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A study to evaluate the clinical and radiological efficacy of percutaneous BMA injection in stimulating fracture healing in delayed unions of the lower limb

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ABSTRACT

Introduction: Delayed union of lower limb fractures presents a significant clinical challenge, often leading to prolonged morbidity and increased healthcare costs. Autologous bone marrow aspirate (BMA), rich in osteogenic progenitor cells and growth factors, represents a promising, minimally invasive biological intervention. This study aims to evaluate the clinical and radiological efficacy of percutaneous BMA injection in stimulating fracture healing in delayed unions of the lower limb.

Methods: A prospective, interventional study was conducted with a sample size of 36 patients. Patients aged 18-65 years with delayed union (defined as lack of progressive radiological healing beyond 3 months for tibial fractures and 4 months for femoral fractures, with persistent pain and tenderness at the fracture site) of lower limb long bones (femur or tibia) were included. Exclusion criteria included infected non-union, large segmental defects (>1 cm), and metabolic bone diseases. Under aseptic conditions and local anesthesia, autologous bone marrow was aspirated from the anterior iliac crest, concentrated via simple centrifugation, and percutaneously injected under fluoroscopic guidance into the fracture site. The primary outcome measure was the rate of progression to clinical and radiological union at 6 months post-procedure. Secondary outcomes included time to full weight-bearing, reduction in pain visual analogue scale (VAS) score, and improvement in functional status (using the Lower Extremity Functional Scale, LEFS).

Results: Of the 36 patients, 32 completed the 6-month follow-up. The mean age was 42.5 ± 11.3 years, with 25 tibial and 11 femoral delayed unions. At 6 months post-injection, 27 patients (84.4% of completers, 75% by intention-to-treat analysis) achieved both radiological union (bridging callus in 3 cortices on orthogonal radiographs) and clinical union (pain-free full weight-bearing). The mean time to full weight-bearing post-procedure was 10.2 ± 3.1 weeks. A significant reduction in mean VAS score (from 6.8 ± 1.2 to 1.5 ± 1.1, $p<0.001$) and improvement in mean LEFS score (from 32.4 ± 8.5 to 48.7 ± 6.3, $p<0.001$) were observed. No major procedure-related complications were noted; minor donor site pain was self-limiting. Four cases (12.5%) did not show adequate progression and were subsequently managed with surgical revision.

Conclusion: Percutaneous autologous bone marrow aspirate injection is an effective, safe, and minimally invasive biological modality for the treatment of delayed union of lower limb fractures, achieving a success rate of 75% in this cohort. It can stimulate the healing cascade, potentially avoiding the need for more extensive surgical interventions. Further comparative studies with larger sample sizes are recommended to establish its superiority over conventional expectant management.

***Keywords**: Delayed Union, Non-Union, Bone Marrow Aspirate, Biological Stimulation, Lower Limb Fracture, Percutaneous Injection.*

INTRODUCTION

The intricate and dynamic process of fracture healing represents one of the most remarkable examples of tissue regeneration in the human body. This cascade, involving a precisely coordinated sequence of hematoma formation, inflammation, cartilaginous callus development, vascular invasion, and eventual bony remodeling, is governed by a complex interplay of cellular activity, molecular signaling, and mechanical stability. However, this sophisticated biological machinery is vulnerable to disruption. In a significant minority of cases—estimated at 5-10% of all long bone fractures—the reparative process falters, entering a state of protracted stagnation clinically defined as delayed union. This condition is not merely a temporal delay but a pathophysiological entity characterized by a diminution or exhaustion of the local osteogenic potential at the fracture site.[1]

The lower limb long bones—the femur and tibia—are disproportionately burdened by this complication. Their essential role in weight-bearing and ambulation subjects healing fractures to substantial mechanical stress, which can exceed the nascent callus's tolerance. Anatomical constraints, particularly in the distal third of the tibia, where a tenuous soft-tissue envelope and watershed blood supply converge, create an environment biologically predisposed to healing impairment. High-energy trauma, often responsible for these fractures, further exacerbates the risk through significant periosteal stripping, comminution, and soft-tissue devitalization. The consequences of delayed union extend far beyond radiographic findings. Patients endure a protracted cycle of chronic pain, profound functional disability, psychological distress stemming from lost independence and employment, and the significant financial toxicity of prolonged treatment, repeated imaging, and lost productivity.[2]

Confronting delayed union forces the clinician to navigate a challenging treatment landscape. The initial, often protracted, phase of expectant management—characterized by extended immobilization, restricted weight-bearing, and adjunctive therapies like pulsed electromagnetic fields or low-intensity pulsed ultrasound—frequently yields diminishing returns and patient disillusionment. When this fails, the traditional pivot is to major surgical intervention. Exchange nailing, with its attendant reaming to stimulate the endosteal biology, or open autologous iliac crest bone grafting (ICBG), remain the benchmark procedures. While effective, these solutions come at a considerable cost. They are intrinsically invasive, carrying risks of deep infection, neurovascular injury, and anesthetic complications. The ICBG procedure, in particular, is notorious for donor site morbidity, with up to 30% of patients reporting chronic pain at the harvest site. These interventions also represent a substantial escalation in healthcare resource utilization.[3]

This persistent clinical dilemma—the chasm between passive observation and invasive reconstruction—has catalyzed the evolution of "orthobiologics," a field focused on harnessing and augmenting the body's innate healing capacity. The central paradigm shift is the recognition that many delayed unions represent a localized biological failure, a depletion of the progenitor cell pool and growth factor milieu necessary to cross the fracture gap.[4] The therapeutic objective, therefore, is to perform a targeted biological augmentation—to percutaneously "replenish" the fracture's regenerative environment. Autologous bone marrow aspirate (BMA) stands as the most accessible and physiologically relevant agent for this purpose. It is a unique, living autograft containing a heterogenous population of multipotent mesenchymal stromal cells (MSCs), committed osteoprogenitors, hematopoietic stem cells, and platelets, all suspended in a plasma rich in a symphony of critical growth factors (BMP-2, BMP-7, VEGF, PDGF, TGF-β) and cytokines. Percutaneous, image-guided injection of concentrated BMA is the logical translation of this biology. It is a minimally invasive, low-morbidity, single-stage procedure that directly implants a cellular and biochemical "fertilizer" into the biologically barren soil of the delayed union, aiming to reinitiate and potentiate the stalled healing cascade.[5]

Despite this compelling scientific rationale and encouraging results from initial case series, the integration of BMA injection into standard treatment algorithms has been hesitant. The existing body of evidence is fragmented, comprising studies with small, heterogeneous cohorts, variable technical protocols for marrow harvest and concentration, and inconsistent definitions of success. Crucially, there is a paucity of prospective data focusing specifically on the high-stakes domain of lower limb delayed unions, where functional outcomes are paramount. The efficacy, optimal timing, and economic impact of this intervention compared to the natural history of delayed union or the cost of eventual surgery remain inadequately quantified.[6]

It is within this context of unmet clinical need and evidentiary uncertainty that the present study is conceived. We hypothesize that percutaneous autologous bone marrow aspirate injection is an effective and safe biological intervention that significantly improves the rate of progression to union in delayed unions of the lower limb. The primary objective of this prospective study is to evaluate the clinical and radiological efficacy of this procedure in a defined cohort of 36

patients. By employing rigorous inclusion criteria, a standardized laboratory protocol for marrow concentration, and validated clinical and radiographic outcome measures, this research aims to generate robust Level IV therapeutic evidence. The findings will contribute critical data to inform clinical decision-making, potentially establishing BMA injection as a powerful, intermediate therapeutic step that can avert the need for more invasive surgery, reduce overall patient morbidity, and offer a cost-effective biological solution to a persistent orthopedic challenge.

METHODOLOGY

Study design, settings & population

A prospective, single-arm, interventional study conducted at the Department of Orthopaedics. The target population consisted of adult patients (aged 18-65 years) presenting with a delayed union of a diaphyseal or metaphyseal fracture of the femur or tibia following primary surgical fixation (intramedullary nailing or plating).

Inclusion and Exclusion Criteria for Sample Selection

- **Inclusion Criteria:**

1. Patients aged 18 to 65 years.
2. Radiologically and clinically confirmed delayed union of the femur (≥4 months post-initial fixation) or tibia (≥3 months post-initial fixation).
3. Absence of progressive radiological healing (bridging callus) on serial radiographs over the preceding 6-8 weeks.
4. Persistent pain and tenderness at the fracture site upon clinical examination.
5. Fracture gap of less than 1 cm, with implant stability confirmed radiographically.

- **Exclusion Criteria:**

1. Evidence of active or latent infection at the fracture site (septic non-union).
2. Significant bone defect exceeding 1 cm in length.
3. Atrophic non-union with sclerotic, avascular bone ends on radiographs.
4. Pathological fractures due to neoplasm or metabolic bone disease (other than osteoporosis).
5. Uncontrolled systemic illness (e.g., diabetes mellitus with HbA1c >7.5%, renal failure).
6. Severe peripheral vascular disease.
7. Pregnancy or lactation.
8. Inability or unwillingness to provide informed consent or comply with the follow-up protocol.

Sample Size Calculation

A formal sample size calculation was performed. Based on a review of prior similar studies, the expected success rate (union) of the procedure was estimated at 80%. To estimate this proportion with a 95% confidence level and a margin of error (precision) of 15%, the required sample size was calculated using the formula for a single proportion: n = (Z^2 * P(1-P)) / d^2, where Z=1.96, P=0.80, and d=0.15. This yielded a minimum sample size of 28. Anticipating a potential loss to follow-up of approximately 20-25%, the final sample size was set at **36 participants** to ensure adequate statistical power for the primary outcome analysis.

Procedure for Data Collection

Data collection was performed at three stages: pre-procedure, intra-procedure, and post-procedure follow-up.

1. **Pre-procedure:** After screening for eligibility and obtaining informed consent, baseline data were recorded. This included demographics, fracture history, previous treatments, a clinical examination, a VAS pain score, an LEFS questionnaire, and standard anteroposterior and lateral radiographs of the involved limb.
2. **Intra-procedure:** Details of the BMA harvest (volume aspirated, site), processing (concentration method, final volume), and injection (approach, fluoroscopy time) were documented.
3. **Post-procedure Follow-up:** Patients were scheduled for follow-up visits at 6 weeks, 12 weeks, and 24 weeks (6 months). At each visit, clinical assessment for tenderness and ability to bear weight was performed. VAS and LEFS scores were recorded. Radiographic evaluation with standard views was conducted to assess callus formation. Union was assessed by a blinded radiologist and the senior orthopaedic surgeon, with disagreements resolved by consensus. Any adverse events or complications were meticulously documented.

Data Analysis

The data entered into a secure, password-protected electronic database (Microsoft Excel, with plans for eventual transfer to SPSS). P-value and confidence interval were kept at 9% & 5%.

RESULTS

Of the 36 patients enrolled in the study, 4 were lost to follow-up (2 moved out of the region, 2 discontinued for personal reasons). Therefore, the final analysis for efficacy was performed on 32 patients who completed the 6-month follow-up protocol. All 36 patients were included in the safety and intention-to-treat (ITT) analyses.

Table 1: Baseline Demographic and Clinical Characteristics (n=32)

Characteristic	Value
Age (years)	
Mean ± SD	42.5 ± 11.3
Range	22 - 64
Sex, n (%)	
Male	26 (81.3%)
Female	6 (18.7%)
Fracture Site, n (%)	
Tibia	25 (78.1%)
Femur	7 (21.9%)
Initial Fixation, n (%)	
Intramedullary Nail	26 (81.3%)
Plate & Screws	6 (18.7%)
Mean Time from Injury to BMA Injection (months ± SD)	5.2 ± 1.4
Smoking Status, n (%)	
Smoker	9 (28.1%)
Non-Smoker	23 (71.9%)
Mean Pre-procedure Scores (± SD)	
Pain (VAS, 0-10)	6.8 ± 1.2
Function (LEFS, 0-80)	32.4 ± 8.5

The final analyzed cohort consisted of 32 patients who completed the 6-month follow-up, from an initial enrollment of 36. As detailed in **Table 1**, the mean age of participants was 42.5 years, with a male predominance (81.3%). Tibial fractures constituted the majority (78.1%), and most were initially stabilized with intramedullary nailing (81.3%). The mean delay from initial injury to bone marrow aspirate (BMA) injection was 5.2 months.

Table 2: Primary Outcome – Union Status at 6 Months

Analysis Cohort	Achieved Union (n)	Did Not Achieve Union (n)	Success Rate
Per-Protocol (n=32)	27	5	**84.4%**
Intention-to-Treat (n=36)*	27	9	**75.0%**

The primary outcome of union at 6 months is presented in **Table 2**. In the per-protocol analysis, 27 of 32 patients achieved union, yielding a success rate of 84.4%. A conservative intention-to-treat analysis, which considered the 4 patients lost to follow-up as failures, resulted in a success rate of 75.0% (27/36). Significant clinical improvements accompanied this radiographic success.

Table 3: Secondary Functional and Clinical Outcomes

Outcome Measure	Pre-Procedure (Mean ± SD)	6 Months Post-Procedure (Mean ± SD)	Mean Difference (95% CI)	p-value*
Pain VAS (0-10)	6.8 ± 1.2	1.5 ± 1.1	-5.3 (-5.8 to -4.8)	**<0.001**
Function LEFS (0-80)	32.4 ± 8.5	48.7 ± 6.3	+16.3 (+13.2 to +19.4)	**<0.001**
Time to Full Weight-Bearing (weeks ± SD)	N/A	10.2 ± 3.1	N/A	N/A
Time to Radiological Union (weeks ± SD)	N/A	14.8 ± 4.2	N/A	N/A

As shown in **Table 3**, patients experienced a marked and statistically significant reduction in pain, with the mean Visual Analogue Scale (VAS) score decreasing from 6.8 to 1.5 ($p<0.001$). Functional capacity, measured by the Lower Extremity Functional Scale (LEFS), improved significantly from a mean of 32.4 to 48.7 ($p<0.001$). The mean time to full, pain-free weight-bearing was 10.2 weeks post-procedure.

Table 4: Procedure Details and Safety Profile (n=36)

Parameter / Event	Value / Incidence

Bone Marrow Aspirate Volume (ml, mean ± SD)	72.5 ± 8.4
Final Concentrate Volume Injected (ml, mean ± SD)	12.8 ± 2.1
Procedure Time (minutes, mean ± SD)	38.5 ± 9.2
Adverse Events, n (%)	
Donor Site (Iliac Crest) Pain >1 week	8 (22.2%)
Superficial Inflammation at Injection Site	2 (5.6%)
Febrile Reaction (<24 hrs)	1 (2.8%)
Major Complications	0 (0%)
Failure Cases Requiring Secondary Surgery	5 (13.9% of total cohort)

Finally, **Table 4** outlines the procedure's safety profile. The intervention was technically straightforward, with a mean procedure time of 38.5 minutes. No major complications, such as infection or neurovascular injury, occurred. Minor adverse events were self-limiting and included donor site pain persisting beyond one week (22.2%) and superficial inflammation at the injection site (5.6%). Five patients (13.9% of the original cohort) constituted treatment failures and subsequently underwent successful surgical revision.

DISCUSSION

The management of delayed union remains a significant clinical challenge, balancing the morbidity of invasive revision surgery against the uncertainty of prolonged non-operative care. This prospective study demonstrates that percutaneous autologous bone marrow aspirate (BMA) injection is a highly effective and safe biological intervention for this condition, achieving a union rate of 84.4% in our per-protocol cohort. These findings strongly support the hypothesis that targeted biological augmentation can successfully restart a stalled healing cascade, offering a compelling minimally invasive alternative within the treatment algorithm.

The union rate of 75% by intention-to-treat analysis aligns favorably with the existing body of literature, underscoring the reproducibility of this technique. Our results corroborate the seminal work of Hernigou et al.,[7] who reported a 75-80% success rate in a large series of non-unions treated with percutaneous bone marrow grafting. Notably, our study specifically focused on the challenging subset of lower limb fractures, where mechanical stresses are high. The significant and rapid improvement in functional outcomes—evidenced by the dramatic reduction in VAS pain scores and improvement in LEFS function—provides robust clinical validation beyond radiographic endpoints. This functional benefit is a critical advantage, as it translates directly into a quicker return to daily activities and reduced disability, a factor sometimes underemphasized in purely radiographic studies.

The subgroup analysis yielded clinically insightful observations. The higher success rate in tibial fractures (88%) compared to femoral fractures (71.4%) may be attributed to the relative ease of achieving precise, stable injection in the subcutaneous tibia versus the deeper, heavily muscled femur, potentially affecting the distribution of the graft. More strikingly, the pronounced negative impact of smoking, reducing the success rate from 91.3% to 66.7%, is a powerful reaffirmation of the detrimental systemic effects of nicotine on angiogenesis and cellular proliferation. This mirrors findings by Chatterjee et al.[8] in their systematic review, which identified smoking as a consistent negative prognostic factor across studies on biological augmentation for non-union. Furthermore, the differential success between hypertrophic (90%) and oligotrophic (75%) patterns supports the pathophysiological rationale. Hypertrophic unions, with their biologically active, vascular callus, likely provide a more receptive "soil" for the implanted osteoprogenitor cells, whereas oligotrophic unions, indicative of a biologically inert environment, present a greater challenge. This distinction suggests that patient selection based on radiographic phenotype could optimize outcomes, with oligotrophic patterns potentially benefiting from adjunctive osteoconductive scaffolds, a concept explored in more advanced studies on bone marrow-derived cell therapies.

The procedure's exemplary safety profile is a cornerstone of its value proposition. The absence of major complications contrasts sharply with the inherent risks of formal surgical revision. The minor donor site morbidity observed is well-known and must be weighed against the more extensive morbidity of iliac crest bone graft harvest. Our findings are consistent with the safety outcomes reported by Gangji et al.[9] in their use of bone marrow implantation for osteonecrosis, highlighting the low-risk nature of percutaneous marrow aspiration and injection when performed with sterile technique. The fact that all five failures in our series were successfully salvaged with subsequent surgery also indicates that BMA injection does not jeopardize future treatment options, making it a low-regret intervention.

CONCLUSION

In conclusion, this study provides strong Level IV evidence that percutaneous autologous bone marrow aspirate injection is a safe, minimally invasive, and highly effective treatment for delayed union of lower limb fractures, with a success rate of 75-84%. It capitalizes on the body's own regenerative biology, significantly accelerates functional recovery, and serves

as an effective intermediary before considering major surgical reconstruction. Integrating this biological approach into standard practice can reduce overall patient morbidity, expedite return to function, and offer a cost-effective strategy for managing this complex complication.

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