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PRP Therapy for the Treatment of Sacral Fracture and Coccydynia: A Case Report

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Background: Platelet-rich plasma (PRP) therapy has shown promising results in promoting healing and reducing inflammation in musculoskeletal injuries. This case report highlights the successful use of PRP injection therapy in a 37-year-old woman pedestrian with a sacral fracture and coccydynia from a pedestrian-vehicle accident.

Case Report: The patient underwent traversing sacral S3 anterior cortex vertebral fracture and sacrococcygeal PRP injection under fluoroscopic guidance. PRP injection therapy led to significant improvement in tailbone pain, and subsequent injection led to further improvement in residual symptoms. Follow-up evaluations showed complete healing of the S3 fracture with good bony fusion and alignment.

Conclusions: PRP injection therapy can be a safe and effective treatment option for bone fractures and injuries, especially those that may be difficult to manage with traditional approaches. As more clinical studies and case reports are conducted, the full potential of PRP in bone healing and regeneration may be further elucidated.

Key words: Platelet-rich plasma, sacral fracture, coccydynia, case report, minimally invasive

BACKGROUND

The sacrum is a crucial bony structure that connects the vertebral column and the pelvic ring, supporting the upper body load and providing stability to the pelvic ring while load-lifting (1). A sacral fracture can result in significant ambulatory impairment and related pathologies (2).

Sacral fractures are caused by various factors, such as motor vehicle collisions, falls, crush injuries, or osteoporosis in the elderly following minor traumas (2-4) . The incidence of non-osteoporotic sacral fractures is reported to be 2.1 per 100,000 cases, while in elderly patients at risk of osteoporosis, the incidence of osteoporotic fractures is found to be 1–5% (5,6). Pelvic fractures are seen in 45% of sacral fractures, and isolated sacral fractures caused by direct impact or fall on the sacrum occur in less than 5% of cases (7). The presence of accompanying injuries often determines the outcome of sacral fracture in patients (8). The increasing age of the population and advancement of diagnostic modalities have led to a rise in the number of cases of both osteoporotic and non-osteoporotic sacral fractures (9-11).

Sacral fractures pose diagnostic and therapeutic challenges, often being misinterpreted and not appropriately treated due to their relative frequency and heterogeneity (12). Diagnosis of sacral fractures is typically delayed because the clinical features are generally ambiguous and unspecific, imitating a range of pathological processes, such as nerve entrapment and metastatic illness, especially in older populations. Diagnosis of sacral fractures is delayed in 25% to 70% of cases (2) due to the typical trauma scenario in which patients suffer unconsciousness, concomitant spine

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injuries, extreme traumatic damage, severe bleeding resulting in hemodynamic instability, and soft tissue engagement (13).

Structural damage to the sacrum may only be fully appreciated by considering its functional features. The sacrum lies in the pelvic ring as the anchor of the spine, transmitting and distributing biomechanical stresses via hip joints into the ilia and the lower limbs (14). Even minor spinal, sacral, and pelvic morphological alterations can result in substantial clinical symptoms among patients due to traumas or osteoporosis (15,16). In particular, sacral fractures can present with lower back pain, which is a common symptom in the general population, with 80% of adults in the United States experiencing one episode of lower back pain during their lifetime, typically occurring between the ages of 45 to 65 years (17).

The mechanism of the fracture plays an essential role in establishing the sequence of the fracture and the method of its management. For example, pedestrians affected by motorized vehicles are at greater risk of lateral compression injury, while diagonal sacral fractures are common in patients falling from a height (3). Misdiagnosis or delayed diagnosis of sacral fractures can lead to increasing deformations, loss of function, and neurological impairment (18), and due to delay in treatment, outcomes become less favorable (19).

Sacral fractures are often challenging to treat surgically due to the risks involved, such as nerve or blood vessel injuries, blood loss, or infections. In this case report, we describe the successful non-surgical treatment of a 37-year-old woman who sustained a sacral (S3) fracture after being hit by a motor vehicle while walking. The patient initially received conservative treatment, including bed rest, pain medication, and physical therapy. However, she continued to experience significant pain and functional limitations, and radiographic imaging revealed poor healing progress and a persistent protrusion at the S3 sacral bone.

Given the patient's persistent symptoms and lack of improvement, we recommended PRP injection as a non-surgical treatment option. Following the injection, the patient reported a significant reduction in pain and improvement in functional capacity. Follow-up radiographic imaging showed evidence of bone remodeling and significant improvement in the protrusion at the S3 sacral bone, consistent with successful fracture healing. The patient was able to resume her daily activities without pain or functional limitations.

This case report adds to the limited literature on the use of PRP for the treatment of sacral fractures. Our experience highlights PRP injection as a potential treatment option for sacral fractures, especially in cases where surgical intervention is not feasible or is associated with high risks.

CASE PRESENTATION

History of Present Illness

A 37-year-old woman pedestrian was struck by a car in December 2020, leading to a sacral fracture. By February 2021, she presented with persistent low back pain radiating from the left hip, buttock, and thigh, with an average Visual Analog Scale (VAS) pain score of 7 out of 10. The pain was more significant on the left side than the right, worsened with movement and while sitting or lying down, and improved with standing.

Post-incident Physical Examination

During her examination, the patient showed acute tenderness upon palpation along the coccyx and sacrococcygeal ligament region, with a positive piriformis stretch more pronounced on the left side than the right. Other examination findings were within normal limits and did not contribute significantly to her presenting complaints.

Initial Management

Following the accident, the patient was diagnosed with lumbar sprain & strain injury, lumbago, lumbar disc disorder, and coccydynia. The initial treatment plan involved pain management with anti-inflammatory, GABA, muscle relaxer, and narcotic medications, complemented by less than 10 sessions of physical therapy. Despite these interventions, her pain and functional limitations persisted, with her VAS pain score remaining at 7 out of 10.

Medical History and Current Medications

The patient's past medical history included major depressive disorder, and she underwent bilateral foot surgery in 2015. At the time of presentation, she was taking a regimen of pain management medications, multivitamins, and vitamin D and B complex. She had no known drugs allergies.

Social History

She reported no history of chronic pain prior to the ac-

cident and was not working at the time of presentation. She was a non-smoker with no known drug allergies.

Clinical Course And Management

Current Evaluation

In accordance with the Declaration of Helsinki, this case report did not require Institutional Review Board (IRB) approval as it involves a single patient and is not considered primary research. The case report presents a detailed analysis of the patient's clinical course and treatment outcomes without altering the standard of care or involving any experimental interventions. Furthermore, all patient information has been de-identified to maintain confidentiality, and informed consent was obtained from the patient for the publication of this case report. Therefore, we believe that an IRB approval was not necessary for the development and submission of this case report.

On January 5, 2021, magnetic resonance imaging (MRI) of the patient's lumbar spine and pelvis revealed a sacral fracture with edema and a 2-millimeter disc protrusion at L4/5. In addition, the imaging indicated a 5-millimeter impaction of the anterior S1 cortex with marrow edema at S3 and S4 levels, soft tissue edema of the piriformis muscles, and neuroforaminal S3 and S4 effacement. These findings suggested that the patient's tailbone pain, which presented as coccydynia, was likely due to the fracture and potentially associated with some involvement of the piriformis muscles. The differential diagnosis included conditions such as S3 and S4 nerve root compression.

Approximately 2 months after the initial MRI, a computed tomography (CT) scan of the sacrum with fine cuts was performed to assess the bone cortical integrity. The CT scan revealed that the anterior cortex had been depressed by approximately 4 mm (Fig. 1), consistent with the prior MRI. The remaining sacral levels appeared intact, and there were no signs of new injuries or complications. The previously identified prevertebral edema at S3 on the MRI was no longer visible. The findings were indicative of subacute trauma and were best visualized on sagittal images. The sacral foramina appeared intact, and the sacroiliac joints demonstrated mild degenerative changes. However, there was no radiographic evidence of callus formation or bridging trabeculae, which are specific indicators of bone healing (20,21). The absence of these features suggests that although there were no signs of new injuries or complications, bone healing has not progressed significantly.

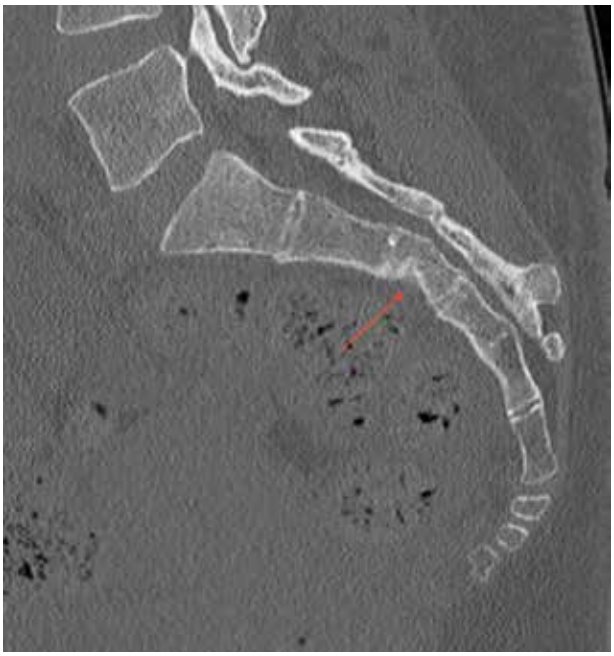

Fig. 1. Sagittal view of S3 sacral bone showing 4 mm protrusion, taken approximately 2 months after the injury.

Current Management

The patient's primary pain complaint continued to be tailbone pain, likely from the S3 fracture and sacrococcygeal ligament sprain injury/coccydynia. A range of treatment options were discussed with the patient, including physical therapy, medication management, pain interventions, and surgical evaluation.

After considering the amount of time that had elapsed since the onset of symptoms, lack of improvement with conservative management, and the MRI and CT scan findings, as well as the patient's medical history and examination, a recommendation was made for traversing sacral S3 anterior cortex vertebral fracture and sacrococcygeal PRP injection under fluoroscopic guidance. This treatment approach was chosen due to its effectiveness in promoting tissue healing and reducing inflammation, as well as its minimally invasive nature (22,23). The consideration of sacroplasty was ruled out, as it is typically indicated for sacral insufficiency fractures often seen in patients with osteoporosis or metastatic disease, which did not apply to this case (24,25). Additionally, sacroplasty is generally used for patients with unstable or displaced fractures, whereas this patient had a non-displaced fracture (26). Furthermore, PRP carries less risk than

sacroplasty, which has potential complications, such as cement leakage and neural issues (27,28). Therefore, given the patient's specific condition and the comparative risks and benefits of the available treatments, PRP was deemed the most appropriate choice.

Procedure

A few months after the patient's injury, the patient provided informed consent, and a sterile prep was performed. Twenty-five mL of her blood was drawn into a 30 mL Genesis CS Platelet Concentrating System, with 5 mL of sodium citrate. The sample was then centrifuged in a Platinum Series Emcyte centrifuge for 2 minutes to isolate the platelet-plasma suspension. The platelet plasma suspension was then transferred into a concentrating accessory tube and centrifuged for 6 minutes to isolate approximately 6 mL of autologous PRP.

The patient was then taken to the operating room and placed in a prone position under monitored anesthesia care. The area over the sacrum was prepped and draped in a sterile fashion. The fluoroscopic head was brought over the sacral spine and using anterior posterior fluoroscopic view, the S3 vertebral body was well-visualized (Fig. 2). The overlying skin was anesthetized with 3 mL of 1% plain lidocaine. A 23 gauge, 3.5-inch spinal needle was then advanced under intermittent fluoroscopic guidance towards the left S3 neuroforaminal opening. The needle was advanced anteriorly until the tip was just past the anterior sacral cortex, reaching the S3 fracture site (Fig. 3)

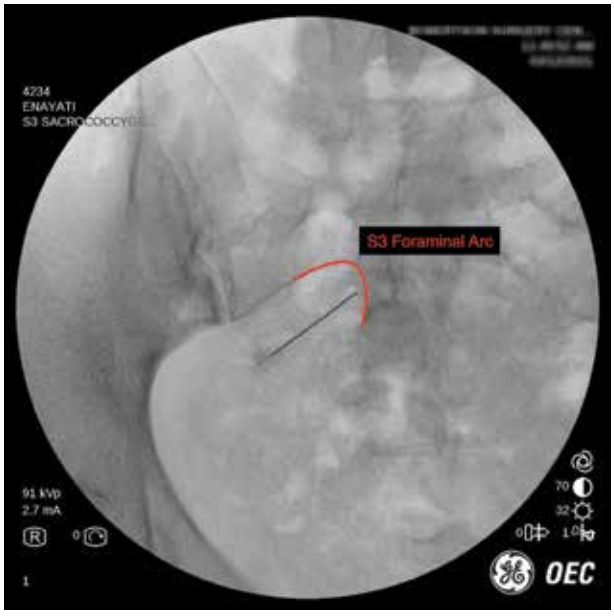

Fig. 2. The AP fluoroscopic view of the patient's sacrum, with the S3 vertebral body and S3 foraminal arc well-visualized. The insertion of a 23-gauge, 3.5-inch spinal needle, which is being advanced under intermittent fluoroscopic guidance. The needle is directed towards the left S3 neuroforaminal arc, lateral to midline, to reach the fracture site.

After negative aspiration, 3 mL of omnipaque 240 was injected to confirm the appropriate spread (Fig. 4), followed by 4 mL of PRP and 1 mL of 0.25% plain bupivacaine. The fluoroscope was then adjusted to visualize the anatomic location of the sacrococcygeal ligament. The needle was retracted and redirected towards the sacrococcygeal ligament. After negative aspiration, 1 mL of omnipaque 240 was injected to confirm appropriate sacrococcygeal ligamentous spread (Fig. 5), followed by 2 mL of PRP and 1 mL of 0.25% plain bupivacaine. The procedure was completed without complications and the patient tolerated the procedure well. Following the procedure, appropriate discharge and follow-up instructions were provided to the patient.

While the patient reported an overall improvement in tailbone pain following the sacral S3 and sacrococcygeal ligament PRP injections, some discomfort persisted, particularly when sitting on hard surfaces. This persistent pain, suggestive of coccydynia, continued to interfere with her daily activities and comfort. Recognizing the need for further intervention, we performed a second-

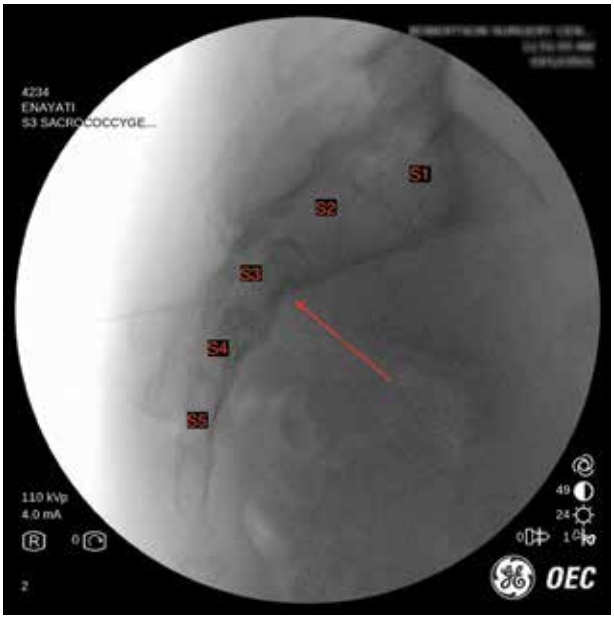

Fig. 3. Lateral fluoroscopic view image depicts the needle having reached the S3 fracture site, as indicated by the red arrow.

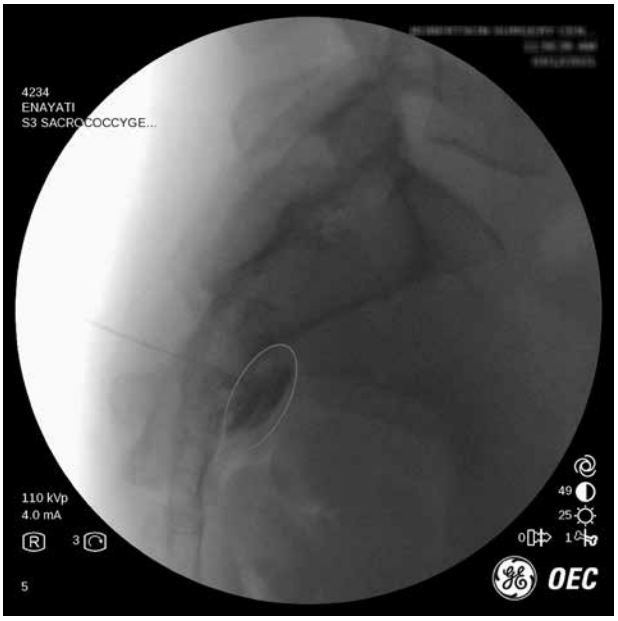

Fig. 4. Lateral fluoroscopic view showing the appropriate spread of the Omnipaque 240 injection at the S3 vertebral fracture site. The area of contrast is indicated by the red circle.

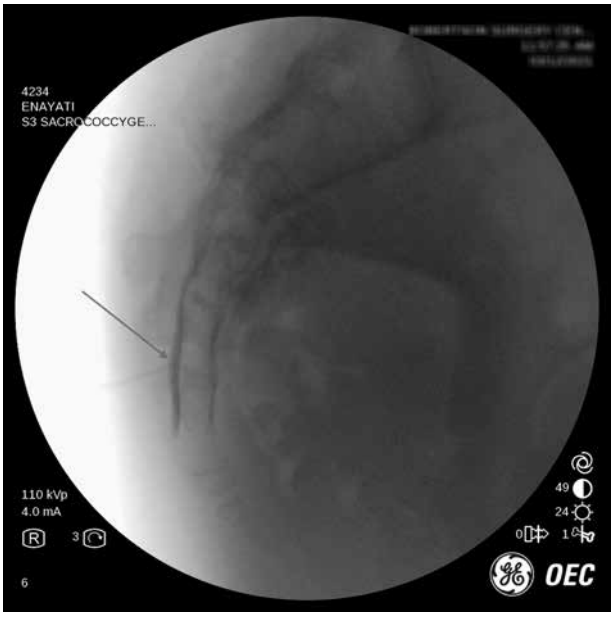

Fig. 5. This lateral view image shows the injection of Omnipaque 240 into the sacrococcygeal ligament, as indicated by the red arrow, revealing appropriate ligamentous spread.

ary PRP injection targeting the coccyx and sacrococcygeal ligament under fluoroscopic guidance, 2 months following the initial treatment.

Outcomes

Approximately 4 months after the injury and 2 months after the initial sacral S3 and sacrococcygeal PRP injection, the patient's symptoms showed significant improvement. Her low back and tailbone pain decreased by 60% and she experienced notable functional improvements, including better sleep quality, ability to sit without feeling limited by pain, and improvement in her ability to perform household chores. Two months later, a second coccyx and sacrococcygeal ligament PRP injection led to a further 30% improvement in her residual symptoms. During postoperative follow-up evaluations, she reported experiencing low back and tailbone pain only intermittently, with an average pain score of 1 out of 10.

Six months after the injury and 2 months after the last PRP injection, a follow-up CT scan was performed to assess the extent of healing of the coccyx fracture. The results showed that the S3 fracture had completely healed with good bony fusion and alignment (Fig. 6). There was no evidence of new fractures or malalignment of the sacrum. The patient was pleased with her

Fig. 6. Radiographic evidence of bony fusion at S3 Sacral bone protrusion following PRP injections. Image obtained approximately 7 months after the injury and 4 months after the PRP procedure.

progress and expressed satisfaction with the treatment outcomes.

DISCUSSION

PRP therapy has gained tremendous importance in recent decades due to its straightforward application and the natural stimulation of the healing process (29,30). Various methodologies have been explored to achieve the desired concentration of platelets and growth factors, which are crucial for the therapy's effectiveness (31). This case report highlights the successful use of PRP injection to initiate the natural healing process of the sacral bone protrusion in a 37-year-old woman pedestrian who was injured in a pedestrian versus automobile accident.

Regenerative biomedicines have witnessed significant advancements in recent years, with a diverse array of treatments emerging such as PRP, mesenchymal stem cells, electroconvulsive shock wave therapy, nitric oxide, and matrix metalloproteinase. Among these, PRP has seen remarkable growth, backed by a surge in clinical application and research interest (32). PRP therapy, which involves injections of concentrated platelets to expedite healing of injuries, has shown potential in the treatment of conditions, such as knee osteoarthritis, sports injuries, and even hair loss (30,32,33). The interest in PRP is due to its high concentration of platelets, which is typically about 5 times more than that in whole blood (34,35). While normal blood contains approximately 200,000 to 400,000 platelets per microliter, PRP can reach up to one million platelets per microliter (36).

The goal of PRP therapy is to directly achieve a high concentration of growth factors, which are frequently found in low concentrations, to sites of collagen damage or degradation. The content of PRP includes circulating growth factors included in the alpha granules, such as platelet-derived (PDGF), transforming (TGF), and insulin-like growth factor (IGF-1), as well as cytokines that are claimed to function as humoral mediators to stimulate the natural healing sequence (37-39). PRP injections also contain an element of needle stimulation, which is hypothesized to initiate localized bleeding and, consequently, help attract and trigger circulation-derived cells, leading to a physiological inflammatory process and the subsequent healing (28). Alpha granules should degranulate to expel their components and initiate the collagen repair and growth cycle. The clotting activity of platelets starts the degranulation release of the growth factors from the platelets. Within 10 minutes after clotting, the release of most growth factors is initiated, and within 60 minutes, most of the growth factors have been released (40).

Outcomes from animal studies have shown that PRP effectively speeds up the recovery process following joint, ligament, and tendon injuries (41-44). Involvement of PRP in the activation of cells circulating at the site of their application was also demonstrated by Kajikawa et al (45) and reported that PRP could reduce inflammation and enhance the proliferation of stem cells and their maturation. It is also assumed that platelets can act as an external source of growth factors to enhance bone formation (46,47).

Studies have reported the beneficial effects of PRP in bone regeneration, with promising results in patients with osteogenesis (48-50). While our case involves a traumatic sacral fracture, the application of PRP therapy can extend to diverse bone and joint issues. To illustrate, a case of a post-surgical knee patient—a 20-year-old soccer player—demonstrates successful recovery after PRP treatment. Despite obvious differences, both scenarios involve osseous structures (sacrum and knee joint) and highlight PRP's potential in stimulating healing in varied tissues, including bone and cartilage (51).

In addition, considering PRP as a potential treatment option may serve as an adjunct or alternative to more aggressive therapies, such as long-term medication management and more invasive interventions, depending on the individual patient's circumstances and response to treatment. PRP employs autologous blood, eliminating the risk of disease transmission or immunogenic responses when using non-autologous blood. Further, PRP acts on the cell membrane instead of the nucleus, eliminating tumor development via negative feedback regulation (28). The current case report, demonstrating significant pain reduction, functional improvements, and complete healing of the sacral fracture with PRP injections, provides direct evidence of PRP's potential as a safe and effective treatment option for sacral fractures and coccydynia. The absence of adverse effects and complications further supports PRP therapy as a safe and minimally invasive approach for bone regeneration. As more clinical studies and case reports are conducted, further evidence will be accumulated to confirm the full potential of PRP in bone healing and regeneration. However, the positive outcome observed in this case report highlights PRP as a promising treatment option for bone fractures and injuries, especially those that may be difficult to

manage with traditional approaches. Clinicians should consider PRP as a viable alternative or adjunct therapy for bone injuries and fractures, particularly for those who may not be ideal candidates for surgery or other invasive interventions.

CONCLUSION

PRP therapy is an emerging modality that has shown promising results in the treatment of bone injuries and fractures. The natural healing cascade of PRP injection, along with its ease of administration, safety, and effectiveness, make it a valuable tool in the armamentarium of clinicians. Moreover, comprehensive evaluation utilizing advanced imaging techniques should be considered to accurately assess and diagnose structural damage to the spinal canal in patients presenting with tailbone symptoms, neck pain, or head pain. In the present case, PRP injection therapy was effective in promoting healing of a sacral fracture and coccydynia, highlighting its potential for treating bone defects and associated soft tissue injuries. However, further research is required to support the effectiveness of PRP as a standalone treatment for bone defects, especially those with protrusion. As more clinical studies and case reports are conducted, we may gain a deeper understanding of the mechanisms behind PRP's effectiveness and how it can be utilized to optimize treatment outcomes for patients with musculoskeletal injuries. Continued research efforts will contribute to expanding the evidence base and refining the application of PRP therapy in bone healing and regeneration.

Author Contributions

Gary Charliyan prepared and wrote the manuscript, collected and analyzed the data, and provided critical revisions. Dr. Joseph Enayati treated the patient and provided critical revisions. Both authors have read and approved the final version of the manuscript.

REFERENCES

1. Vleeming A, Schuenke MD, Masi AT, et al. The sacroiliac joint: an overview of its anatomy, function and potential clinical implications. *J Anat* 2012; 221:537-567.
2. Santolini E, Kanakaris NK, Giannoudis PV. Sacral fractures: issues, challenges, solutions. *EFORT Open Rev* 2020; 5:299-311.
3. Rodrigues-Pinto R, Kurd MF, Schroeder GD, et al. Sacral fractures and associated injuries. *Global Spine J* 2017; 7:609-616.
4. Rawlings CE 3rd, Wilkins RH, Martinez S, et al. Osteoporotic sacral fractures: a clinical study. *Neurosurgery* 1988; 22(1 Pt 1):72-76.
5. Bydon M, De la Garza-Ramos R, Macki M, et al. Incidence of sacral fractures and in-hospital postoperative complications in the United States: An analysis of 2002-2011 data. *Spine* 2014; 39:E1103-E1109.
6. Chang KP, Center JR, Nguyen TV, et al. Incidence of hip and other osteoporotic fractures in elderly men and women: Dubbo osteoporosis epidemiology study. *J Bone Miner Res* 2004; 19:532-536.
7. Bonnin JG. Sacral fractures and injuries to the cauda equina. *J Bone Joint Surg* 1945; 27:113-127.
8. Alnaib M, Waters S, Shanshal Y, et al. Combined pubic rami and sacral osteoporotic fractures: A prospective study. *J Orthop Traumatol* 2012; 13:97-103.
9. Wagner D, Ossendorf C, Gruszka D, et al. Fragility fractures of the sacrum: How to identify and when to treat surgically? *Eur J Trauma Emerg Surg* 2015; 41:349-362.
10. Zheng J, Feng X, Xiang J, et al. S2-alar-iliac screw and S1 pedicle screw fixation for the treatment of non-osteoporotic sacral fractures: A finite element study. *J Orthop Surg Res* 2021; 16:651.
11. Lyders EM, Whitlow CT, Baker MD, et al. Imaging and treatment of sacral insufficiency fractures. *AJNR Am J Neuroradiol* 2010; 31:201-210.
12. Schneider R, Yacovone J, Ghelman B. Unsuspected sacral fractures: Detection by radionuclide bone scanning. *AJR Am J Roentgenol* 1985; 144:337-341.
13. Lykomitros VA, Papavasiliou KA, Alzeer ZM, et al. Management of traumatic sacral fractures: A retrospective case-series study and review of the literature. *Injury* 2010; 41:266-272.
14. Kiapour A, Joukar A, Elgafy H, et al. Biomechanics of the sacroiliac joint: Anatomy, function, biomechanics, sexual dimorphism, and causes of pain. *Int J Spine Surg* 2020; 14(Suppl 1):3-13.
15. Acevedo Gonzalez JC, Perez Rodriguez JC. Unidad lumbosacrococcígea. Desarrollo conceptual. *Rev Colomb Ortop Traumatol* 2017; 21:55-62.
16. Ames CP, Smith JS, Scheer JK, et al. Impact of spinopelvic alignment on decision making in deformity surgery in adults. *J Neurosurg Spine* 2012; 16:547-564.
17. Freburger JK, Holmes GM, Agans RP, et al. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
18. Schmidek HH, Smith DA, Kristiansen TK. Sacral fractures. *Neurosurgery* 1984; 15:735-746.
19. Routt ML, Jr, Simonian PT, Swiontkowski MF. Stabilization of pelvic ring disruptions. *Orthop Clin North Am* 1997; 28:369-388.
20. Adelved A, Tötterman A, Hellund JC, et al. Radiological findings correlate with neurological deficits but not with pain after operatively treated sacral fractures. *Acta Orthop* 2014; 85:408-414.
21. Thomas JD, Kehoe JL. Bone nonunion. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): *StatPearls Publishing* 2023. www.ncbi.nlm.nih.gov/books/NBK554385/
22. Oneto P, Etulain J. PRP in wound healing applications. *Platelets*

2021; 32:189-199.

23. Etulain J. Platelets in wound healing and regenerative medicine. *Platelets* 2018; 29:556-568.
24. Kortman K, Ortiz O, Miller T, et al. Multicenter study to assess the efficacy and safety of sacroplasty in patients with osteoporotic sacral insufficiency fractures or pathologic sacral lesions. *J Neurointerv Surg* 2013; 5:461-466.
25. Chandra V, Wajswol E, Shukla P, et al. Safety and Efficacy of sacroplasty for sacral fractures: A systematic review and meta-analysis. *J Vasc Interv Radiol* 2019; 30:1845-1854.
26. Gupta AC, Chandra RV, Yoo AJ, et al. Safety and effectiveness of sacroplasty: A large single-center experience. *AJNR Am J Neuroradiol* 2014; 35:2202-2206.
27. Clark AC, Butani D. Percutaneous sacroplasty for sacral insufficiency fractures: Case series and review of presentation, diagnosis, and treatment. *Am J Interv Radiol* 2019; 3:1-11.
28. American Academy of Orthopaedic Surgeons. Platelet-rich plasma (PRP). https://orthoinfo.aaos.org/en/treatment/platelet-rich-plasma-prp/. Accessed 5/26/2023.
29. F. Mirasol. Gaining ground: The rise of regenerative medicines. *BioPharm International* 2022; 35:16–17.
30. Cleveland Clinic. https://my.clevelandclinic.org/health/treatments/21102-platelet-rich-plasma.
31. Arthur Vithran DT, Xie W, Opoku M, et al. The efficacy of platelet-rich plasma injection therapy in the treatment of patients with achilles tendinopathy: A systematic review and meta-analysis. *J Clin Med* 2023; 12:995.
32. Everts P, Onishi K, Jayaram P, et al. Platelet-rich plasma: New performance understandings and therapeutic considerations in 2020. *Int J Mol Sci* 2020; 21:7794.
33. Gentile P., Calabrese C., De Angelis B., et al. Impact of the different preparation methods to obtain autologous non-activated platelet-rich plasma (A-PRP) and activated platelet-rich plasma (AA-PRP) in plastic surgery: Wound healing and hair regrowth evaluation. *Int J Mol Sci* 2020; 421:431.
34. Kaye AD, Edinoff AN, Rosen YE, et al. Regenerative medicine: Pharmacological considerations and clinical role in pain management. *Curr Pain Headache Rep* 2022; 26:751-765.
35. Grossen AA, Lee BJ, Shi HH, et al. Platelet-rich plasma injections: Pharmacological and clinical considerations in pain management. *Curr Pain Headache Rep* 2022; 26:741-749.
36. Dashore S, Chouhan K, Nanda S, et al. Preparation of platelet-rich plasma: National IADVL PRP taskforce recommendations. *Indian Dermatol Online J* 2021; 12(Suppl 1):S12-S23.
37. Mosesson MW, Siebenlist KR, Meh DA. The structure and biological features of fibrinogen and fibrin. *Ann N Y Acad Sci* 2001; 936:11-30.
38. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop* 2010; 34:909-915.
39. Duran S, Yasar S, Aytekin P, et al. Duran clinical and histopathological evaluation of the effects of platelet rich plasma, platelet poor plasma and topical serum physiologic treatment on wound healing caused by radiofrequency electrosurgery. *Deri Hastaliklari ve Frengi Arsivi* 2018; 52:44-50.
40. Ko GD. Platelet-rich plasma prolotherapy for low back pain caused by sacroiliac joint laxity. *Human Studies* 2010; 13:15.
41. DesRosiers EA, Yahia L, Rivard CH. Proliferative and matrix synthesis response of canine anterior cruciate ligament fibroblasts submitted to combined growth factors. *J Orthop Res* 1996; 14:200-208.
42. Yoshikawa Y, Abrahamsson SO. Dose-related cellular effects of platelet-derived growth factor-BB differ in various types of rabbit tendons in vitro. *Acta Orthop Scand* 2001; 72:287-292.
43. Lyras DN, Kazakos K, Verettas D, et al. Effect of combined administration of transforming growth factor-b1 and insulin-like growth factor I on the mechanical properties of a patellar tendon defect model in rabbits. *Acta Orthop Belg* 2010; 76:380-386.
44. Matsui M, Tabata Y. Enhanced angiogenesis by multiple release of platelet-rich plasma contents and basic fibroblast growth factor from gelatin hydrogels. *Acta Biomater* 2012; 8:1792-1801.
45. Kajikawa Y, Morihara T, Sakamoto H, et al. Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. *J Cell Physiol* 2008; 215:837-845.
46. Linkhart TA, Mohan S, Baylink DJ. Growth factors for bone growth and repair: IGF, TGF beta and BMP. *Bone* 1996;19(1 Suppl):1S-12S.
47. Bolander ME. Regulation of fracture repair by growth factors. *Proc Soc Exp Biol Med* 1992; 200:165-170.
48. Ai-Aql ZS, Alagl AS, Graves DT, et al. Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. *J Dent Res* 2008; 87:107-118.
49. Yamada Y, Ueda M, Naiki T, et al. Autogenous injectable bone for regeneration with mesenchymal stem cells and platelet-rich plasma: Tissue-engineered bone regeneration. *Tissue Engineering* 2004; 10(5-6):955-964.
50. Kitoh H, Kitakoji T, Tsuchiya H, et al. Transplantation of culture expanded bone marrow cells and platelet rich plasma in distraction osteogenesis of the long bones. *Bone* 2007; 40:522-528.
51. Sánchez M, Azofra J, Anitua E, et al. Plasma rich in growth factors to treat an articular cartilage avulsion: A case report. *Med Sci Sports Exerc* 2003; 35:1648-1652.