Biodentine in managing mandibular fractures.

CONCLUSION

Osteoinduction is a necessary process that can enhance bone repair. Bone grafts with additional materials such as PRF or Biodentine may have a role in supporting soft tissue healing or bone regeneration. Biodentine facilitates bone repair by promoting the proliferation and attachment of osteoblast-like cells and increasing their differentiation. PRF is enriched with platelets containing a plethora of growth factors that encourage the mending of both bone and soft tissues. In this literature, there was no significant difference in the osteoinduction effect of PRF and Biodentine, even though these materials have different mechanisms of action for bone repair.

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Conflict of Interest

All authors have no conflict of interest.

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None.

Author Contribution

MAN contributes to the conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, provision of study materials or patients, and collection and assembly of data. IM and AJK contribute to the critical revision of the article for important intellectual content and final approval.

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