ORIGINAL ARTICLE

Early Weight-bearing Accelerates Regenerate Bone Mineralisation: A Pilot Study Comparing Two Post-operative Weight-bearing Protocols Following Intramedullary Limb Lengthening Using the Pixel Value Ratio

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Abstract

Introduction: Limb lengthening is increasingly accomplished by internal lengthening nails. Previous versions of the magnetic lengthening nails made from titanium alloy allowed limited weight-bearing. In contrast, the newer nails made of stainless steel allow increased weight-bearing. An objective comparison of the rate of healing of the regenerate bone based on the weight-bearing capabilities of these two types of lengthening nails has not been evaluated. The hypothesis for the study is that earlier commencement of full weight-bearing in patients treated with the stainless steel STRYDE® nail will lead to faster healing of the regenerate bone during intramedullary limb lengthening compared with those treated with the titanium PRECICE® nail.

Materials and methods: Thirty patients, divided into two groups of 15 each, underwent antegrade intramedullary lengthening of the femur using a magnetic lengthening nail between May 2017 and November 2020. The pixel value ratio (PVR) obtained from serial digital radiographs was used to quantitatively determine the regenerate bone's mineralisation rate. We compared the rate of healing of the regenerate bone in both groups of patients using the PVR.

Results: Patients treated with the STRYDE® nail achieved unassisted full weight-bearing significantly earlier than patients treated with the PRECICE® nail (12 weeks vs 17 weeks for STRYDE® and PRECICE® nail-lengthened patients, respectively, $p = 0.003$). There was no difference in the PVR between both groups of patients at the time of full weight-bearing ($p = 0.0857$). However, patients treated with the STRYDE® nail attained a PVR of 1 significantly earlier than those treated with the PRECICE® nail (0.0317).

Conclusion: The STRYDE® nail provides an earlier return of function and full weight-bearing compared with the PRECICE® lengthening nail. Earlier commencement of weight-bearing ambulation leads to more rapid mineralisation of the regenerate bone in patients undergoing intramedullary limb lengthening.

Keywords: Intramedullary limb lengthening, Pixel value ratio, Magnetic lengthening nail, Weight-bearing.

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Introduction

Limb lengthening surgery is increasingly being accomplished with internal lengthening nails. Not only have these nails demonstrated remarkable accuracy in lengthening, but they have also gained popularity due to their lower complication rates in comparison to external fixator-assisted lengthening procedures.[1,2] Magnetic lengthening nails are one of the common current internal lengthening nails available. These nails consist of a telescoping assembly, where lengthening (or compression) is achieved by a system of internal gears driven by magnets contained in the nail and in an external remote controller (ERC) device. First used in 2011, the PRECICE® magnetic lengthening nail (NuVasive Specialized Orthopedics, San Diego, California) requires limited weight-bearing following surgery.[3] Only 50–75 lbs of weight is permitted, creating prolonged periods of assisted weight-bearing recovery and slowing functional return. The STRYDE® nail, a 3rd-generation magnetic lengthening nail, was cleared for use in the USA by the FDA in 2018. It is composed of Biodur 108 alloy stainless steel and is designed to accommodate greater loads (150–250 lbs of weight). The increased strength of the design allowed patients to start, immediately after surgery, with partial to full weight-bearing (depending on their body weight). This accommodation was beneficial to patients undergoing simultaneous bilateral lengthening.[4]

Some studies suggest that early weight-bearing stimulates faster healing during distraction osteogenesis.[5–7] The potential to perform earlier weight-bearing with the STRYDE® nail is an attractive option since it could allow an accelerated rehabilitation and return

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Table 1: Summary statistics for both groups of patients

	STRYDE®	*PRECICE®*	*p-value*
Age at time of surgery (years)	16.9 ± 4.5	15 ± 2.6	0.2877
M:F	11:4	8:7	
LLD (cm)	3.2 ± 1.4	4.4 ± 2.4	0.0843
Duration of distraction (days)	39.7 ± 19	43.9 ± 19	0.5729
Length gained (cm)	3 ± 1.6	3.6 ± 1.2	0.1072
Duration of hardware (days)	334 ± 124.7	396.5 ± 211.8	0.1198
Time to FWB (days)	85.7 ± 26	120.7 ± 37.1	0.003

LLD, limb length discrepancy, FWB, full weight-bearing, cm, centimetres

of function. Although the STRYDE® nail has been shown to achieve the same functional results as the PRECICE® nail,[8] to the best of our knowledge, an objective comparison of the rate of mineralisation of the regenerate has not been evaluated.

There are several objective measures for evaluating bone healing following distraction osteogenesis, and these range from computerised tomography scans to bone mineral density measurements.[9–12] One of the significant limitations of these techniques is their cost. The PVR is an inexpensive alternative measurement that can be obtained from plain radiographs. It has been proven to correlate well with quantitative measures of regenerate bone mineralisation.[13,14] The PVR has also been utilised as an objective determinant of regenerate bone healing following external and internal bone lengthening procedures.[14–18]

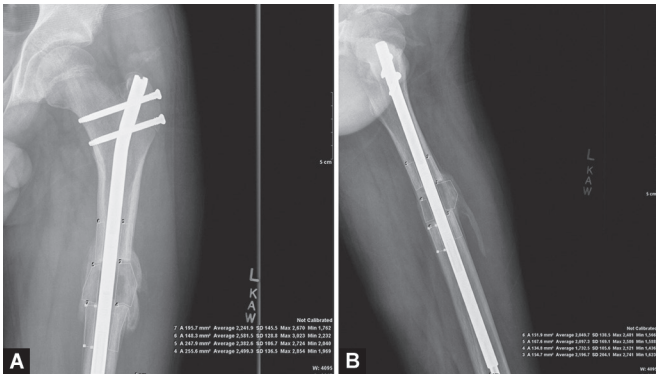
This study hypothesises that the earlier weight-bearing in patients treated with the STRYDE® nail will lead to faster healing of the regenerate bone during intramedullary limb lengthening compared with patients treated with the PRECICE® nail. Using the PVR as a measure of bone remineralisation, the healing rate will be compared between femoral lengthening using the STRYDE® nail and lengthening using the PRECICE® lengthening nail.

Materials and Methods

This was a retrospective chart review conducted following Institutional Review Board Approval. The aim was to compare two different Post-operative weight-bearing protocols (early full weight-bearing vs delayed full weight-bearing) in patients who had antegrade intramedullary femoral lengthening.

Thirty subjects who had undergone intramedullary lengthening with a magnetic lengthening nail between May 2017 and November 2020 were included in this review. They were divided into two groups of 15 subjects each, based on the type of magnetic lengthening nail used. Patients in group A had lengthening with the STRYDE® magnetic lengthening nails, while those in group B had lengthening with the PRECICE® magnetic lengthening nail. The aetiologies were congenital in 6 cases (3 in either group), post-traumatic in 2 cases (1 in each group), developmental in 15 cases (8 in the STRYDE® nail and 7 in the PRECICE® nail group), neurologic in 3 cases (all lengthened with the STRYDE® nail), metabolic in 1 case (lengthened with a STRYDE® nail) and neoplastic in 3 cases (all lengthened with the PRECICE® nail).

All patients had antegrade nail insertion for the lengthening procedure carried out by a single surgeon (the senior author). Patient demographics are as shown in Table 1. Following a latency period of 6–7 days, all patients were distracted at a rate of 0.75 mm/day. Outpatient follow-up was done weekly during the lengthening phase of treatment and then every 3–4 weeks during the consolidation phase of treatment. Digital orthogonal X-rays of the thigh showing the entire femur were carried out at every Post-operative follow-up visit until removal of the lengthening nails (including X-rays taken immediately following removal of the nails).



Figs 1A and B: Radiographs showing the determination of pixel values using the 'region of interest' feature in PACS. (A) Anteroposterior view, (B) Lateral view images of the proximal femur of a patient treated with a STRYDE® nail

The STRYDE® nail can accommodate 150–250 lbs of load per the manufacturer's recommendations, so patients lengthened with the STRYDE® nail had partial weight-bearing from day 1 and were gradually advanced to full weight-bearing with assistance at the end of distraction. They were allowed unassisted full weight-bearing upon radiologic confirmation of bridging callus on 3 out of 4 cortices on review of digital X-rays. In contrast, patients lengthened with the PRECICE® nail, which, per manufacturer's recommendations, can only carry loads limited to 50–75 lbs, started with touch-down weight-bearing only during distraction and the first month of consolidation. They were advanced monthly from partial to full weight-bearing with assistance and then finally to full unassisted weight-bearing if they had no pain on partial weight-bearing ambulation and bridging callus was visible on 3 out of 4 cortices on digital X-rays.

The 'region of interest' feature in GE centricity Picture Archiving and Communication Systems (PACS) version 4.0.11E software was used to assess the PVR for the regenerate bone on the lateral, medial, anterior and posterior regions of all radiographs taken during the Post-operative period (Fig. 1). The anterior and posterior PVRs were assessed from lateral view X-ray images, while the medial and lateral PVRs were assessed from anteroposterior view X-ray images.

In calculating the PVR, the formula,

$$\left(\frac{0.5\ (proximal\ segment\ pixel\ value + distal\ segment\ pixel\ value)}{regenerate\ bone\ segment\ pixel\ value}\right)$$

Table 2: Comparison of mean PVR for the various cortical regions of the regenerate at 12 and 17 weeks for both groups of patients (STRYDE® and PRECICE® nail-lengthened patients were full weight-bearing at 12 and 17 weeks, respectively)

	Mean PVR at 12 weeks			*Mean PVR at 17 weeks*		
Cortical region	*STRYDE®*	*PRECICE®*	*p-value*	*STRYDE®*	*PRECICE®*	*p-value*
Lateral	0.88	0.90		0.91	0.92	
Medial	0.92	0.92		0.95	0.95	
Anterior	0.90	0.90		0.93	0.92	
Posterior	0.90	0.91		0.93	0.93	
All cortices	0.90	0.91	0.6571	0.93	0.93	>0.9999

was used.[14] To represent increasing radio-opacity as healing progresses, the inverse ratio was utilised to express the results.[17,18] All PVR measurements were carried out by two authors (AB and MD). In obtaining PVR measurements, care was taken to avoid including areas of soft tissue overlap or hardware.

Statistical analysis was carried out using GraphPad Prism version 9.0.0 (121) (Software Inc., San Diego, California, USA). Measures of central tendency and variance were expressed as mean and standard deviation, respectively. Where indicated, the *t*-test was used to compare means for continuous variables. Mann–Whitney *U* test was used for post-hoc analysis. Results were considered significant at p values < 0.05.

Results

There was no statistically significant difference between the two groups of patients in terms of age at the time of surgery, amount of length discrepancy present, duration of distraction, and amount of length gained (Table 1). Patients who had lengthening with the STRYDE® nail had a significantly shorter time to full unassisted weight-bearing compared with patients lengthened with the PRECICE® nail using the same visualisation criteria of bridging callus on 3 out of 4 cortices (12 weeks vs 17 weeks, $p = 0.003$).

The mean PVR at the time of full unassisted weight-bearing was 0.90 and 0.93 for STRYDE® and PRECICE® nail lengthened patients, respectively (Table 2). We found no statistically significant difference between the mean PVR for the two groups at the time of full unassisted weight-bearing ($p = 0.0857$) or at 12 and 17 weeks ($p = 0.6571$ and >0.9999, respectively).

The medial cortex showed the fastest healing in both groups of patients, while the lateral cortex was the slowest to heal. Patients treated with the STRYDE® nail were found to achieve a PVR of 1 significantly earlier than patients treated with a PRECICE® nail (Fig. 2 and Table 3).

Patients were followed-up for an average of 15 months. There was no incidence of failure of the lengthening nail in either group of patients. At the time of this review, the lengthening nails had been removed in all but one patient in the STRYDE® nail group at a mean time of 47.7 weeks and 56.6 weeks following surgery for STRYDE® and PRECICE® nail patients, respectively.

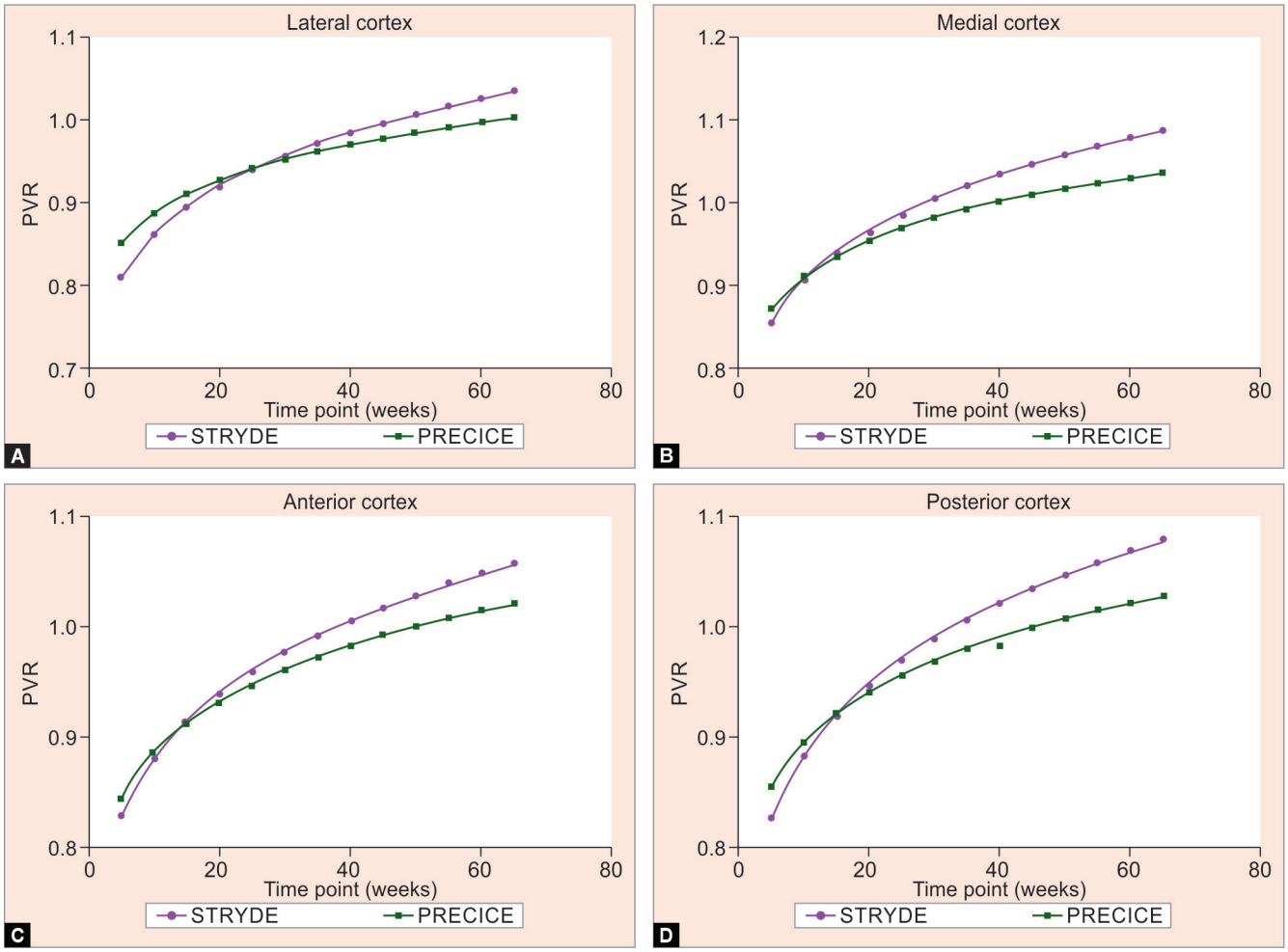
Discussion

This retrospective study compared the rate of the mineralisation of the regenerate bone following two different weight-bearing protocols in patients who had antegrade intramedullary lengthening of the femur. We utilised the PVR as an objective measure of healing to compare the effects of early versus delayed unassisted full weight-bearing on the rate of mineralisation of the regenerate bone in these patients. Our data demonstrate that during the initial 20 weeks following surgery, patients who commenced unassisted full weight-bearing early (those treated with the STRYDE® nail) and those who had delayed unassisted full weight-bearing (those treated with the PRECICE® nail) had similar rates of regenerate mineralisation as measured by the PVR. However, beyond 20 weeks following surgery, patients treated with the STRYDE® nail undergo more rapid mineralisation compared with those treated with the PRECICE® lengthening nail.

In distraction osteogenesis, new bone is formed under conditions of tension stress.[19] This represents an interplay of mechanical and biological stimuli. As the bone ends are gradually separated, new bone is formed adjacent to the cut ends of the bone by intramembranous ossification and arranged in columns parallel to the distraction axis. The interzone is filled with fibrous tissue in the early stages, but this gradually undergoes ossification as healing progresses.

The biological response of the regenerate following mechanical stimulation has been the subject of previous scientific research.[20–22] Physiologic loading has been shown to stimulate bone healing and maturation during distraction osteogenesis. The quantitative and qualitative changes, represented by an increase in callus volume, bone mineral content and strength of the regenerate, are triggered by micro-motion during the consolidation phase of healing.[5,23] Micro-tomography also suggests that weight-bearing stimulates angiogenesis during distraction osteogenesis.[24] This manifests clinically as an increase in the radiographic density of the regenerate.[25] These features of increased osteoblastic activity are mediated by ALP, TGFβ1, osteocalcin, BMP 2 and 4, as well as type I collagen, whose expression is increased by early weight-bearing.[5,26]

The biology of internal bone lengthening has not been studied. However, studies in rats have shown that during the distraction phase of lengthening with an external fixator, the regenerate is histologically similar between weight-bearing and non-weight-bearing subjects, suggesting a delay in the morphological manifestations of the effects weight-bearing.[26] Furthermore, the microstrain created across the distraction gap is believed to prime the regenerate bone to respond to compressive forces created during weight-bearing, thereby enhancing the rate of bone formation in conditions of weight-bearing.[5] This is perhaps why in this study, the difference between the PVR for both groups was statistically insignificant in the early stages of healing. Most animal studies have looked at radiological, histological and histochemical changes in the early and intermediate stages of regenerate healing. There are no long-term follow-up studies with these models. Most studies also do not document a time relationship between weight-bearing and the appearance of the radiological



Figs 2A to D: Graphical comparisons between rate of change of PVR for the various regenerate cortices between STRYDE® and PRECICE® nail lengthening patients

Table 3: Comparison of the mean duration required to achieve a PVR of 1 for all cortices for STRYDE® and PRECICE® nail-lengthened patients

	Time taken to achieve PVR of 1 (weeks)		
Cortical region	*STRYDE® nail*	*PRECICE® nail*	*p-value*
Lateral	46.0	60.8	
Medial	28.1	38.7	
Anterior	37.7	49.7	
Posterior	33.1	45.1	
All cortices	36.2	48.6	0.0317

effects of weight-bearing. Maffulli et al. showed that bone mineral content continues to increase after clinical and radiological healing during distraction osteogenesis.[27] We believe that the earlier commencement of weight-bearing in patients treated with the STRYDE® nail contributed to the more rapid increase in bone mineralisation noticed radiologically from the 20th week onwards in this study. The 'time-lag phenomenon' described by Frost lends support to this theory.[28] In this phenomenon, adaptive bone remodelling lags behind mechanical stimuli. Constitutive models of bone remodelling have also demonstrated the time delay in the process of bone remodelling following mechanical stimulation.[29] This time delay represents the sequence of events and the relationship between the mechanical and biological processes involved in the remodelling of bone. The process begins with mechanoreceptors like integrins, ion channels and ATP channels which undergo structural deformation induced by mechanical loading. Once triggered, these receptors activate a cascade of signalling pathways and biological processes that lead to osteogenesis.

This study had several limitations. The retrospective nature of this study and the relatively small sample size means that we were unable to achieve precise age and sex-matched pairs. However, our comparison of the two groups revealed statistically insignificant differences, which validates our results and encourages us to plan for a prospectively designed study with a larger sample size in the future. A lack of histological analysis of the regenerate bone formed under both conditions and assays of biochemical markers of bone formation are further limitations of this study. Histology and histochemistry would provide information on the structural effects of early weight-bearing while correlating levels of biomarkers with radiological and clinical findings would be helpful in monitoring the healing process. Biochemical markers of bone formation like

osteocalcin and bone-specific alkaline phosphatase, which are expressed during the mineralisation phase of osteoblastic activity, have been found useful in monitoring bone healing.[30,31]

The STRYDE® nail provides an earlier return of function and full weight-bearing compared with the PRECICE® lengthening nail. This study documents the beneficial effect of earlier weight-bearing on the rate of regenerate bone mineralisation as measured by the PVR.

References

1. Kirane YM, Fragomen AT, Rozbruch SR. Precision of the PRECICE® internal bone lengthening nail. Clin Orthop Relat Res 2014;472(12):3869–3878. DOI: 10.1007/s11999-014-3575-0.
2. Paley D. PRECICE intramedullary limb lengthening system. Expert Rev Med Devices 2015;12(3):231–249. DOI: 10.1586/17434440.2015.1005604.
3. Rozbruch SR, Birch JG, Dahl MT, et al. Motorized intramedullary nail for management of limb-length discrepancy and deformity. J Am Acad Orthop Surg 2014;22(7):403–409. DOI: 10.5435/JAAOS-22-07-403.
4. Robbins C, Paley D. Stryde weight-bearing internal lengthening nail. Tech Orthop 2020;35(3):201–208. DOI: 10.1097/BTO.0000000000000475.
5. Leung KS, Cheung WH, Yeung HY, et al. Effect of weightbearing on bone formation during distraction osteogenesis. Clin Orthop Relat Res 2004;419:251–257. DOI: 10.1097/00003086-200402000-00041.
6. Fink B, Krieger M, Strauss JM, et al. Osteoneogenesis and its influencing factors during treatment with the Ilizarov method. Clin Orthop Relat Res 1996;323:261–272. DOI: 10.1097/00003086-199602000-00036.
7. Pacicca DM, Moore DC, Ehrlich MG. Physiologic weight-bearing and consolidation of new bone in a rat model of distraction osteogenesis. J Pediatr Orthop 2002;22(5):652–659. DOI: 10.1097/01241398-200209000-00016.
8. Galal S, Shin J, Principe P, et al. STRYDE versus PRECICE magnetic internal lengthening nail for femur lengthening. Arch Orthop Trauma Surg 2022;142(12):3555–3561. DOI: 10.1007/s00402-021-03943-8.
9. Babatunde OM, Fragomen AT, Rozbruch SR. Noninvasive quantitative assessment of bone healing after distraction osteogenesis. HSS J 2010;6:71–78. DOI: 10.1007/s11420-009-9130-y.
10. Aronson J, Shin HD. Imaging techniques for bone regenerate analysis during distraction osteogenesis. J Pediatr Orthop 2003;23(4):550–560. DOI: 10.1097/01241398-200307000-00025.
11. Eyres KS, Bell MJ, Kanis JA. Methods of assessing new bone formation during limb lengthening. Ultrasonography, dual energy x-ray absorptiometry and radiography compared. J Bone Joint Surg Br 1993;75(3):358–364. DOI: 10.1302/0301-620x.75b3.8496200.
12. Saran N, Hamdy RC. DEXA as a predictor of fixator removal in distraction osteogenesis. Clin Orthop Relat Res 2008;466(12):2955–2961. DOI: 10.1007/s11999-008-0514-y.
13. Hazra S, Song H-R, Biswal S, et al. Quantitative assessment of mineralization in distraction osteogenesis. Skeletal Radiol 2008;37(9):843–847. DOI: 10.1007/s00256-008-0495-7.
14. Song SH, Agashe M, Kim TY, et al. Serial bone mineral density ratio measurement for fixator removal in tibia distraction osteogenesis and need of a supportive method using the pixel value ratio. J Pediatr Orthop Part B 2012;21(2):137–145. DOI: 10.1097/BPB.0b013e32834f04f3.
15. Zhao L, Fan Q, Venkatesh KP, et al. Objective guidelines for removing an external fixator after tibial lengthening using pixel value ratio: A pilot study. Clin Orthop Relat Res 2009;467(12):3321–3326. DOI: 10.1007/s11999-009-1011-7.
16. Muzaffar N, Hafeez A, Modi H, et al. Callus patterns in femoral lengthening over an intramedullary nail. J Orthop Res 2011;29(7):1106–1113. DOI: 10.1002/jor.21353.
17. Vulcano E, Markowitz JS, Ali S, et al. Assessment of bone healing during antegrade intramedullary rod femur lengthening using radiographic pixel density. J Am Acad Orthop Surg 2018;26(18):e388–e394. DOI: 10.5435/JAAOS-D-16-00949.
18. Bafor A, Duncan ME, Iobst CA. Evaluating the utility of the pixel value ratio in the determination of time to full weight-bearing in patients undergoing intramedullary limb lengthening. Strategies Trauma Limb Reconstr 2020;15(2):74–78. DOI: 10.5005/jp-journals-10080-1461.
19. Ilizarov GA. Clinical application of the tension-stress effect for limb lengthening. Clin Orthop Relat Res 1990;250:8–26. DOI: 10.1097/00003086-199001000-00003.
20. Leung KS, Lee KM, Chan CW, et al. Mechanical characterization of regenerated osseous tissue during callotasis and its related biological phenomenon. Life Sci 1999;66(4):327–336. DOI: 10.1016/S0024-3205(99)00594-9.
21. Vauhkonen M, Peltonen J, Karaharju E, et al. Collagen synthesis and mineralization in the early phase of distraction bone healing. Bone Miner 1990;10(3):171–181. DOI: 10.1016/0169-6009(90)90260-M.
22. Huang C, Ogawa R. Mechanotransduction in bone repair and regeneration. FASEB J 2010;24(10):3625–3632. DOI: 10.1096/fj.10-157370.
23. Kassis B, Glorion C, Tabib W, et al. Callus response to micromovement after elongation in the rabbit. J Pediatr Orthop 1996;16(4):480–483. DOI: 10.1097/00004694-199607000-00011.
24. Moore DC, Leblanc CW, Müller R, et al. Physiologic weight-bearing increases new vessel formation during distraction osteogenesis: A micro-tomographic imaging study. J Orthop Res 2003;21(3):489–496. DOI: 10.1016/S0736-0266(02)00234-6.
25. Fink B, Krieger M, Schneider T, et al. Factors affecting bone regeneration in Ilizarov callus distraction. Unfallchirurg 1995;98(12):633–639. PMID: 8584945.
26. Radomisli TE, Moore DC, Barrach HJ, et al. Weight-bearing alters the expression of collagen types I and II, BMP 2/4 and osteocalcin in the early stages of distraction osteogenesis J Orthop Res 2001;19(6):1049–1056. DOI: 10.1016/S0736-0266(01)00044-4.
27. Maffulli N, Cheng JCY, Sher A et al. Bone mineralization at the callotasis site after completion of lengthening. Bone 1999;25(3):333–338. DOI: 10.1016/S8756-3282(99)00168-4.
28. Frost HM. Skeletal structural adaptations to mechanical usage (SATMU): 3. The hyaline cartilage modeling problem. Anat Rec 1990;226(4):423–432. DOI: 10.1002/ar.1092260404.
29. Hazelwood SJ, Bruce Martin R, Rashid MM, et al. A mechanistic model for internal bone remodeling exhibits different dynamic responses in disuse and overload. J Biomech 2001;34(3):299–308. DOI: 10.1016/S0021-9290(00)00221-9.
30. Bansal MS, Dwivedi DD, Kumar S, et al. Role of bone turnover marker-bone specific alkaline phosphatase evaluation in monitoring healing of tibial shaft fractures managed by closed reduction. Int J Orthop Sci 2020;6(2):795–800. DOI: 10.22271/ortho.2020.v6.i2m.2139.
31. Leung KS, Fung KP, Sher AHL, et al. Plasma bone-specific alkaline phosphatase as an indicator of osteoblastic activity. J Bone Joint Surg Br 1993;75(2):288–292. DOI: 10.1302/0301-620x.75b2.8444951.