ORIGINAL STUDY

acta orthopaedica belgica, 2026, 92, ePub ahead

doi.org/10.52628/92.1.12938

Efficacy of low-intensity pulsed ultrasound in surgically managed lower limb fractures: a randomised controlled trial

N. MAGIDA[1,2], H. MYEZWA[2], W. MUDZI[3], E. MUSENGE[4], S. A. MOHAMED KHAN[5], M. A. GRAHAM[6]

[1]Department of Physiotherapy, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa; [2]Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; [3]Postgraduate School, University of the Free State, Bloemfontein, South Africa; [4]Department of Statistics, University of the Witwatersrand, Johannesburg, South Africa; [5]Steve Biko Academic Hospital, Pretoria, South Africa; [6]Department of Mathematics Education, University of South Africa, Pretoria, South Africa.

Correspondence at: Nontembiso Magida, Department of Physiotherapy, School of Healthcare Sciences, University of Pretoria, Pretoria, South Africa. Tel: +2712 356 3230. E-mail: nontembiso.magida@up.ac.za

ABSTRACT

Although there have been improvements in surgical fixation techniques, the process of fracture healing continues to pose challenges, especially for patients with additional health issues. Low-intensity pulsed ultrasound (LIPUS) has been proposed as a non-invasive method to facilitate faster bone recovery; however, its effectiveness in clinical settings remains unclear. This study aimed to assess the impact of LIPUS on the healing of lower limb fractures. A double-blinded, prospective, randomised controlled trial was conducted in two hospitals in Gauteng, South Africa. The study was approved by the University of the Witwatersrand (M150236). Ninety-four individuals aged 18 years and older with lower limb fractures were consecutively recruited and randomly assigned to either the LIPUS or control group. The intervention group underwent 20-minute LIPUS sessions every alternate day for a duration of 20 days during their hospitalisation, followed by follow-up after discharge. Callus formation, cortical bridging, fracture gap, and overall radiographic healing were evaluated at 6, 12, and 18 weeks. An intention-to-treat analysis was performed to accommodate missing radiographs and loss to follow-up. No statistically significant differences were found between the intervention and control groups concerning callus formation, cortical bridging, fracture gap, or overall healing at any assessment time. A high rate of loss to follow-up and unavailability of radiographs diminished the analysis's power. LIPUS did not show a notable improvement in fracture healing when compared to standard care. Its clinical use may need to be reevaluated, especially in low– and middle-income countries, where cost-effectiveness is a crucial factor.

INTRODUCTION

Fractures commonly occur in trauma cases, and complications such as malunion, delayed healing, or non-union may lead to permanent disability. In approximately 5% of patients, recovery is hindered, possibly leading to non-union[1]. Once non-union occurs, no further spontaneous healing can be expected[2]. Fracture non-union may require additional surgical intervention to facilitate healing, which is costly for the patient and the healthcare system[3]. Patients with lower limb fractures who have delayed healing may endure long-term consequences such as impaired mobility and productivity[4]. Individuals with non-union fractures need to work closely with healthcare professionals to develop a comprehensive treatment plan that addresses both the physical and psychosocial aspects experienced.

Various methods have been proposed to promote fracture healing and reduce non-union occurrence[5-7]. Low-intensity pulsed ultrasound (LIPUS), used in physiotherapy, is one such option[8,9]. Non-invasive LIPUS treatment has been shown to strengthen fracture callus formation and improve fracture healing time, which may reduce or minimise associated disability and cost to patients and improve quality of life[9-11]. Studies investigating the use of LIPUS have reported reasonable compliance rates with daily treatment sessions of only 20 minutes[9,12-13]. LIPUS has the disadvantage of being expensive due to the high cost of the equipment[14], which must be considered when evaluating gains in fracture healing time and patients' ability to participate in activities and return to work[15]. More than 20 years of research on the effect of LIPUS on fracture healing has been conducted, and several studies contradict its

beneficial impact on bone healing[12,16]. Amalgamated data from all studies indicated that LIPUS treatment resulted in a non-significant reduction in healing time of approximately forty days[15,17]. However, limited research has investigated the use of LIPUS in cases of surgically managed fractures[18]. More research is thus needed to assess the efficacy of LIPUS on healing surgically managed fractures, particularly in the lower limbs. Furthermore, studies on the effectiveness of LIPUS for patients with fractures who have comorbidities such as human immunodeficiency virus (HIV), diabetes, and hypertension, which have commonly been associated with a greater risk of slow fracture healing, are also limited. Many of these comorbidities[19] co-occur, and their impact on fracture healing has not been well studied. Limited studies have investigated the efficacy of LIPUS on fracture healing in Africa, possibly due to restricted access and the prohibitive equipment cost.

MATERIALS AND METHODS

This prospective, randomised, controlled, double-blinded study with an evidence level of one is reported according to CONSORT guidelines (Figure 1)[19]. The study was conducted at two tertiary hospitals in Pretoria, Gauteng. Written informed consent was obtained from the hospital chief executive officers of the two hospitals and from the patients who agreed to participate in this study. The patients were informed of their right to withdraw without reason, and their withdrawal would not affect the services they received from their hospital. Between January and September 2016, 115 patients diagnosed with lower limb fractures and managed with open reduction internal fixation or external fixation were recruited from the orthopaedic ward and screened for eligibility; 94 were enrolled. Patients were recruited using a consecutive sampling method.

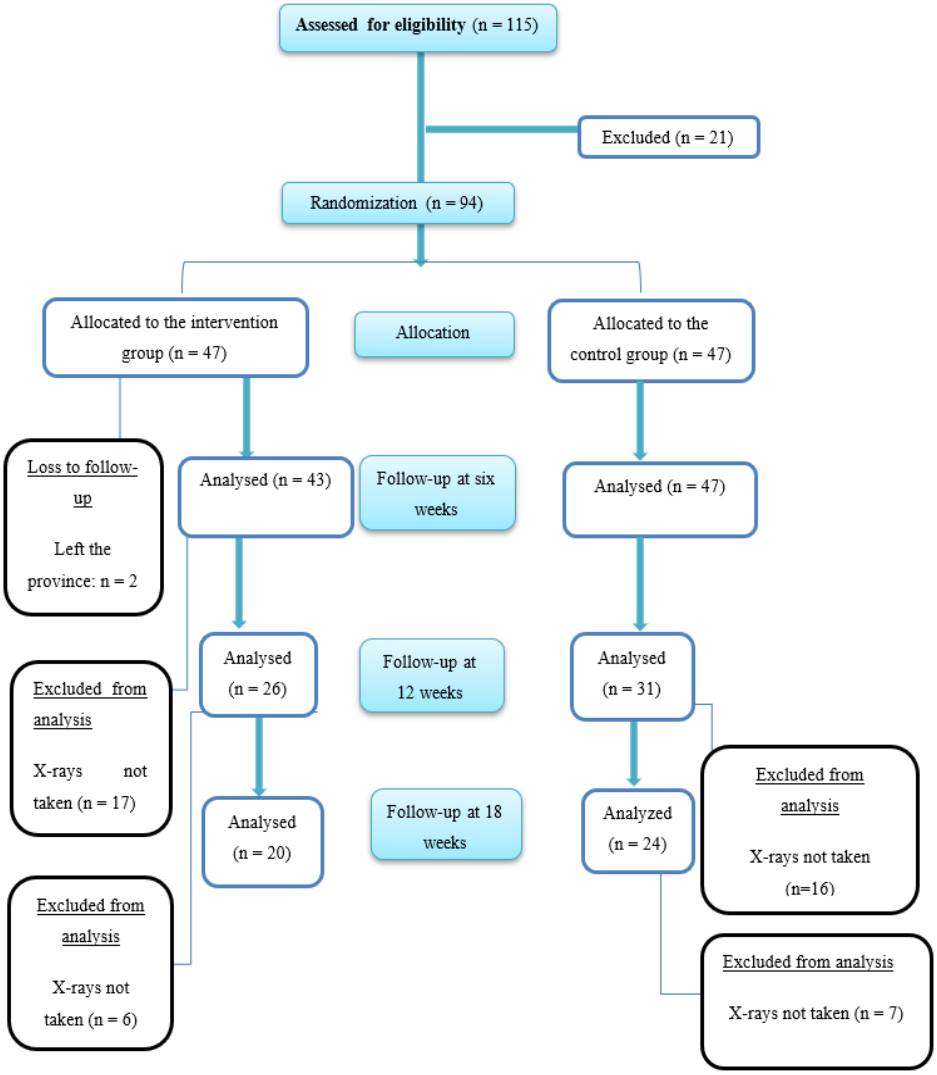

Fig. 1 — CONSORT flow diagram evaluating the efficacy of LIPUS in fracture healing.

We calculated that 90 participants had 80% power to detect a significant difference between participants treated with or without LIPUS at the 0.05 significance level. In blocks of six, with a 1:1 ratio, computer-generated random sampling was used to allocate patients to either the intervention or control group. The researchers, the radiologist appointed to interpret X-rays, and the patients were blinded to which machine was the actual or sham LIPUS. Only the technician from the sponsoring company was aware of the treatment allocation. The technician labelled the two machines as A or B machines. All patients aged 18 years and older with lower limb fractures managed with open reduction, internal fixation, or external fixation were enrolled in the study. We excluded patients with multiple fractures in one long bone, as the healing of one fracture may be hindered by other fractures. We also excluded patients who resided more than ten kilometres radius from the research settings to enable follow-up. Finally, we excluded patients with pathological fractures, which may alter bone healing outcomes. Patients were positioned comfortably, and the fractured area was fully exposed. The intervention group was treated with a LIPUS machine, and the control group was treated with an identical sham LIPUS machine. The technician pre-set both devices according to the instructions from the principal researcher at an intensity of 0.03 W/cm², a frequency of 1.5 MHz, and a pulsed width of 200 µs 10. Patients were treated for 20 days, with treatments administered every second day for 20 minutes. Patients were not kept at the hospital for 40 days of LIPUS treatment, but were followed up on discharge and treated at home. Follow-up X-rays were taken at six, 12, and 18 weeks, according to the hospital's routine. Due to ethical concerns about exposing the patients to radiation, the researcher was unable to take any X-rays if they were not asked to return for follow-up X-rays. A radiologist reported on the outcomes used to establish signs of fracture healing.

Patient demographics and operative information were documented before the surgery. Baseline X-rays were also reported before surgery, at six, 12 and 18 weeks of LIPUS intervention. The outcomes assessed were callus formation, cortical bridging, fracture gap and overall healing[20-22]. Callus formation was scored on a scale of 1 (yes) or 0 (no)[23]. We used the cortical bridging index to score the four cortices on a scale of one to four[24,25]. The presence of a fracture gap was scored on a scale of 1 (yes) or 0 (no). Primary healing of fractures can occur through either contact healing or reduction of the fracture gap. If the gap between the bone ends is less than 0.01 mm, the fracture can heal through contact healing[26]. The fracture was considered consolidated if there was callus formation; four cortices observed in the anteroposterior and lateral radiographic views were bridged, and overall healing was achieved if there was no fracture gap[21]. This study was exploratory in nature and did not include a pre-specified primary endpoint; multiple radiographic indicators were assessed to describe healing patterns. Following arguments by many researchers[27,28], we did not apply Bonferroni or similar adjustments because they test the universal null hypothesis (that all comparisons are simultaneously accurate), which is rarely relevant in clinical research. Our focus was on evaluating each radiographic indicator individually. Although multiple comparisons were performed, we believe that transparent reporting and framing the study as exploratory mitigates undue concern about inflated Type I error. When modelling a multivariate analysis for the timeframe of six to 18 weeks, using overall healing at six weeks in the control group as a reference, no significant interaction over time was found for the control group at 12 and 18 weeks, and the intervention group at six, 12, and 18 weeks. The findings reflect the reported lack of overall fracture healing by 18 weeks in the current study.

Statistical Analysis

An intention-to-treat (ITT) analysis was also conducted on the data, as the literature indicates that this analysis is essential for avoiding bias in the analysis of randomised trials[29]. Although controversy exists about whether ITT analysis should be completed with a strict view that no analysis with missing outcomes can be described, the European Medicines Agency has suggested that missing data should be imputed in clinical trials[30]. It has been suggested that an ITT analysis should be completed to accommodate the loss of outcomes and missing data, as emphasised by the Consolidated Standards of Reporting Trials (CONSORT) guidelines, to provide an unbiased estimate of the treatment effect[31]. Since the loss to outcome X-rays in this study was greater than 20%, the results of the ITT analyses are presented separately from the per-protocol analysis.

The missing data in this study could be considered missing at random (MAR) based on the loss of X-rays or not being taken due to the health care system in which the patients were treated. An analysis suited to MAR, a Generalised Estimation Equation (GEE) (Westgeest et al.) analysis to analyse (ITT) was used. The GEE analysis is well-suited for MAR in

longitudinal data with small sample sizes[32]. Following this, multivariate GEE models were fitted by adding gender and age as cofounding variables to adjust for potential confounding factors in the GEE models. Although several baseline variables were considered, multicollinearity diagnostics indicated instability when including all (age, diabetes, fracture site, fixation type, smoking); therefore, only gender and age were retained as confounding variables in the final models. Age and gender were included because they are fundamental demographic factors that may act as proxies for health-related variables. Older individuals often present with comorbidities such as diabetes or hypertension, which can delay bone repair, while gender differences are associated with hormonal influences, bone density, and lifestyle habits such as smoking and physical activity. Including these covariates helps partially account for these underlying variations without introducing multicollinearity from highly correlated clinical variables.

RESULTS

A total of 94 patients (100%) were enrolled in the study, and only 95.7% (n = 90) were analysed at six weeks (Figure 1). Due to unforeseen circumstances and a poor socioeconomic background, two patients were unable to be followed because they lacked electricity at home and were unable to attend hospital appointments for further LIPUS management. In contrast, the other two patients lived beyond the 10-kilometre radius of the healthcare facilities and were transferred to the local clinic for further management. Poor hospital follow-up to take X-rays prevented the researcher from recording all the outcomes at 12 and 18 weeks, as some patients felt restored and were therefore excluded from the study. This left 60.6 % (n = 57) and 46.8% (n = 44) of patients analysed at 12 and 18 weeks, respectively. This study had more male (68%) than female patients, though it was not statistically significant. The female patients were, on average, ten years older than the males; the youngest patient was 18, and the oldest was 82, both of whom were women. Femur fractures were the most prevalent fracture (60%) and were distributed relatively equally between the intervention and control groups (58.62% vs 61.40%, respectively). Open reduction internal fixation was the most common surgical management tool used (78.26%), with approximately 20% of patients in both groups treated using external fixation. Both groups had similar demographic characteristics, including smoking, diabetes, hypertension, and human immunodeficiency virus. There were significantly more hypertensive patients in the control group ($p < 0.05$) than in the intervention group.

Comparison of fracture healing in intervention and control groups over time

Callus formation

At six, 12 and 18 weeks, the ITT analysis results confirmed a greater increase in callus formation for the intervention group at all three time periods. Although there was no significant difference between the intervention and control groups in callus formation at six and 12 weeks, upon analysing the missing data, the difference between the groups at 18 weeks was significant.

Cortices bridged

The ITT results at six and 12 weeks showed that a higher percentage of participants in the intervention group had no cortices, with no significant difference between the two groups. At 18 weeks, a significantly higher percentage (84.44%) of participants in the intervention group had cortices present compared to those in the control group (53.06%), with a significant difference ($p = 0.013$).

Fracture gap

The ITT analysis yielded similar results to the per-protocol results, with a higher percentage of patients in the control group (83.63%; n = 40) having a fracture gap at six weeks and 57.14% (n = 28) at 12 weeks. The fracture gap was present in a lower percentage of participants, 23 (51.11%), in the intervention group, compared to the control group (63.27%; n = 31), at 18 weeks, although this difference was not statistically significant.

Overall healing

The ITT analysis yielded similar results, with no healing observed at six weeks and a small percentage of healing in both the intervention and control groups at 12 and 18 weeks. There was no significant difference between the groups for overall healing at any of the assessment periods. Although few patients had fractured healed at 12 weeks, the percentage was higher in the intervention group on the ITT analysis.
In summary, the ITT analysis indicates that the intervention group had a higher percentage of participants with callus formation and overall healing at six, 12 and 18 weeks. The control group had more cortices bridged and no fracture gap at both six and 12 weeks. In contrast, the intervention group had a

significantly higher percentage of participants with bridged cortices and a lower percentage with a fracture gap at 18 weeks. Although by 18 weeks, the rate of participants in the intervention group with positive signs of fracture healing was higher, this difference was not significantly greater than that of the control group, and the difference in radiological outcomes varied across the three time periods. It appears that, with callus formation, the LIPUS intervention may have accelerated callus formation in the first six weeks, with a significantly greater percentage of participants having bridged cortices at 18 weeks, as indicated by the ITT analysis.

Change in within-group outcomes related to fracture healing over time

Callus formation

The results for the ITT analysis of callus formation within the intervention and control groups differed from those of the per-protocol analysis in that both groups showed a significant change in callus formation from no callus formation at six to 12 weeks. The control group had one participant who changed from having calluses to no calluses formed, with an odds ratio of 0.07 (CI 0-0.46).

At 12 – 18 weeks, as in the per-protocol analysis, neither group showed significance in the change for the presence of callus, but in the control group, nine participants with an odds ratio of 1.28 (CI = 0.42 - 4.06) moved from callus formation to no callus formation. For the intervention group at 12 weeks, the odds for change in the presence of callus were 0.25 (CI=0-2.52) times lower than no change or an absence of callus formation. This indicates a higher odds ratio change for no callus formation in the control group over this time period. When the entire time period from six to 18 weeks was considered, both groups showed statistical significance in terms of change in the presence of callus formation for the per-protocol analysis. However, the ITT analysis indicated that the control group had a greater likelihood of change from callus to no callus formation in nine participants over the six- to 18-week period, as the odds were 0.42 (CI = 0.15-1.00) times lower for callus formation in this group.

This is confirmed in Figure 2, where, over the entire period of six to 18 weeks, the ITT analysis indicated that the intervention group had a higher mean callus formation throughout the study.

Cortical bridging

The results of cortical bridging on the ITT analysis reflected those on the per-protocol analysis for the study period. The difference for cortical bridging was also significant in the ITT analysis at six to 12 weeks and six to 18 weeks (Figure 3). At 12-18 weeks, the odds ratio for change from cortices bridged to no cortices bridged in the control group was higher at 16 (CI=2.48-670.96), which was statistically significant ($p<0.003$), while in the intervention group, the odds ratio in this period was only 0.2 (CI=0 – 1.78). On the ITT analysis from six to 18 weeks, however, the control group had an odds ratio of 0.26 (CI=0.07 – 0.72), a change from cortices bridged to no cortices bridged in the control group, compared to odds of zero (CI=0 - 0.14) for the intervention group. Over the entire study period of six-18 weeks, the mean cortices bridged was greater for the intervention group.

Fracture gap

The results for the ITT analysis were similar to those for the per-protocol analysis and showed statistical

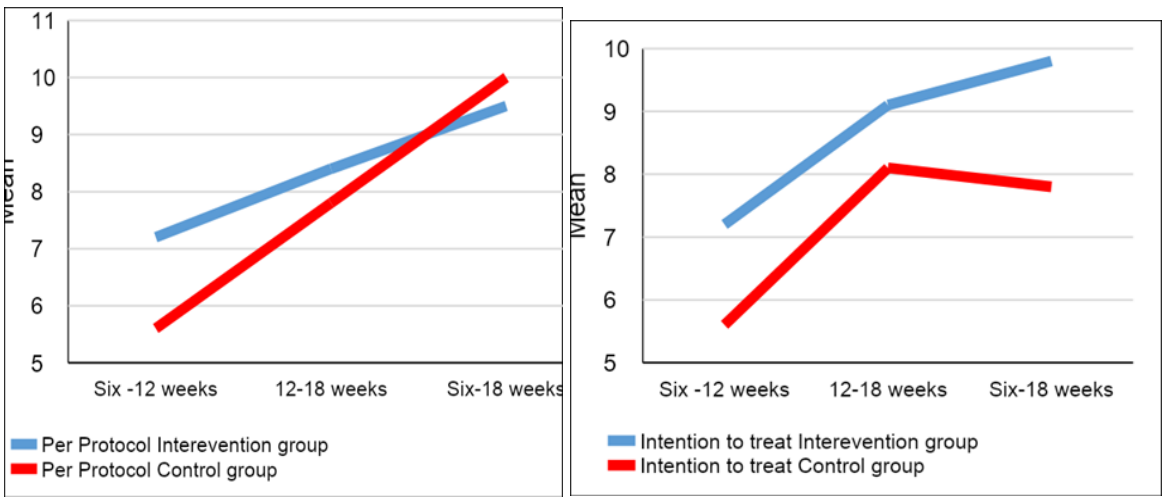

Fig. 2 — Callus formation over time – per protocol and intention to treat analysis.

significance for both the intervention and control groups (p = 0.000) in the reduction of the fracture gap at six to 12 weeks. The intervention group, however, had odds of 25 (CI = 4.09 - 1026.40) for less change in the presence of the fracture gap, while the control group had an odds ratio of zero (CI = 4.66 – 0) for less change in the presence of the fracture gap. On the ITT analysis, both groups showed statistically significant for change in the fracture gap with the intervention group having odds for change in the fracture gap 0.16 (CI = 0.01 - 0.74) and the control group of 0.23 (CI = 0.042 - 0.83) between 12-18 weeks where the ITT analysis indicated 12 and 13 participants changed from no fracture gap to a fracture gap.

As confirmed in Figure 4, the fracture gap resolution was lower in both groups between 12-18 weeks. The ITT analysis was also statistically significant at six to 18 weeks, indicating that fracture gap reduction was greater in the intervention group. The odds ratio for the change from no fracture gap to fracture gap was 0.56 (CI = 1.63 - 30.18) for the intervention group and 0.55 (CI = 1.20 - 51.06) for the control group, differing from the per-protocol analysis. These results were statistically significant, indicating similar results for both groups.

Overall healing

The results of the ITT analysis for overall healing were similar to those of the per-protocol analysis, with greater healing observed in both groups at 12-18 weeks. As for the per-protocol analysis, only participants in the control group changed from overall healing to no overall healing, with a slightly higher odds ratio of 2 (0.10 - 117.99). This finding was confirmed in Figure 5, which showed that the intervention group experienced greater overall healing on the ITT analysis at 12-18 weeks.

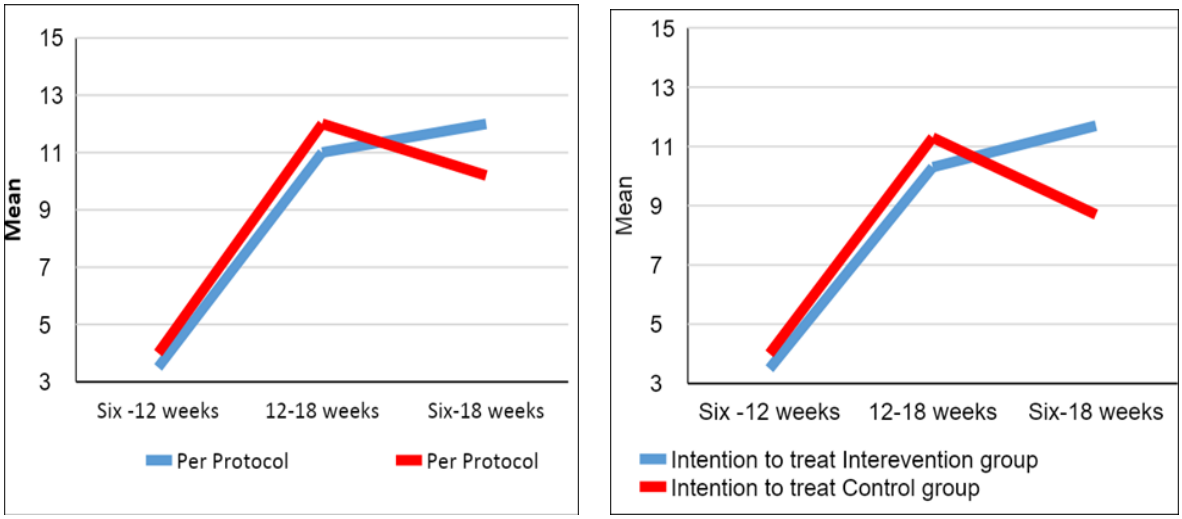

Fig. 3 — Cortices bridged over time – per protocol and intention to treat analysis.

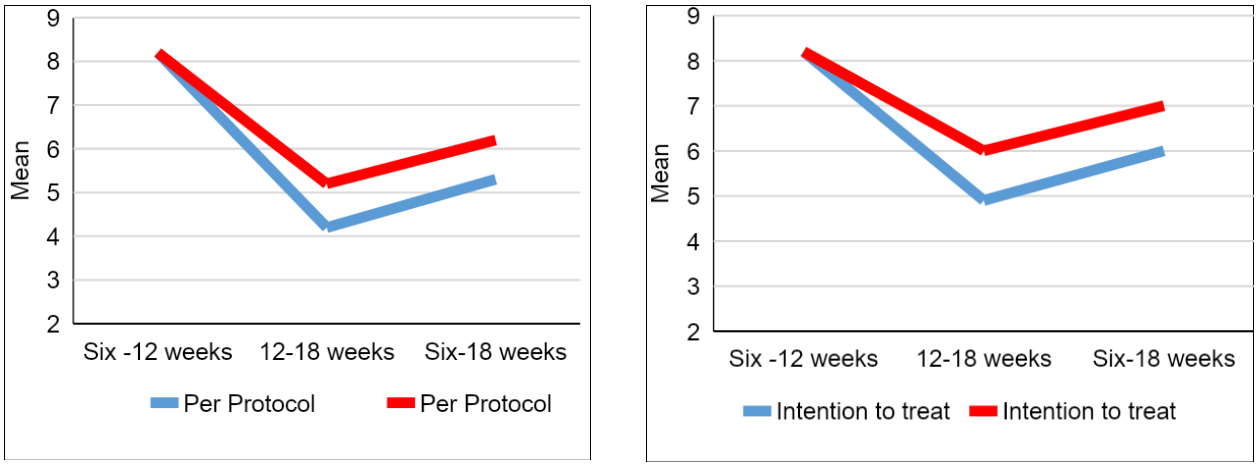

Fig. 4 — Presence of fracture gap over time – per protocol and intention-to-treat analysis.

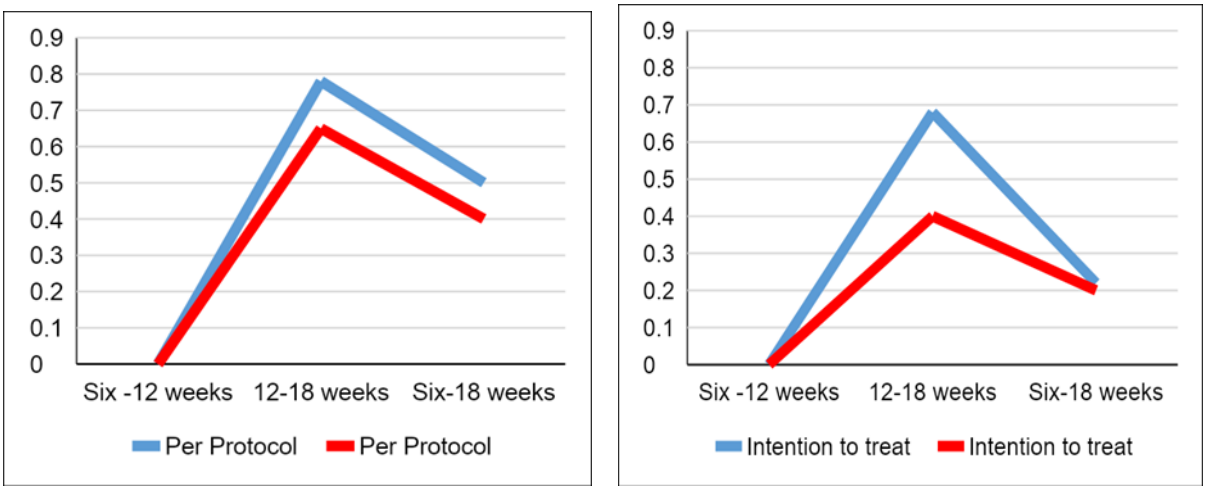

Fig. 5 — Overall healing over time – per protocol and intention to treat analysis.

In summary, the ITT analysis for the change within the groups indicates the intervention group and control groups had similar odds for fracture healing between six and 12 weeks, except for callus formation, which was greater by six weeks and during the six- to 12-week period for the intervention group. The odds ratio for change from callus formation or cortices bridged, no fracture gap and overall healing to no callus formation or cortices bridged, a fracture, and no overall healing was higher in the control group, indicating more consistent healing in the intervention group between 12 and 18 weeks, with lower odds ratios. These confirmed findings presented in the per-protocol analysis indicate that the LIPUS intervention may have protected the intervention group from as much deterioration in fracture healing as seen in the control group.

On the ITT analysis over the entire period from six to 18 weeks, the ITT analysis indicated the intervention group achieved greater mean callus formation, cortical bridging and reduction of the fracture gap than the control group.

Controlling for confounding variables

Multivariate GEE models were constructed to account for repeated measures across 6, 12, and 18 weeks and included age and gender as covariates. After adjustment, the group effect (intervention vs control) was not statistically significant for callus formation ($p = 0.249$), cortical bridging ($p = 0.783$), fracture gap ($p = 0.660$), or overall healing ($p = 0.884$). This indicates that, even when demographic factors and within-subject correlation were taken into account, the intervention did not demonstrate a significant effect. While earlier ITT and per-protocol analyses suggested some trends, such as slightly better callus formation early and cortical bridging later in the intervention group, these were unadjusted. The multivariate GEE results confirm that these trends do not persist after adjustment, suggesting that observed differences were likely due to random variation or demographic imbalance rather than a true intervention effect. However, given the substantial loss to follow-up and missing radiographic data, interpretation of these adjusted models should be cautious. The limited sample size at later time points reduces statistical power; therefore, these analyses complement rather than replace the simpler ITT and per-protocol findings. That being said, only the latter (the simpler ITT and per-protocol findings) are considered in the discussion which follows.

DISCUSSION

This study evaluated the efficacy of LIPUS treatment on lower-limb fracture healing in surgically managed patients. Our results indicate that the patterns of callus formation varied between the intervention and control groups in both per-protocol and intention-to-treat (ITT) analyses. During the per-protocol analysis, the intervention group exhibited consistent callus formation from 6 to 12 weeks, whereas the control group, starting with a lower initial level, showed a more pronounced increase and eventually outpaced the intervention group by 18 weeks. This implies that the intervention may enhance early callus formation, while the control group experiences a delayed but compensatory healing process. These observed trends align with the established biological mechanisms of fracture healing, in which callus formation speeds up between weeks 6 and 12, followed by phases of remodelling[6].

In contrast, the ITT analysis revealed that the intervention group consistently exhibited higher scores for callus formation over time, showing steady improvements up to 18 weeks. The control group demonstrated initial improvement but reached a plateau and began to decline after weeks 12 to 18. These results emphasise the ongoing advantage of the intervention in facilitating callus consolidation when all randomised participants are taken into account. Prior research has similarly demonstrated that LIPUS stimulates early cellular activity at the site of fractures, encouraging chondrocyte proliferation and mineralisation of the callus[8,11]. The per-protocol results further support the notion that the most considerable callus formation occurs within the initial 12 weeks, aligning with the biological period of secondary bone healing[6]. Importantly, while both groups reached their peak around weeks 12 to 18, the intervention group continued to show growth, in contrast to a slight decline in the control group. This sustained progression suggests that the intervention may help prevent regression or delayed union, a conclusion corroborated by clinical research that observes quicker fracture healing and enhanced callus morphology associated with LIPUS[33].

Although various systematic reviews have raised doubts regarding the clinical effectiveness of LIPUS in healing fractures, especially in those managed surgically. Our results align with studies suggesting that LIPUS can provide benefits in accelerating early callus formation and sustaining consolidation[15,34]. The discrepancy between per-protocol and intention-to-treat outcomes in our research highlights the importance of adherence, as the practical effectiveness of such treatments may diminish if patients fail to follow treatment guidelines. In summary, our results indicate that the intervention seems to promote early callus formation and support its consolidation compared to standard care. This holds significant clinical implications for mitigating delayed healing and non-union; however, additional research with larger participant groups and extended follow-up is necessary to verify functional outcomes.

Our results show a gradual increase in the number of cortices bridged between 6–12 weeks and 12–18 weeks, followed by a relative stabilisation during the 6–18 week period. This trend aligns with the anticipated development of secondary bone healing, where a callus forms and progressively connects multiple cortices before achieving complete cortical continuity[35]. The sharp rise observed from 6 to 18 weeks indicates active maturation and mineralisation of the callus, highlighting a critical phase of endochondral ossification[36].

When comparing the per-protocol and ITT analyses, both groups exhibited similar healing patterns, although minor differences in slope suggest potential variations in biological or mechanical factors. The intervention group (based on ITT) seemed to show a slight advantage in cortical bridging compared to the control group during the 6–18 week period. However, this effect was not consistently maintained across both analytical methods, reflecting findings from larger randomised controlled trials that have questioned the additional benefit of adjunctive therapies, such as LIPUS on cortical bridging[12,37].

The rise in the number of bridged cortices observed at 12–18 weeks aligns with the timeline for radiographic signs of union in most diaphyseal fractures, reinforcing the clinical relevance of cortical bridging as a proxy marker for healing[38]. Nevertheless, the slight levelling off that follows suggests that while bridging advances early on, full consolidation may take longer than 18 weeks, particularly in cases with biological or mechanical complications[39]. From a clinical perspective, these findings emphasise the importance of monitoring cortical bridging at regular intervals to assess healing progression and identify delayed union at an early stage. Therefore, radiographic evaluations should be combined with clinical assessments, such as pain and function, to provide a more reliable indicator of readiness for weight-bearing or the removal of hardware[40].

Our results indicate that the fracture gap first decreases between 6 to 12 weeks, then increases at 12–18 weeks, and shows partial reduction again between 6 to 18 weeks. This fluctuating trend differs from the consistent reduction noted in other studies on fracture healing, implying that bone repair may not always progress in a linear manner. The variability in gap progression may be due to differences in biological healing stages, mechanical loading conditions, or patient-related factors, such as adherence to weight-bearing limitations[35,40]. The temporary widening of the fracture gap between 12 to 18 weeks could signify delayed callus maturation or micro-motion at the fracture location, both of which can hinder mineralisation and bridging[41]. Prior research has emphasised that mechanical stability plays a crucial role in gap behaviour, with insufficient stability resulting in widening or persistence of gaps prior to eventual bridging[42]. In both per-protocol and ITT analyses, the control group exhibited smaller fracture gaps relative to the intervention group. This

observation raises the possibility that LIPUS had a minimal impact on hastening fracture union in this population, consistent with recent high-quality RCTs indicating little clinical advantage of biophysical stimulation for long-bone healing[12,37]. The continued superiority of the control group across both analyses bolsters the dependability of this finding.

The clinical note is that support for fracture healing should focus not only on encouraging early callus development but also on maintaining sustained mechanical stability and favourable biological conditions for closing the gap over the medium term. Emphasising rehabilitation strategies that avoid early loading, along with close radiographic monitoring, may help identify and manage mid-term widening before it adversely affects healing outcomes.

Our results indicate that overall healing significantly improved from the 6 to 12-week period to the 12 to 18-week mark, followed by a slight decrease at the 6 to 18-week mark. This pattern aligns with the biological stages of fracture healing, where the mid-phase is characterised by callus formation and cortical bridging, followed by a gradual remodelling process and a reduction in radiographic change as consolidation continues[35]. The peak seen at 12–18 weeks corresponds to the crucial phase of endochondral ossification and mineralisation, which are key processes that provide radiographic indicators of union in long bones[6].

When comparing the intervention and control groups, the intervention group exhibited slightly higher healing indices during the mid-phase. However, this difference was not sustained during the later 6 to 18-week follow-up period, where the trends aligned. This pattern aligns with findings from extensive multicenter studies, which suggest that adjunctive treatments, such as low-intensity pulsed ultrasound, may enhance early radiographic signs of healing but do not have a significant impact on long-term outcomes[12,37]. The eventual decline noted at the 6–18 week timeframe may signify the shift from callus formation to remodelling, during which radiographic indicators of healing reach a plateau despite ongoing biological repair[41].

The clinical significance of these results suggests that radiographic evaluations of healing should be considered in conjunction with functional recovery and symptom relief. Although early progress may indicate biological responsiveness, the long-term path is influenced by various factors such as mechanical stability, overall health, and patient compliance with rehabilitation[39,40]. Thus, overall healing indices provide important insights into the temporal progression of fracture healing, but should be seen in conjunction with cortical bridging and fracture gap assessments for a complete evaluation of union.

CONCLUSION

This research indicated that the healing of fractures, evaluated through cortical bridging, gap size, and overall healing metrics, progressed along a nonlinear path over the 18-week span. Cortical bridging served as a reliable measure of union, while the variability in the fracture gap illustrated the mechanical conditions and biological intricacies involved in the healing process. The overall healing reached its highest point between 12 and 18 weeks, underscoring the vital phase of callus maturation, but did not continue to improve afterwards. Although additional treatments seemed to slightly enhance mid-term radiographic outcomes, they did not offer lasting advantages when compared to control groups. Notably, the results were affected by a significant number of participants lost to follow-up and missing radiographic data, which calls for careful interpretation. Further studies with improved patient retention, comprehensive imaging records, and larger participant groups are necessary to strengthen the evidence and support clinical decision-making in the treatment of fractures.

Limitations

The research encountered significant challenges due to missing information, primarily inaccessible radiographs and patients who failed to attend their scheduled follow-ups. This resulted in a considerable loss to follow-up, potentially leading to attrition bias and diminishing the statistical strength of the analyses. Due to the high attrition rate and large proportion of missing data at later time points, sensitivity analysis (complete-case vs. non-complete-case) was not performed, as the required sample size for meaningful comparison would have been too small to yield reliable estimates. Although an intention-to-treat approach using GEE was utilised to mitigate the impact of these losses under the assumption of MAR, it was insufficient to fully address the missing imaging data, limiting the ability to accurately evaluate healing patterns across all participants. As a result, the findings should be interpreted with caution regarding their generalisability. Furthermore, advanced longitudinal models such as Kaplan-Meier survival analysis, Cox regression, or mixed-effects models were not employed due to the exploratory nature of the study

and the high attrition rate, which reduced the feasibility of these complex approaches. Future research should incorporate these methods to strengthen inference and mitigate concerns about multiplicity. Moreover, radiographic assessment in this study relied on simple categorical measures (presence of callus, number of bridged cortices) rather than validated scoring systems such as RUST or RUSH. This was due to resource constraints and the pragmatic nature of the trial in a low-resource setting, where implementing standardised scoring systems and training multiple assessors was not feasible. Inter-observer agreement (e.g., kappa or ICC) was not assessed, limiting the ability to confirm the consistency and reliability of radiographic interpretations. Future research should incorporate validated scoring systems and assess inter-observer agreement to enhance methodological rigour.

Recommendations

Future research should focus on approaches to reduce loss to follow-up, such as implementing patient tracking systems, making reminder calls, and utilising digital platforms to boost retention and ensure access to radiographic data. Integrating electronic health records may also promote more comprehensive data collection and reduce reliance on retrospective imaging. Furthermore, conducting sensitivity analyses that include both per-protocol and modified intention-to-treat methods is advised to strengthen findings when dealing with missing data. Lastly, multicentre trials involving larger, more diverse populations could enhance the generalizability of results and provide deeper insights into fracture healing patterns in real-world settings.

Funding: The study was self-funded.

Competing interests: The authors declare no competing interests. ENRAF Mediotronics sponsored the LIPUS machines, but no funding was provided. The authors declare no conflicts of interest with the sponsoring company.

Author Contribution Statement: All authors contributed to the conception and design of the study. Nontembiso Magida, Hellen Myezwa and Witness Mudzi performed material preparation. Nontembiso Magida wrote the first draft of the manuscript. Eustasius Musenge, Marien Alet Graham and Aneesa Mohamad Khan contributed to the data acquisition, analysis, and interpretation. All authors commented on all the versions of the manuscript. All authors read and approved the final version of the manuscript.

Ethical Approval: The study was approved by the Ethics and Research Committee of the University of the Witwatersrand (M150236). This study was performed in line with the Declaration of Helsinki.

Consent to participate: Informed written consent was obtained from all participants prior to data collection.

Consent to publish: Participants were informed of the publication during data collection.

Acknowledgement: We acknowledge Prof Cheryl Tosh (University of Pretoria) for editing and supporting this manuscript.

REFERENCES

1. Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, et al. Epidemiology of fracture nonunion in 18 human bones. JAMA Surgery. 2016; 151(11):e162775-e.
2. Leighton R, Watson JT, Giannoudis P, Papakostidis C, Harrison A, Steen RG. Healing of fracture nonunions treated with low-intensity pulsed ultrasound (LIPUS): A systematic review and meta-analysis. Injury. 2017; 48(7):1339-47. doi:10.1016/j.injury.2017.05.016
3. Ekegren CL, Edwards ER, De Steiger R, Gabbe BJ. Incidence, costs and predictors of non-union, delayed union and malunion following long bone fracture. International journal of environmental research and public health. 2018; 15(12):2845.
4. Singaram S, Naidoo M. The physical impact of long bone fractures on adults in KwaZulu-Natal. The South African journal of physiotherapy. 2020; 76(1):1393. doi:10.4102/sajp.v76i1.1393
5. Bennett PM, Stewart SK, Dretzke J, Bem D, Penn-Barwell JG. Preclinical therapies to prevent or treat fracture non-union: A systematic review. PloS one. 2018; 13(8):e0201077. doi:10.1371/journal.pone.0201077
6. Einhorn TA, Gerstenfeld LC. Fracture healing: Mechanisms and interventions. Nature Reviews. Rheumatology. 2015; 11(1):45-54. doi:10.1038/nrrheum 2014.164
7. Gómez-Barrena E, Rosset P, Lozano D, Stanovici J, Ermthaller C, Gerbhard F. Bone fracture healing: Cell therapy in delayed unions and nonunions. Bone. 2015; 70:93-101. doi:10.1016/j.bone.2014.07.033
8. Palanisamy P, Alam M, Li S, Chow SKH, Zheng Y-P. Low-intensity pulsed ultrasound stimulation for bone fracture healing: A review. Journal of ultrasound in medicine: official journal of the American Institute of Ultrasound in Medicine. 2022; 41(3):547-63. doi:10.1002/jum.15738
9. Romanò CL, Kirienko A, Sandrone C, Toro G, Toro A, Valente EP, et al. Low-intensity pulsed ultrasound in the treatment of nonunions and fresh fractures: A case series. Trauma Care. 2022; 2(2):174-84. doi:10.3390/traumacare2020014
10. Harrison A, Lin S, Pounder N, Mikuni-Takagaki Y. Mode & mechanism of low intensity pulsed ultrasound (lipus) in fracture repair. Ultrasonics. 2016; 70:45-52.
11. Song MH, Kim T-J, Kang SH, Song H-R. Low-intensity pulsed ultrasound enhances callus consolidation in distraction osteogenesis of the tibia using the lengthening over the nail technique. BMC Musculoskeletal Disorders. 2019; 20(1):108. doi:10.1186/s12891-019-2490-7
12. Busse JW, Bhandari M, Einhorn TA, Schemitsch E, Heckman JD, Tornetta P, 3rd, et al. Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (trust): Randomised clinical trial. BMJ (Clinical research ed.). 2016; 355:i5351. doi:10.1136/bmj.i5351
13. Pounder NM, Jones JT, Tanis KJ. Design evolution enhances patient compliance for low-intensity pulsed ultrasound device usage. Medical devices (Auckland, N.Z.). 2016; 9:423-7.

14. Tarride JE, Hopkins RB, Blackhouse G, Burke N, Bhandari M, Johal H, et al. Low-intensity pulsed ultrasound for treatment of tibial fractures: An economic evaluation of the trust study. The bone & joint journal. 2017; 99-B(11):1526-32. doi:10.1302/0301-620X.99B11.BJJ-2017-0737
15. Schandelmaier S, Kaushal A, Lytvyn L, Heels-Ansdell D, Siemieniuk RAC, Agoritsas T, et al. Low intensity pulsed ultrasound for bone healing: Systematic review of randomised controlled trials. The BMJ. 2017; 356 doi:10.1136/bmj.j656
16. Poolman RW, Agoritsas T, Siemieniuk RA, Harris IA, Schipper IB, Mollon B, et al. Low intensity pulsed ultrasound (lipus) for bone healing: A clinical practice guideline. Bmj. 2017; 356
17. Berber R, Aziz S, Simkins J, Lin SS, Mangwani JDoORNJMSBSNNJUSA. Low intensity pulsed ultrasound therapy (lipus): A review of evidence and potential applications in diabetics. Journal of Clinical Orthopaedics and Trauma: Supplement 4. 2020; 11(Supplement 4):S500-S5. doi:10.1016/j.jcot.2020.03.009
18. Kinami Y, Noda T, Ozaki T. Efficacy of low-intensity pulsed ultrasound treatment for surgically managed fresh diaphyseal fractures of the lower extremity: Multi-centre retrospective cohort study. Journal of Orthopaedic Science. 2013; 18(3):410-8.
19. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. Consort 2010 statement: Extension to randomised pilot and feasibility trials. BMJ [Internet]. 2016; 355. [cited Access Year Access Date|]|. Available rom: URL
20. Azevedo FASd, Cotias RB, Azi ML, Teixeira AAdA. Reliability of the radiographic union scale in tibial fractures (RUST). Revista Brasileira de Ortopedia. 2017; 52:35-9.
21. Hungri JOS, Mercadante MT. Open tibial shaft fractures. Treatment with intramedullary nailing after provisional stabilisation with a non-penetrating external fixator. Revista Brasileira de Ortopedia. 2013; 48:482-90.
22. Kooistra BW, Dijkman BG, Busse JW, Sprague S, Schemitsch EH, Bhandari M. The Radiographic Union Scale in Tibial Fractures: Reliability and Validity. Journal of Orthopaedic Trauma. 2010; 24:S81-S6.
23. Eastaugh-Waring S, Joslin C, Hardy J, Cunningham J. Quantification of fracture healing from radiographs using the maximum callus index. Clinical Orthopaedics and Related Research®. 2009; 467(8):1986-91.
24. Azevedo Filho FASd, Cotias RB, Azi ML, Teixeira AAdA. Reliability of the radiographic union scale in tibial fractures (rust). Revista Brasileira de Ortopedia. 2017; 52(1):35-9.
25. Bhandari M, Chiavaras MM, Parasu N, Choudur H, Ayeni O, Chakraverty R, et al. Radiographic union score for the hip substantially improves agreement between surgeons and radiologists. BMC Musculoskeletal Disorders. 2013; 14(1):70.
26. Marsell R, Einhorn TA. The biology of fracture healing. Injury. 2011; 42(6):551-5.
27. Barnett MJ, Doroudgar S, Khosraviani V, Ip EJ. Multiple comparisons: To compare or not to compare, that is the question. Research in Social and Administrative Pharmacy. 2022; 18(2):2331-4.
28. Perneger TV. What's wrong with Bonferroni adjustments? Bmj. 1998; 316(7139):1236-8.
29. Newell DJ. Intention-to-Treat Analysis: Implications for Quantitative and Qualitative Research. International journal of epidemiology. 1992; 21(5):837-41.
30. European Medicines Agency [Internet]. Guideline on missing data in confirmatory clinical trials. 2010 [cited 2018 5th March]. Available from: http://www.ema.europa.eu/ema/pages/includes/document/open-document.jsp.
31. Gupta SK. Intention-to-treat concept: A review. Perspectives in clinical research. 2011; 2(3):109-12. doi:10.4103/2229-3485.83221
32. Shen CW, Chen YH. Model selection for generalised estimating equations accommodating dropout missingness. Biometrics. 2012; 68(4):1046-54. doi:10.1111/j.1541-0420.2012.01758.x
33. Kamath JB, Jayasheelan N, Reddy B, Muhammed S, Savur A. The effect of low-intensity pulsed ultrasound therapy on fracture healing. Muller Journal of Medical Sciences and Research. 2015; 6(1):49-53.
34. Poolman RW, Agoritsas T, Siemieniuk RAC, Harris IA, Schipper IB, Mollon B, et al. Low intensity pulsed ultrasound (lipus) for bone healing: A clinical practice guideline. BMJ [Internet]. 2017; 356. [cited Access Year Access Date|]|. Available rom: URL
35. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. Nature Reviews Rheumatology. 2012; 8(3):133.
36. Laubach M, Hildebrand F, Suresh S, Wagels M, Kobbe P, Gilbert F, et al. The concept of scaffold-guided bone regeneration for the treatment of long bone defects: Current clinical application and future perspective. Journal of functional biomaterials. 2023; 14(7):341.
37. Griffin XL, Parsons N, Costa ML, Metcalfe D. Ultrasound and shockwave therapy for acute fractures in adults. 2014; doi:10.1002/14651858.CD008579.pub3
38. Whelan DB, Bhandari M, Stephen D, Kreder H, McKee MD, Zdero R, et al. Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation. Journal of Trauma and Acute Care Surgery. 2010; 68(3):629-32.
39. Giannotti S, Bottai V, Dell'Osso G, Pini E, De Paola G, Bugelli G, et al. Current medical treatment strategies concerning fracture healing. Clinical cases in Mineral and Bone Metabolism. 2013; 10(2):116.
40. Morshed S. Current options for determining fracture union. Advances in medicine. 2014; 2014
41. Augat P, von Rüden C. Evolution of fracture treatment with bone plates. Injury. 2018; 49:S2-S7.
42. Epari DR, Kassi J-P, Schell H, Duda GN. Timely fracture-healing requires optimisation of axial fixation stability. JBJS. 2007; 89(7):1575-85.