Follow us @BoneJointOpen

Freely available online OPEN ACCESS

BJO

GENERAL ORTHOPAEDICS

Is a staged reloading protocol effective to time the removal of circular frames?

A RETROSPECTIVE ANALYSIS

V. Sadekar,
A. T. Watts,
E. Moulder,
P. Souroullas,
Y. Hadland,
E. Barron,
R. Muir,
H. K. Sharma

From Hull Royal Infirmary, Hull, UK

Aims

The timing of when to remove a circular frame is crucial; early removal results in refracture or deformity, while late removal increases the patient morbidity and delay in return to work. This study was designed to assess the effectiveness of a staged reloading protocol. We report the incidence of mechanical failure following both single-stage and two stage reloading protocols and analyze the associated risk factors.

Methods

We identified consecutive patients from our departmental database. Both trauma and elective cases were included, of all ages, frame types, and pathologies who underwent circular frame treatment. Our protocol is either a single-stage or two-stage process implemented by defunctioning the frame, in order to progressively increase the weightbearing load through the bone, and promote full loading prior to frame removal. Before progression, through the process we monitor patients for any increase in pain and assess radiographs for deformity or refracture.

Results

There were 244 frames (230 patients) included in the analyses, of which 90 were Ilizarov type frames and 154 were hexapods. There were 149 frames which underwent single-stage reloading and 95 frames which underwent a two-stage reloading protocol. Mechanical failure occurred after frame removal in 13 frames (5%), which suffered refracture. There were no cases of change in alignment. There was no difference between refracture patients who underwent single-stage or two-stage reloading protocols ($p = 0.772$). In all, 14 patients had failure prevented through identification with the reloading protocol.

Conclusion

Our reloading protocol is a simple and effective way to confirm the timing of frame removal and minimize the rate of mechanical failure. Similar failure rates occurred between patients undergoing single-stage and two-stage reloading protocols. If the surgeon is confident with clinical and radiological assessment, it may be possible to progress directly to stage two and decrease frame time and patient morbidity.

Cite this article: *Bone Jt Open* 2022;3-5:359–366.

Keywords: dynamization, frame removal, ilizarov, reloading, failure, refracture, hexapod, nonunion, deformity

Correspondence should be sent to Arun T Watts; email: arun_watts@hotmail.co.uk;arun.watts2@nhs.net

doi: 10.1302/2633-1462.35.BJO-2021-0179.R1

Bone Jt Open 2022;3-5:359–366.

Introduction

Ilizarov methods were introduced to the western world in the early 1980s by the Lecco group. In the initial period, the Ilizarov technique was primarily used in salvage situations; however, the indications have broadened, and it is now the primary device for a number of complex and sometimes simple orthopaedic conditions.[1,2]

Circular frame surgery can cause pain, pin site infections, and morbidity in patients. Early frame removal can lead to refracture or change in alignment (plastic deformation), while unduly prolonging the time in frame increases the patient morbidity and complications.[3]

Radiological assessment of union with a circular frame in situ can be challenging due to multiple opaque metal parts obscuring the view. Complex fracture patterns also make radiological assessment difficult. Despite there being multiple techniques to determine fracture union, including imaging, mechanical testing, and serum markers,[3,4,5,6] the most prevalent are the clinical assessment (pain or tenderness) of the fracture site and imaging (e.g. radiography, CT).[3] Difficulty in weightbearing can be used to identify patients with delayed union or nonunion. However, in patients with a circular frame, pin site infection and the frame hardware can make the clinical and radiological assessment more difficult.[7,8] CT is a commonly used imaging technique, but often does not provide the desired confidence to clinicians, and often over reports nonunion.[9,10]

Nonunion or premature frame removal has a significant social and psychological impact on the patient, with huge financial implications for both the patient and society through healthcare costs and loss of earnings. Repeat procedures cause patient morbidity, and increased bed occupancy in hospitals.[4,6-8,11,12]

Previous work by the Chertsey Group[3] found that a staged reloading protocol was a safe, simple, and reliable technique to determine the time for removal of a circular frame. This was a study conducted on a small cohort of 36 tibial fracture patients using an Ilizarov type frame, and they reported no incidence of refracture, nonunion, or malunion at 12 months.

A staged reloading protocol is the preferred approach for frame removal in our unit. We designed this study to assess the effectiveness of a staged reloading protocol in all patients with a circular frame of any design and investigated the risk factors for mechanical failure.

The aims of this study are:

1. To assess the effectiveness of a staged reloading protocol and describe the incidence of mechanical failure of the bone following frame removal;
2. To analyze associated risk factors for mechanical failure; and
3. To describe the incidence of refracture and change in alignment in patients undergoing a single-stage and two-stage reloading protocol.

Mechanical failure is defined as either a refracture or radiological deformity of > 5° in either plane during the three-month follow-up period.

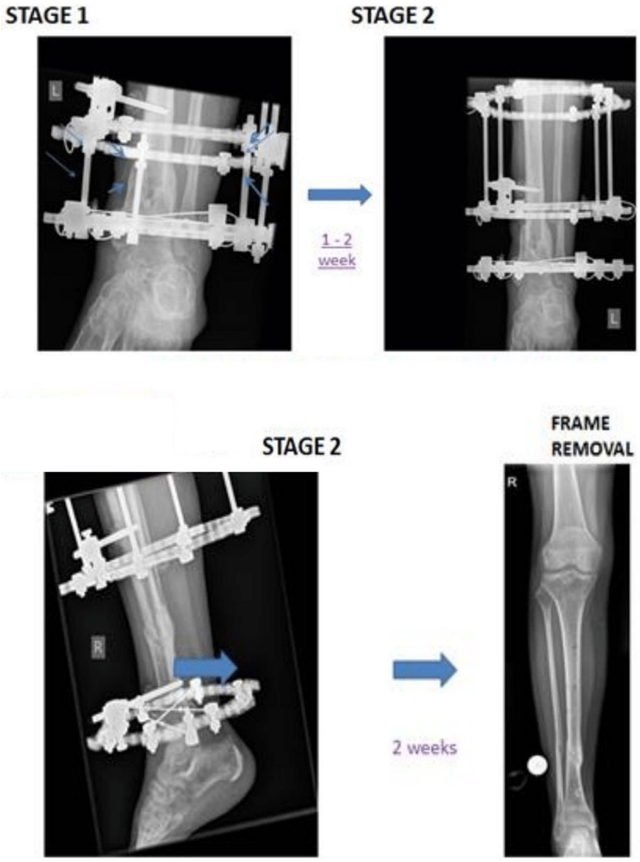

Fig. 1

The protocol in standard scenarios. Stage one: the nuts are loosened at the end of each threaded rod to allow axial movement across the fracture site. Stage two: the rods are removed to allow free movement. The protocol can proceed directly to stage two in hexapod frames, with removal of the hexapod struts to allow free movement.

Methods

This was a retrospective study undertaken at Hull Royal Infirmary, UK, a tertiary limb reconstruction referral centre. The study was registered and had institutional approval (no: 2017.137). Consecutive patients were identified from our department frame database, and electronic patient records were reviewed. Both trauma and elective cases were included of all ages, frame types, and pathologies who underwent circular frame treatment. Patients were excluded from the study if they were lost to follow-up, or if their treatment deviated from the reloading protocol, either by clinician or patient choice.

We consider dynamization to be a process which decreases the stiffness of the frame, to shift part of the load from the frame to the bone. This is performed by loosening the threaded rod nuts or struts of the frame then retightening the construct. This shifts some load from the frame to the bone, but there is no material shift in the frame. Dynamization may be done according to the clinical and radiological findings at any stage in the management of the patient, but is often practiced in early stages of the treatment.

We use the term reloading for the final stages of frame management. We defunction the frame to load the bone to test the integrity of the fracture or regenerate site, henceforth referred to as the fracture site. Stage one reloading provides full axial loading, with torsional and cantilever support from the threaded rods. Stage two reloading fully loads the bone in all axes. This improves

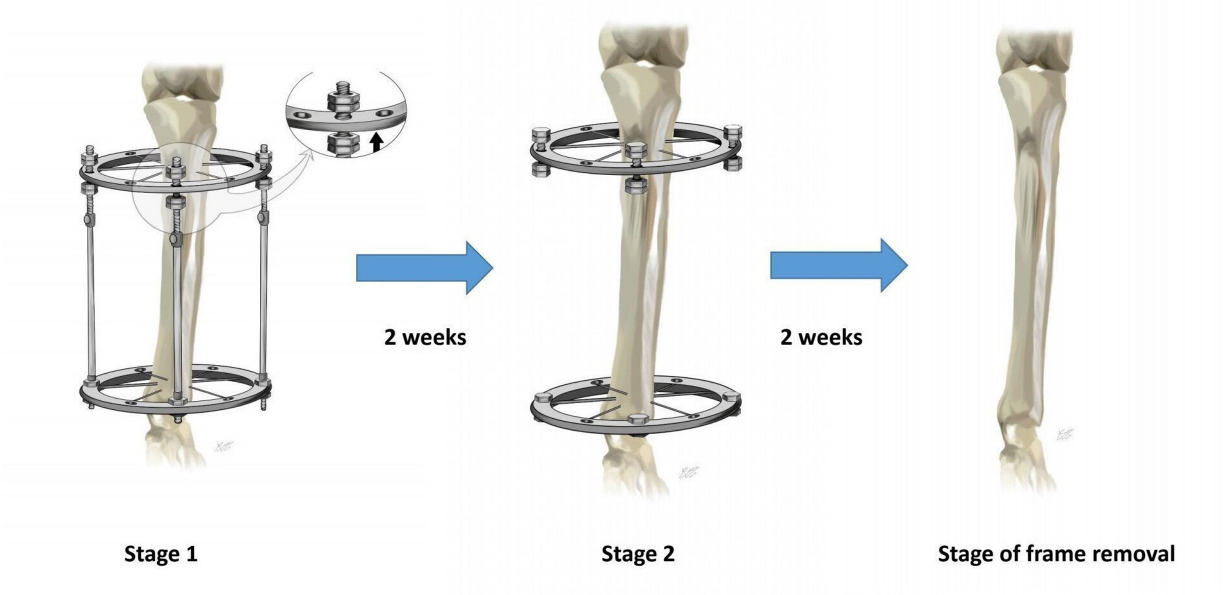

Fig. 2

Schematic representation of our protocol. (Picture credit: Ms Savni Panandikar).

Table I. Showing single-stage and two-stage groups well matched.

Variable	Two-stage protocol	Single-stage protocol	p-value*
Mean age, yrs (SD)	46 (16)	42 (18)	0.133
Sex, n			
Male	64	103	0.084
Female	31	46	
Immunosuppressed	0	1	
Condition, n			
Rickets	0	3	
Osteogenesis imperfecta	1	1	
Asthma/COPD	3	10	0.232
Steroid use	1	3	
Current/previous cancer history	2	2	
Peripheral vascular disease	1	1	
Cardiovascular disease	5	6	0.651
Diabetes	6	16	0.241
Smoking status	42	52	0.183

*Chi-squared test.
COPD, chronic obstructive pulmonary disease; SD, standard deviation.

radiological assessment and allows for assessment of clinical union to prevent premature frame removal.

The two stages (Figure 1) are described below, with a schematic description in Figure 2. Patients with a Hexapod frame can proceed to directly to stage two (Figure 1) or have their struts exchanged for threaded rods and proceed through stage one. Patients who proceed directly to stage two are considered to have had a single-stage reloading protocol. Patients who proceed through stage one and stage two are considered to have had a two-stage reloading protocol.

Most patients were allowed to fully weightbear throughout, although this was at the clinician's discretion. If necessary, the reloading stage was reversed based on clinical and radiological assessment by the clinician. After frame removal, patients were seen at two weeks for clinical assessment, then for radiological and clinical assessment at six weeks.

Stage one. The nuts are loosened at one end of each of the threaded rods which span the fracture site. As the patient mobilizes, the loose nuts may move and fall off the threaded rod. To prevent this, an extra nut is tightened against the ultimate nut. The nuts are not completely removed as the patient is taught to stabilize the construct in the event of pain at the fracture site, or excessive irritation at the wire sites overnight when in bed. This stage provides full axial load bearing through the bone, but provides some support in torsion and cantilever loading. Preservation of the ultimate nuts also provides a 'stopper' to prevent catastrophic failure of the construct. Before the patient leaves the hospital, they are asked to walk for 20 minutes. If they report an increase in pain at the fracture site, this reloading step is reversed and the patient is reviewed again in four to six weeks. If there are no clinical concerns, they are reviewed in a further one to two weeks and progressed to stage two. No routine imaging is done in between stage one and stage two.

Stage two. Following successful completion of stage one, patients are progressed to stage two. In this stage, all rods across the fracture sites are removed, or all struts are loosened. This removes all support from the frame across the fracture site and allows full and normal loading in all three axes. Before the patient leaves the hospital, they are

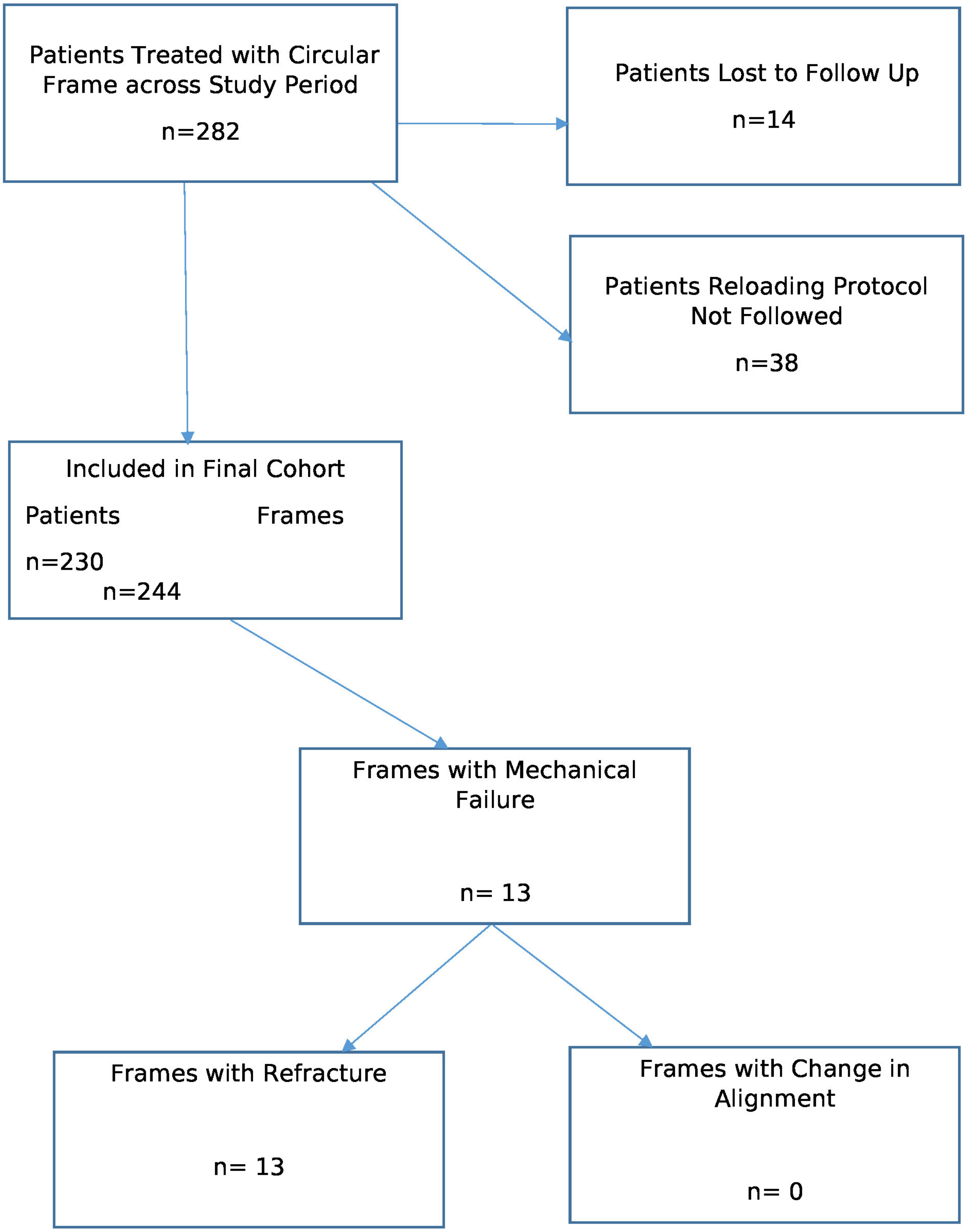

Fig. 3

Flow diagram of patients who were included in the study.

asked to walk for 20 minutes. If they report an increase in pain at the fracture site, this reloading step is reversed and the patient is reviewed again in four to six weeks. The patient should be warned to expect an increase in pin site pain and irritation during this stage, and may need to take some rods or struts home to stabilize the frame when sleeping. Patients are reviewed in a further one to two weeks where radiological and clinical healing is confirmed prior to frame removal.

Statistical analysis. Data were collected on demographics, comorbidities, treatment indications, and frame types. Digital radiographs were analyzed on a picture archiving and communication system (PACS). If data were missing, they were excluded for that variable. Data were analyzed on SPSS (version 28; IBM, USA). Patient characteristics were assessed for comparability between those undergoing single-stage and two-stage procedures. Data were assessed for normality, and for non-parametric data a chi-squared test was performed. A multivariate analysis with 95% confidence intervals were used to assess risk factors for refracture. A p-value < 0.05 was considered significant.

Results

We identified 282 patients who had undergone circular frame treatment during the study period. Of these, 230 patients (244 frames) underwent a reloading protocol and were included in the present analysis. Figure 3 shows the flow diagram of patients included in the study.

Of the 244 frames, 167 were male and 77 were female. The mean age was 44 years (42 to 46). Patient demographics and comorbidities are summarized in Table I. There were no significant differences between patients undergoing a single-stage and a two-stage reloading protocol. There were 149 and 95 patients who underwent a single-stage and two-stage protocol, respectively. The mean time until commencement of the reloading protocol was 201 days (standard deviation (SD) 7), and 180 days (SD 9) for single-stage and two-stage, respectively. Table II shows characteristics, including indications and bone segments of patients undergoing both single-stage and two-stage protocols. The tibial shaft was the most commonly injured bone segment. The elective indications included ankle fusions, knee arthrodesis following failed arthroplasty, limb lengthening, femoral osteomyelitis, infected tibial nail, tibial nonunion, and deformity corrections. A pin site or other infection was identified in 46 frames (19%) and secondary bone grafting was performed in 26 frames (11%).

During the reloading process, 14 frames had the protocol reversed; 11 in stage one and three in stage two of the reloading protocol. All of these patients were successful in their subsequent reloading and frame removal.

A total of 144 frames were removed in clinic, under Entonox, while 100 were removed in theatre. A total of 234 limb segments were allowed to fully weightbear immediately post-frame removal. However, at the surgeons' discretion, three were non-weightbearing and seven were partial weightbearing for a period of up to six weeks, and ten patients were treated in a plaster cast.

Table II. Frame characteristics.

Variable	Two-stage protocol	Single-stage protocol
Type of frame, n		
Hexapod	6	148
Ilizarov	89	1
Type of procedure, n		
Trauma	84	112
Elective	11	37
Type of fracture, n		
Open	18	41
Closed	77	108
Bone segment, n		
Femur	2	3
Tibia	31	104
Ankle	39	27
Knee	23	13

Following frame removal, 13 out of 244 frames (5%) had mechanical failure. There were 13 patients who had a refracture. No patients had change in alignment (> 5°) without fracture. One patient sustained the refracture during a fall.

Multivariate logistic regression analysis was performed to identify factors associated with refracture during treatment (See Table III). Age ($p = 0.006$) was the only factor considered significant for refracture. Refracture was not associated with choice between single-stage or two-stage reloading ($p = 0.772$).

Further treatment options were discussed with all patients with mechanical failure, of which six had further surgery, one refused further surgery, and six were treated conservatively.

Discussion

We have demonstrated that a staged reloading protocol for circular frame removal has a low rate of mechanical failure with 5% risk of refracture and no cases of significant deformation at three months. This was using a method similar to that described by the Chertsey Group,[3] who reported no incidence of nonunion or refracture at 12-months follow-up. However, their study was only in 36 patients. We demonstrated a low failure rate in 244 frames, confirming the effectiveness of this protocol in all frame types and reloading protocols, for all indications.

Determination of bony union can be challenging, particularly in circular frames where external devices obscure the fracture site. Successful bony union leads to normal weightbearing and the return to functional activities. This can be clinically used to confirm bony union.

The radiographic union score for tibia (RUST) score was developed to determine bony union in the tibia, according to the assessment of the callus and fracture line visibility of each cortex.[13,14] The score can vary from a minimum of four (no healing) to a maximum of 12

Table III. Multivariate analysis for refracture.

Refracture experienced	p-value*	Odds ratio	95% CI
Age, yrs	0.006	1.07	1.02 to 1.17
Sex	0.165	0.33	0.07 to 0.58
Smoker	0.392	0.58	0.17 to 2.00
Infection during treatment	0.478	0.61	0.15 to 2.40
Other comorbidities	0.855	1.13	0.30 to 4.30
Type of frame	0.163	6.33	0.47 to 84.0

*Multivariate analysis.

(complete healing). Whelan et al[15] found that the interobserver variation decreased significantly when the scoring system was employed. However, the beam hardening phenomenon of radiographs by circular frames can make it difficult to assess the scores. Skaggs et al[16] recommended removal of a femoral external fixator after three out of four cortices, of 2 mm, are identified on radiographs. They found that refracture was directly proportional to the number or cortices healed, reporting rates of 4%. Fischgrund et al[17] reported refracture rate of 3% following neocortical formation using an Ilizarov frame for distraction osteogenesis. In the present analysis, all of our patients had three or four cortices healed at 68% and 32%, respectively. However, all but one of our patients who suffered refracture had three cortices healed. Digital radiography has been used to assess bony healing and is correlated with fracture stiffness, but this has not yet been validated in the clinical setting.[18,19]

A CT scan can help quantify bone healing and is useful in periarticular and complex fractures, although nonunion may be over diagnosed. As despite being 100% sensitive, specificity remains low.[9,10] Quantitative CT scan has been shown to be helpful when planning removal of a circular frame.[20] Although some centres have found metal subtraction CT imaging useful to quantify bone healing, it is the authors' opinion that it does not correlate with clinical findings. In our practice, we have often successfully removed the frame, despite a CT report of persistent nonunion and vice versa. Furthermore, CT scans give a significant radiation dose. Bryant et al[21] found that patients with distal tibia fractures who underwent CT scanning and treatment with a circular frame had median radiation exposure of 0.182 mSv; 13-times higher than those whose treatment did not require CT investigation. This radiation can be avoided by the staged reloading protocol. Saran and Hamdy[22] used monthly DEXA scans to guide external-fixator removal following limb lengthening, with a fracture rate of 3.6%. However, this study only included 28 bone segments, with a mean age of 12 years, and concluded that DEXA cannot be used as a sole method to determine when to remove a fixator.

Finite element modelling, ultrasound techniques[23-26] and positron emission tomography scans[27] have all been evaluated for bone healing. However, there is a lack of validated clinical interpretation models and requirement for specialist equipment, and personnel can limit their utility. Furthermore, serological markers have been studied to help predict fracture union.[28] CTX, TRACP 5b, TGF B1, and total n-terminal propeptide of type I collagen have shown promising results,[29-31] but are non-specific and have not translated into clinical use.[32]

Age was the only factor significantly associated with refracture (Table III). Therefore, more caution should be taken when commencing reloading in older patients. However, numbers were small for the multivariate analysis, as demonstrated by the wide confidence intervals, and therefore a larger study would be needed to better quantify associations.

In the present study, 14 patients (6%) had the reloading process reversed, 11 patients in stage 1 and three patients in stage two. None of these patients suffered refracture or a change in alignment > 5° with subsequent reloading and frame removal. The authors believe that the reloading protocol has prevented mechanical failure in this group of patients. Fracture union can be confirmed clinically when a patient is able to fully weightbear without pain or subsequent deformity. Weightbearing after tibial fracture and external fixation has been correlated with fracture stiffness.[7] However, there are individual and cultural differences in perception and tolerance of pain among patients.[11,12] Ideally, pain scores should be used to quantify pain assessment during the reloading protocol.

We have demonstrated no increase in refracture rates between patients undergoing single-stage and two-stage reloading protocols ($p = 0.772$, chi-squared test). Although this was a retrospective study, our patient groups were well matched (see Table I). It may therefore be possible, if the surgeon is confident with clinical and radiological assessment, for the patient to progress directly to stage two and undergo single-stage reloading. This could precipitate faster patient recovery, satisfaction and return to work, as well as lowering healthcare costs.

A reloading protocol increases the time in frame by two to four weeks, with a subsequent increase in pin site infections, joint stiffness, disuse atrophy and psychological stress. However, there are significant advantages of a staged reloading protocol for frame removal. In patients who were symptomatic on reloading, we simply retightened the construct to support the bone. Had we progressed directly to frame removal, the mechanical failure rate would have been significantly increased.

The mean time to commence a single-stage protocol was three weeks more than that of a two-stage protocol at 180 and 201 days, respectively. This three-week delay could have mitigated any increased risk of refracture caused by a single-stage reloading protocol. The majority of our patients who followed the single-stage protocol had hexapod frames, and the majority of those who followed the two-stage protocol had ilizarov frames. Despite the differences in the mechanical properties of hexapod and Ilizarov frames, the failure ratio (9:4) is comparable to the number of frames in each group (154:90) of hexapod to Ilizarov frames. Furthermore, multivariate analysis showed no association between type of frame and refracture (p = 0.163). Ideally, to explore the effect of single-stage versus two-stage reloading, the type of frame should be standardized across patient groups. This is a retrospective study and based on a small number of patients, and therefore we cannot make any firm conclusions. Further research is needed to identify bone healing accurately to eliminate the risk of refracture.

This study is not without limitations. We have assumed no issues with the construct of the circular frames and the compliance of patients could not be confirmed in all patients. The relationship of the protocol to pin site infection and fracture subtype were not explored. This protocol is not suitable for non-weightbearing bone segments. The decision to proceed to reloading was decided by the senior surgeons in the team. Surgeon experience may have had an impact on the rate of mechanical failure, and in deciding whether a patient should undergo a single-stage or two-stage reloading protocol.

In conclusion, the staged reloading protocol is a safe, simple, inexpensive, and clinically effective method to determine the timing of circular frame removal. A staged reloading protocol can reduce the risk of mechanical failure. There are similar rates of mechanical failure following single-stage and two-stage reloading protocols. If the surgeon is confident with clinical and radiological assessment, it may be possible for patients to progress directly to stage two and undergo single-stage reloading.

Take home message

- A staged reloading protocol can reduce the risk of mechanical failure.
- There are similar rates of mechanical failure following single-stage and two-stage reloading protocols.
- If the surgeon is confident with clinical and radiological assessment, it may be possible for patients to progress directly to stage two and undergo single-stage reloading.

References

1. **Paley D**. Problems, obstacles, and complications of limb lengthening by the Ilizarov technique. *Clin Orthop Relat Res*. 1990;250(amp;NA):81.
2. **Calhoun JH**, **Li F**, **Ledbetter BR**, **Gill CA**. Biomechanics of the Ilizarov fixator for fracture fixation. *Clin Orthop Relat Res*. 1992;280:15–22.
3. **Jabbar Y**, **Jeyaseelan L**, **Khaleel A**. Staged complete dynamisation of the Ilizarov fixator: the Chertsey experience. *Eur J Orthop Surg Traumatol*. 2011;21(7):521–526.
4. **Morshed S**, **Corrales L**, **Genant H**, **Miclau T**. Outcome assessment in clinical trials of fracture-healing. *J Bone Joint Surg Am*. 2008;90 Suppl 1-A:62–67.
5. **Morshed S**. Current options for determining fracture union. *Adv Med*. 2014;2014:708574.
6. **Corrales LA**, **Morshed S**, **Bhandari M**, **Miclau T**. Variability in the assessment of fracture-healing in orthopaedic trauma studies. *J Bone Joint Surg Am*. 2008;90-A(9):1862–1868.
7. **Joslin CC**, **Eastaugh-Waring SJ**, **Hardy JRW**, **Cunningham JL**. Weight bearing after tibial fracture as a guide to healing. *Clin Biomech (Bristol, Avon)*. 2008;23(3):329–333.
8. **Lethaby A**, **Temple J**, **Santy-Tomlinson J**. Pin site care for preventing infections associated with external bone fixators and pins. *Cochrane Database Syst Rev*. 2013;12:CD004551.
9. **Bhattacharyya T**, **Bouchard KA**, **Phadke A**, **Meigs JB**, **Kassarjian A**, **Salamipour H**. The accuracy of computed tomography for the diagnosis of tibial nonunion. *J Bone Joint Surg Am*. 2006;88-A(4):692–697.
10. **Schnarkowski P**, **Rédei J**, **Peterfy CG**, **et al**. Tibial shaft fractures: assessment of fracture healing with computed tomography. *J Comput Assist Tomogr*. 1995;19(5):777–781.
11. **Campbell CM**, **Edwards RR**. Ethnic differences in pain and pain management. *Pain Manag*. 2012;2(3):219–230.
12. **Hoffman KM**, **Trawalter S**, **Axt JR**, **Oliver MN**. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci USA*. 2016;113(16):4296–4301.
13. **Azevedo Filho F**, **Cotias RB**, **Azi ML**, **Teixeira A**. Reliability of the radiographic union scale in tibial fractures (RUST)). *Rev Bras Ortop*. 2017;52(1):35–39.
14. **Leow JM**, **Clement ND**, **Tawonsawatruk T**, **Simpson CJ**, **Simpson AHRW**. The radiographic union scale in tibial (RUST) fractures: reliability of the outcome measure at an independent centre. *Bone Joint Res*. 2016;5(4):116–121.
15. **Whelan DB**, **Bhandari M**, **Stephen D**, **et al**. Development of the radiographic union score for tibial fractures for the assessment of tibial fracture healing after intramedullary fixation. *J Trauma*. 2010;68(3):629–632.
16. **Skaggs DL**, **Leet AI**, **Money MD**, **Shaw BA**, **Hale JM**, **Tolo VT**. Secondary fractures associated with external fixation in pediatric femur fractures. *J Pediatr Orthop*. 1999;19(5):582–586.
17. **Fischgrund J**, **Paley D**, **Suter C**. Variables affecting time to bone healing during limb lengthening. *Clin Orthop Relat Res*. 1994;301:31.
18. **Hazra S**, **Song H-R**, **Biswal S**, **et al**. Quantitative assessment of mineralization in distraction osteogenesis. *Skeletal Radiol*. 2008;37(9):843–847.
19. **Kolbeck S**, **Bail H**, **Weiler A**, **Windhagen H**, **Haas N**, **Raschke M**. Digital radiography. A predictor of regenerate bone stiffness in distraction osteogenesis. *Clin Orthop Relat Res*. 1999;366:221–228.
20. **Aronson J**, **Shin H-D**. Imaging techniques for bone regenerate analysis during distraction osteogenesis. *J Pediatr Orthop*. 2003;23(4):550–560.
21. **Bryant H**, **Dearden PMC**, **Harwood PJ**, **Wood TJ**, **Sharma HK**. Ionising radiation exposure in patients with circular frame treatment of distal tibial fractures. *Injury*. 2015;46(8):1597–1600.
22. **Saran N**, **Hamdy RC**. DEXA as a predictor of fixator removal in distraction osteogenesis. *Clin Orthop Relat Res*. 2008;466(12):2955–2961.
23. **Babatunde OM**, **Fragomen AT**, **Rozbruch**. Noninvasive quantitative assessment of bone healing after distraction osteogenesis. *HSS J*. 2010;6(1):71–78.
24. **Craig JG**, **Jacobson JA**, **Moed BR**. Ultrasound of fracture and bone healing. *Radiol Clin North Am*. 1999;37(4):737–751, .
25. **Moed BR**, **Subramanian S**, **van Holsbeeck M**, **et al**. Ultrasound for the early diagnosis of tibial fracture healing after static interlocked nailing without reaming: clinical results. *J Orthop Trauma*. 1998;12(3):206–213.
26. **Mundi R**, **Petis S**, **Kaloty R**, **Shetty V**, **Bhandari M**. Low-intensity pulsed ultrasound: fracture healing. *Indian J Orthop*. 2009;43(2):132–140.
27. **Blokhuis TJ**, **Patka P**, **Bakker FC**, **et al**. Quantitative assessment of fracture healing using positron emission tomography. *Eur J Nucl Med Mol Imaging*. 2003;30(2):329–330.
28. **Sousa CP**, **Dias IR**, **Lopez-Peña M**, **et al**. Bone turnover markers for early detection of fracture healing disturbances: a review of the scientific literature. *An Acad Bras Cienc*. 2015;87(2):1049–1061.
29. **Barnes GL**, **Kostenuik PJ**, **Gerstenfeld LC**, **Einhorn TA**. Growth factor regulation of fracture repair. *J Bone Miner Res*. 1999;14(11):1805–1815.
30. **Moghaddam A**, **Müller U**, **Roth HJ**, **Wentzensen A**, **Grützner PA**, **Zimmermann G**. TRACP 5b and CTX as osteological markers of delayed fracture healing. *Injury*. 2011;42(8):758–764.
31. **Sarahrudi K**, **Thomas A**, **Mousavi M**, **et al**. Elevated transforming growth factor-beta 1 (TGF-$\beta 1$) levels in human fracture healing. *Injury*. 2011;42(8):833–837.
32. **Pountos I**, **Georgouli T**, **Pneumaticos S**, **Giannoudis PV**. Fracture non-union: can biomarkers predict outcome? *Injury*. 2013;44(12):1725–1732.

Author information:
- V. Sadekar, MBBS, MS (Ortho), Clinical Fellow Trauma and Orthopaedics
- A. T. Watts, MBChB, BMedSci (Epidemiology), MRCS, Clinical Research Fellow Trauma and Orthopaedics
- E. Moulder, MBChB, FRCS, Consultant Limb Reconstruction Surgeon Trauma and Orthopaedics

- P. Souroullas, MBBS, MRCS, MD, Specialist Registrar Trauma and Orthopaedics
- Y. Hadland, Frame Nurse Trauma and Orthopaedics
- E. Barron, BSc(Hons), MCSP, Clinical Lead Physiotherapist Hull Limb Reconstruction Service
- R. Muir, BA, VetMB, MRCVS, BMBCh, MSc, FRCS, Consultant Orthopaedic Surgeon Trauma and Orthopaedics
- H. K. Sharma, FRCS (Orth), MS (Orth), M Ch (Orth), FRCS (Glas.), FRCS (Lon.), Consultant Limb Reconstruction Surgeon Trauma and Orthopaedics
  Hull University Teaching Hospitals NHS Trust, Hull, UK.

Author contributions:
- V. Sadekar: Data curation, Investigation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.
- A. T. Watts: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.
- E. Moulder: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.
- P. Souroullas: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing.
- Y. Hadland: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.
- E. Barron: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.
- R. Muir: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.
- H. K. Sharma: Conceptualization, Project administration, investigation, Supervision, Writing – original draft, Writing – review & editing.

Funding statement:
- The author(s) received no financial or material support for the research, authorship, and/or publication of this article.

ICMJE COI statement:
- E. Moulder reports consulting fees, and participation on a data Safety monitoring board or advisory board, for Orthofix; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, and support for attending meetings and/or travel from Orthofix and Smith & Nephew, all of which is unrelated to this work. H. K. Sharma declares research grants from B Braun and Orthofix; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, and equipment for research from Orthofix and Smith & Nephew; and being President Elect and past Treasurer of the British Limb Reconstruction Society, and chair of the Chair, limb reconstruction committee, of SICOT, all of which is also unrelated.

Acknowledgements:
- We would like to acknowledge the contribution of Ms Savni Panandikar for creation of graphical representation of our protocol.

Open access funding
- The authors report that they received open access funding for this manuscript from the Trauma & Orthopaedic Research Fund, Hull University Teaching Hospitals, Hull, UK.