Does The Lengthening Frequency Affect The Outcome of Distraction Osteogenesis? Comparing Two Times a Day with Four Times a Day Lengthening Protocol

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ABSTRACT

Objective: Distraction osteogenesis (DO) is a well-known technique. The traditional method utilized the lengthening frequency of four times a day (QID). Many mechanical factors may affect the DO outcome. However, the effect of distraction frequency has not been proven clinically. Therefore, we aim to investigate whether the two times a day (BID) and QID lengthening frequency affect the healing index and complications of the DO.

Materials and Methods: We retrospectively reviewed patients who had undergone DO from 2010 – 2021. The patient was divided into BID and QID groups. Demographics, lengthening outcomes, and complications between the two groups were compared. We used the inverse probability of treatment weighting (IPTW) to determine the effect of treatment.

Results: The median healing index (HI) of the patients whose lengthening was done QID is 41.36 (IQR 32.72 - 67.68) days/cm, and BID is 49.12 (IQR 35.28 - 62.54) days/cm, which did not differ significantly. The Odds ratio of achieving HI < 45 days/cm for patients receiving QID lengthening compare to BID is 1.12 (95% CI 0.31-3.99, p = 0.862). The IPTW did not show a difference in average treatment effects between QID and BID lengthening. The rates of minor and major complications were not significantly different between the two groups (26.1% in QID group and 32.1% in BID group).

Conclusion: The frequency of QID and BID lengthening results in comparable HI and complications for patients who undergo DO. However, prospective research is needed to evaluate the effect of frequency differences in a clinical setting.

Keywords: Distraction osteogenesis; limb lengthening; healing index; lengthening frequency (Siriraj Med J 2024; 76: 373-380)

INTRODUCTION

Distraction osteogenesis (DO) is a well-known method in orthopedic surgery.[1,2] This technique creates new bone formation using the principle of Tension-Stress. Under a slow and gradual traction force, the cells in the distraction gap become metabolically active, leading to osteogenesis.[3,4] DO is used in adult and pediatric patients. In adults, it is used mainly for bone defects caused by trauma, infection, or tumor. In pediatric patients, conditions such as congenital limb deficiency,

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https://doi.org/10.33192/smj.v76i6.266954

physeal arrest, or osteomyelitis that result in limb length discrepancy (LLD) are major indications.[5,6]

DO includes the initial, distraction, and consolidation phases. The rate and frequency during distraction have been shown to affect the quality of osteogenesis.[3,4,7] In a detailed animal model study, It was demonstrated that the optimal speed for lengthening is around 1 mm per day. In addition, increasing the frequency of distraction may improve osteogenesis, but this has not been proved in a clinical study. Many factors can also affect the healing index (HI), for examplem, the patient's age, the extent of the lengthening, the lengthened bone segment, the device used, and etiologies.[7-10] Many devices have been used for DO. The two most commonly used devices were the ring external fixator and the monolateral fixator. These can be combined with some form of internal fixation to reduce time in the external fixator, called integrated lengthening.

In our institution, a lengthening frequency of four times a day (QID) is the standard method. However, some patients do not fully follow the protocol and prefer a lower frequency of distraction. Therefore, two times a day (BID) lengthening was used in some patients. However, the effect of lengthening frequency has not been tested clinically. Therefore, here our objective is to compare the results and complications between the lengthening frequency of BID and QID.

MATERIALS AND METHODS

Study design and setting

The institutional review board has approved this retrospective cohort study. Patients who underwent DO in our institution over ten years from January 2010 to January 2020 were recruited.

Participants and data collection

The inclusion criteria for this study are patients who received DO at our institution. All types of devices used, consolidation methods and all etiologies for DO were included. Patients were excluded if a concurrent correction for deformity was also performed. Patients who did not have clinical and radiological follow-up until the DO process was complete were also excluded. At the time of operation, demographic data such as age, body weight, body height, and gender were collected. The patient's diagnosis was collected. DO data were recorded, including bone segment, devices used, consolidation method, lengthening rate, and lengthening frequency. The decision to use a mono-lateral fixator or Illizarov apparatus and the lengthening frequency was up to the surgeon's preferences. Radiographs were reviewed for initial bone length, length gain, and callus quality. All complications during and after the DO process were recorded.

Outcome measurement

The healing index (HI) is the primary outcome of this study. It is computed by dividing the number of days spent on DO by the length of the developed callus in centimeters (cm).[8,11] In our study, the duration of DO starts on the day of osteotomy and ends when the callus is fully consolidated, and full weight bearing is permitted for the patient. HI should be less than 45 days/cm to achieve optimal treatment time.[12] External fixator index (EI) is calculated similarly, but the period is from applying the external fixator until it was removed.

Secondary outcomes involve the quality of the callus formed and the complications that occur. The callus quality is assessed using the callus's shape, density, and pathway according to Li et al.[13] The callus shape is classified into fusiform, cylindrical, concave, lateral, and central. Fusiform and cylindrical shapes were grouped as "Good callus shapes".

The callus pathway was categorized into four distinct types: sparse, homogeneous, heterogeneous, and lucent. Each of these categories is subsequently subdivided into three density levels: low, intermediate, and normal. Homogeneous and heterogeneous types with intermediate and normal density callus are grouped as "Good callus density". The callus score when the external fixator was removed was also recorded.[14] Complications were classified into problems, obstacles, minor and major complications according to Paley et al.[5] The subsidence of the callus is defined as the change in callus > 10% or angulation > 10 degrees.[14]

Treatment protocol

Osteotomy technique: All patients received the same technique for osteotomy. We did an osteotomy at the metaphysodiaphyseal area of the distal femur and proximal tibia. The bone was drilled, and the osteotomy was completed with an osteotome. We checked the osteotomy completion by slight distraction under a fluoroscope.

External fixator application: Two types of exernal fixators were used in our patients. The decision to use the Illizarov frame or monolateral fixators is based on surgeon's preferences. For the Ilizarov frame, it was assembled and applied to the bone proximally and distally. Transosseous elements that engage at least four cortices in each segment using Shanz pins and wires were inserted according to the safe zone. For the monolateral fixator, we inserted three Shanz pins, size 5.0 mm – 6.0 mm, into the proximal shaft and the distal shaft area.

Lengthening Protocol: The initial phase is seven days for all patients. The patient and caregiver were then instructed to manually distract the device BID (0.5 mm x two steps) or QID (0.25 mm x four steps). Both groups utilize the same rate of one mm/day.

Follow-up and Consolidation methods: Serial radiographs and clinical exams were scheduled every two weeks. If the patient complains of pain or has a reduced range of motion, the rate can be modified. The actual distraction rate was calculated when the distraction is fisnished by dividing the length gained by the days used. After reaching the desired length, if plate fixation or casting were chosen as a consolidation method, the external fixator was kept until some ossification of the lengthening site was observed, then converted to plate or casting. However, the cut point for conversion to plate/ cast consolidation is up to the surgeon's preferences. After solid consolidation was observed, the patients were allowed to bear weight.

Statistical analysis

A histogram and the Shapiro-Wilk test were used to investigate data distribution patterns. The independent T-test was used to test normally distributed continuous data with mean ± SD. The Mann-Whitney U test was used to evaluate nonnormally distributed continuous variables with median and interquartile range (IQR). Categorical data were provided as counts and percentages, and Fisher's exact probability test was used to test them. The statistical significance level was chosen at p 0.05. STATA 16 (StataCorp, LLC, College Station, TX, USA) was used for all statistical analyses.

We use the inverse probability of treatment weighting (IPTW) to balance baseline covariates between the two treatment groups. The IPTW is a propensity score method that will weigh treatment effects with the probability of receiving treatments to account for potential selection biases in the non-randomized study. The IPTW was calculated based on baseline covariates, including options of conversion for consolidation, external fixator type (Ilizarov or Monolateral fixator), the etiology being congenital limb deficiency, the magnitude of length gain, distraction rate, patient's age, and bone lengthed (femur or tibia). Subsequently, the average treatment effects (ATE) between the QID and BID groups for HI, the probability of having good callus density and shape, and complications were calculated under IPTW. Any covariates demonstrating a weighted absolute Standardized Difference (STD) of greater than 10% were included for a double robustness adjustment in the weighted analysis.

RESULTS

We included 72 patients in our study. The demographic data of patients who received BID and QID lengthening is compared in (Table 1). There were significantly more male patients in the QID group. More patients in the QID group were lengthened with Illizarov frame and converted to cast for consolidation. Sixteen patients (21.6%) had LLD from congenital causes, which comprised six Fibular hemimelia (8.1%), four Congenital femoral deficiency (5.4%), three Tibial hemimelia (4.1%) and three Hemihypertrophy (4.1%). Fifteen patients (20.3%) had limb undergone DO due to physeal injury from either traumatic or infectious causes. Eight patients (10.8%) had chronic osteomyelitis (COM), requiring DO to reconstruct the bone defect. We used DO for Congenital tibial dysplasia in four cases (5.4%). The remaining 31 patients have various causes leading to LLD, which are six Perthes diseases (8.1%), six Developmental hip dysplasia (8.1%), four Syndrome associated (5.6%), three Blount's disease (4.1%), three Posteromedial tibial bowing (4.1%), three Bone tumor (4.1%), two skeletal dysplasia (2.7%), two Malunion (2.7%), one Arthrogryposis (1.4%), and one Cerebral palsy (1.4%). The lengthening outcomes and complications of the two groups are compared in (Table 2), showing no significant differences between the two groups.

Effects of Lengthening Frequency on Healing Index

A higher proportion of patient in QID group achieved H-index < 45 days/cm; QID group (27 out of 46 patients, 58.7%) vs. BID group (12 out of 28 patients, 42.9%). However the difference did not reach statistical significant, P = 0.2786). Subgroup analysis for factors that influence HI were evaluated by univariate and multivariate analysis (Table 3). QID lengthening has an OR of 1.89 (95%CI 0.73-4.90, p = 0.188) for achieving HI <45 days/ cm. The multivariable analysis results in OR of 1.12 (95%CI 0.31-3.99, p = 0.862). Influencing factors were adjusted using IPTW to determine the average effect of lengthening frequency treatment (QID vs. BID) (Fig 1). QID lengthening did not have a significant impact on HI (52.8±24.0 days/cm vs. 50.5±17.1 days/cm, Average treatment effect (ATE) = 2.3 (-5.8 to 10.4), p = 0.577). In other words, if all patients received QID lengthening instead of BID lengthening, the HI would be about 2.3 days/cm more. QID lengthening also did not significantly affect achieving good callus shape and density.

Effects of Lengthening Frequency on Complications

The complication rate of DO, which included Problems (28.57% vs. 19.57%, p = 0.404), Obstacles (39.28% vs. 28.26%, p = 0.443), Minor and Major complications

TABLE 1. Demographic data of patients receiving distraction osteogenesis by lengthening frequency

Demographic data	2 times/day (BID) (n=28, 37.8 %)		4 times/day (QID) (n=46, 62.2 %)		P-value
	Mean	±SD	Mean	±SD	
Clinical characteristics					
Age (years)	15.3	8.6	13.4	9.8	0.410
Sex (n,%)					
Male	9	32.1	27	58.7	0.033*
Female	19	67.9	19	41.3	
Body weight (kg)	42.7	18.6	38.9	18.0	0.384
Body height (cm)	144.2	20.9	137.2	22.8	0.187
Bone lengthened (n, %)					
Femur	17	60.7	24	52.2	0.630
Tibia	11	39.3	22	47.8	
Lengthening device (n, %)					
Ilizarov frame	16	57.1	37	80.4	0.038*
Wagner frame	12	42.9	9	19.6	
Consolidation method (n, %)					0.020*
No conversion	2	7.1	6	13.0	
Conversion to Casting	12	42.9	34	73.9	
Conversion to plate fixation	14	50.0	6	13.1	
Etiologies of LLD[1] (n, %)					0.138
Congenital limb deficiency	9	32.1	7	15.2	
Physeal injury	6	21.4	9	19.6	
Chronic osteomyelitis	1	3.6	7	15.2	
Congenital pseudarthrosis of tibia	0	0.0	4	8.7	
Other acquired causes	12	42.9	19	41.3	

[1]LLD, Limb length discrepancy; Normally distributed continuous data were compared using an Independent T-test. Categorical data were analyzed using Fisher's Exact Test for small sample sizes and Pearson's Chi-Square Test for larger samples.

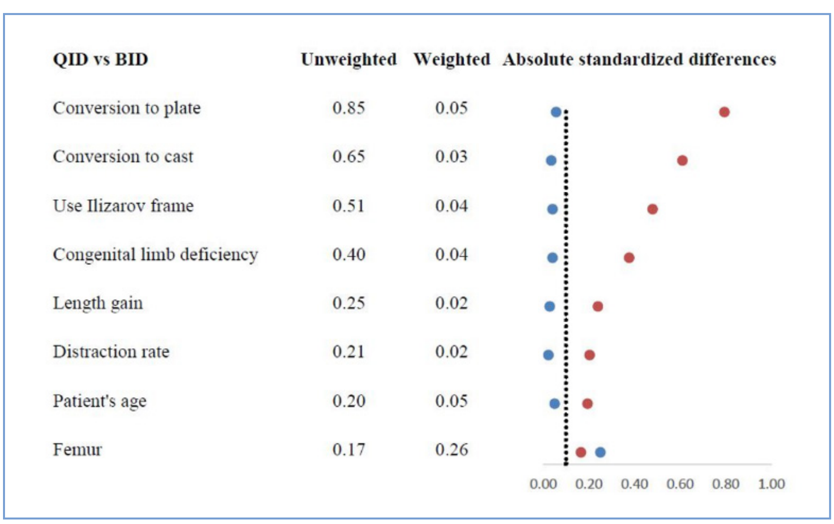

Fig 1. An inverse probability of treatment weighting (IPTW) graph showing the weighted effect of variables affecting the Healing Index before (Red dot) and after (Blue dot) adjusting.

TABLE 2. Lengthening outcomes and complications of patients receiving distraction osteogenesis by frequency of distraction

	2 times/day (BID) (n=28, 37.8 %)		4 times/day (QID) (n=46, 62.2 %)		P-value
	Mean	±SD	Mean	±SD	
Lengthening data					
Initial Bone length (cm)	31.62	8.68	29.44	8.67	0.299
Length gain (cm)	6.14	2.40	5.55	2.31	0.294
Lengthening rate (mm/days)	0.71	0.15	0.75	0.19	0.391
Lengthening outcomes					
Healing index < 45 days/cm (n, %)	12	42.9	27	58.7	0.279
Callus qualities					
Achieved Good callus density (n, %)	9	32.14	15	32.6	1.000
Achieved Good callus shape (n, %)	11	39.28	26	56.52	0.231
Callus score	5.89	1.75	6.57	1.71	0.108
Callus subsidence (n, %)	9	32.14	18	39.13	0.623
Complications					
Problems (n, %)	8	28.57	9	19.57	0.404
Obstacles (n, %)	11	39.28	13	28.26	0.443
Minor and Major complications (n, %)	9	32.14	12	26.09	0.604

Normally distributed data was compared with an Independent T-test. Categorical data was compared with Fisher's Exact Test.

TABLE 3. Univariable and multivariable logistic regression for factors predicting good healing index (<45 days/cm)

Characteristics	Univariable analysis				Multivariable analysis			
	uOR	95%CI		p-value	mOR	95%CI		p-value
Conversion to plate	0.49	0.17	1.41	0.187	0.59	0.16	2.29	0.736
Illizarov	2.29	0.81	6.45	0.117	3.56	0.85	14.96	0.083
Congenital causes	0.32	0.10	1.04	0.060	0.13	0.02	0.72	0.019
Length > 5 cm	2.13	0.84	5.41	0.110	2.22	0.72	6.81	0.163
Rate < 0.7 mm/day	2.12	0.83	5.42	0.118	3.09	0.97	9.81	0.056
Age < 10	1.33	0.518	3.433	0.551	3.16	0.69	14.48	0.137
Femur	2.12	0.83	5.40	0.114	3.93	1.11	13.97	0.034
QID[1] lengthening	1.89	0.73	4.90	0.188	1.12	0.31	3.99	0.862

[1]QID, 4 times per day

(32.14% vs. 26.09%, p = 0.604) did not differ between the BID and QID lengthening group. (Table 2). Using IPTW, the result shows no significant effect of QID vs. BID lengthening on minor and major complications (Table 4).

DISCUSSION

This is the first study to clinically evaluate the effects of lengthening frequency on distraction osteogenesis (DO) for limb lengthening. We found that BID and QID lengthening did not significantly affect HI, callus quality, and minor and major complications.

Effects of Lengthening Frequency on Distraction Osteogenesis Outcomes

Mechanical factors have been shown to affect callus healing in DO significantly.[1,3,7,8,15,16] The optimal distraction rate and mechanical techniques, such as distraction–compression, have improved osteogenesis in animal studies.[17,18] However, the frequency of distraction appears to be of lesser interest and is used most frequently as a standard number. A classic in vivo study by Ilizarov[3] showed that increasing the frequency of distraction positively affects osteogenesis activity; however, the frequency studied was one time/day, four times/day, and 60 times/day. Our study compares BID with QID lengthening, which might explain why the multivariate analysis shows a slight trend towards a better chance of achieving HI < 45 days/cm for the QID group, but the difference is not statistically significant. Therefore, the frequency difference might need to be greater to yield different clinical outcomes.

Mizuta et al. studied the frequency of distraction in a tibial open-edge osteotomies. They reported a higher bone mineral density in the distraction area and a shorter external fixator time for patients who received eight-step distraction compared to four-step.[15] A recent computational modeling study by Fu et al.[19] suggested that a variable distraction rate could improve osteogenesis. Therefore, even though a BID lengthening frequency may cause less patient burden and confusion, it may not be the most suitable frequency of distraction.

The quality of callus formation has been associated with a decrease in HI and the subsidence rate of the callus.[13,14] Although a higher frequency of distraction should lead to better callus quality due to improved osteogenesis activity, it did not show a significant result in a clinical setting. It is well known that many factors can affect the quality of HI and callus. The sample size may not be big enough, and the heterogeneity of patients is high, which may lead to a nonstatistically significant result.

The median healing index in our study is 42.8 days/cm, which is comparable to other studies that did not use an intramedullary magnetic nail for lengthening.[5,8,10,11,20-22] One of the significant factors influencing HI in our study is the bone lengthened being the femur. This is consistent with the findings of De Bastiani et al., Maffulli et al and Koczewski et al.[10,11,22] The femur has more muscle enveloping the bone, resulting in a more robust blood supply and improved osteogenesis.

We found that congenital etiologies had a significantly lower probability of having HI<45days/cm. Maffuli et al. also observed a higher HI for congenital limb deficiency compared to acquired causes.[10] Congenital limb deficiency is characterized not only by bone shorthening, but also by soft tissue contracture and joint instability. Therefore, complications frequently arise in these patients that may

TABLE 4. Average treatment effects (ATE) between QID and BID lengthening groups

Outcomes	QID[1]		BID[2]		Δ[3] ATE[4]	95% CI	*p*-value
Primary outcome (mean±SD)							
Healing index (days/cm)	52.8±24.0		50.5±17.1		2.3	-5.8 to 10.4	0.577
Secondary outcome (Risk, 95%CI)							
Good callus shape	0.57	0.43 to 0.71	0.50	0.31 to 0.70	0.06	-0.18 to 0.30	0.614
Good callus density	0.34	0.21 to 0.48	0.41	0.22 to 0.60	-0.07	-0.30 to 0.17	0.577
Minor and major complications	0.27	0.14 to 0.40	0.24	0.13 to 0.37	0.02	-0.16 to 0.20	0.813

[1]QID, 4 times/ day; [2]BID, 2 times/ day; [3]Δ, differences; [4]ATE, Average Treatment Effects

lead to increased HI. The inherent growth potential abnormality may also be a contributing factor.

Age is one of the most discussed factors regarding osteogenesis. We found that younger patients (less than ten years old) are more likely to achieve HI < 45 days/cm. Many studies also show that older patients tend to have a higher HI with various cutpoints from ten to 18 years of age.[8-10,22,23] The younger individual has a thicker periosteum and more robust blood supply with a higher re-modeling potential, leading to improved healing of the distraction site and decreased HI. Although our study did not achieve a significant statistical result, we agreed that the patient's age has a significant impact on the result of DO.

The increase in lengthening magnitude is also associated with a lower HI. Although the time in the distraction phase depends on the length needed, the time in the consolidation phase does not increase in the same proportion. This result is also evidenced in other studies.[8,9,22] The device used for DO also affects HI. Aaron et al.[24] found that the use of the Ilizarov apparatus resulted in a significantly lower healing index compared to the Wagner device. Our study reports the same result but without statistical significance.The Ilizarov method can provide a biomechanically stronger construction because it can incorporate fixation of wires and pins, resulting in greater engagement of the cortex.[25] A more stable construct may contribute to a better mechanical environment and osteogenesis.

The distraction rate is typically one mm/day. However, many studies show that the actual distraction rate achieved is less than that and ranges from 0.5 – 0.8 mm/day.[26-29] Balci et al. found that the lengthening speed of 0.56 mm/day is optimal for lengthening in congenital tibial dysplasia.[30] We also reported a mean distraction rate of 0.73 mm/day and found that a distraction rate < 0.7 mm/day results in almost statistically strong odds of achieving good HI. The importance of the distraction rate should be further investigated as the widely recommended rate of one mm/day might not be the most suitable for all patients.

Effects of Lengthening Frequency on Distraction Osteogenesis Complications

Our study reported a high rate of total complications. However, it is generally accepted that limb lengthening procedures are associated with many difficulties.[5,7-10,24] Ankle equinus frequently accompanies tibial lengthening and is one of the most common complications.[31] Our study reveals a similar result with the most common problems being ankle equinus and pin tract infection. However, most of these problems were successfully treated during the DO period. Minor and major complications persist after the DO period and are considered significant for the patient's outcome. We found that BID and QID lengthening results in similar minor and major complication rates. However, since not many patients faced significant complications, we may need more patients in a study to achieve a statistically significant difference.

Limitations

There are some limitations to our study. First, the DO in our research was done using either the Ilizarov apparatus or the monolateral fixator device. However, there are other methods for lengthenging, such as magnetic intramedullary nail lengthening and other integrated techniques, which also show promising results.[27,32-34] Therefore, the results may not be directly applicable to other distraction techniques, and warrant further research. Second, many factors contribute to HI. Although we tried to control these factors using IPWT, we may still need a larger number of patients for a more accurate result. Furthermore, the heterogeneity of patients in the study might result in non-significant findings. A more extensive study focused on an interested subgroup, such as congenital limb deficiency, is still needed. Finally, although we cannot verify the effect of the lengthening frequency in this study, we still believe that it contributes significantly to the results of the DO. Therefore, further prospective studies are needed to prove the result.

CONCLUSION

BID and QID lengthening results in comparable HI and complications for patients who undergo distraction osteogenesis with either the Ilizarov or monolateral fixator. However, more research is required to evaluate the effect of lengthening frequency in a clinical setting.

ACKNOWLEDGMENTS

The authors thank Miss Suchitphon Chanchoo for her contribution to data analysis.

DECLARATIONS

On behalf of all authors, the corresponding author states that there is no conflict of interest

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

The authors have no relevant financial or non-financial interests to disclose.

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