OPEN

Combination Treatment by Cross-Union of the Tibia and Fibula, Autogenic Iliac Bone Grafting, Reliable Fixation and Bone Morphogenetic Proteins for the Treatment of Refractory Congenital Pseudarthrosis of the Tibia

Chunxing Wu, MD, Guizhou Zheng, MD,† Dahui Wang, MD, PhD,* Dror Paley, MD,‡ and Bo Ning, MD, PhD**

Background: The treatment of congenital pseudarthrosis of the tibia (CPT) remains a challenge because of the difficulties of achieving and maintaining bone union, as well as complications of joint deformity and limb-length discrepancy. The purpose of this study was to evaluate the efficacy of cross-union of the tibia and fibula in achieving union and preventing refracture for patients with refractory CPT as a complementary approach to improve upon conventional surgical treatments.

Methods: A retrospective study including patients with refractory CPT who attended our department between June 2014 and August 2020. Eighteen CPT patients, who had sustained refracture that required cast immobilization or secondary surgery, and were managed by pseudarthrosis resection, cross-union of the tibia and fibula, bone morphogenetic protein-2 and autogenous iliac bone grafting, were included. Clinical outcomes of the bone union rate and the frequency of refracture after performing cross-union of the tibia and fibula were assessed during the follow-up period.

Results: The mean follow-up period was 4.3 years (range: 1.5 to 6.25 y). The mean age of the patients at surgery was 5.4 years (range: 2.6 to 10 y), and all 18 (100%) of the 18 patients had final healing at the site of pseudarthrosis. The average time spent to achieve radiologic bone union of the pseudarthrosis after operation was 2.96 months (range: 2.2 to 4.1 mo). Two (11.1%) patients had an average 2.5 cm limb-length discrepancy, none (0%) sustained refracture which needed cast immobilization or secondary surgery. Patients were all pain-free and move actively.

Conclusions: Cross-union of the tibia and fibula is a promising complementary procedure for treating refractory CPT patients.

Level of Evidence: Level IV—case series.

Key Words: congenital pseudarthrosis of tibia, cross-union of tibia and fibula, refracture

(*J Pediatr Orthop* 2022;42:e623–e629)

Congenital pseudarthrosis of the tibia (CPT) is a rare disease with various clinical manifestations characterized by segmental dysplasia of the tibia and absence of normal bone formation, accompanied by angular deformities, pathologic fractures, and bone nonunion. The incidence is reported to be between 1:140,000 to 1:250,000.[1] CPT is commonly associated with neurofibromatosis[2] and to a lesser extent with fibrous dysplasia or osteofibrous dysplasia.[1,3,4] There is a fair amount of data to suggest that CPT is a disease of the periosteum.[5] Even nowadays, the physiopathology of CPT has still not been clearly defined, and its treatment is still one of the most difficult challenges for the pediatric orthopaedist because of the frequent bone nonunion, residual deformities and mediocre functional prognosis.

Four primary approaches—internal fixation with intramedullary rodding[2,6,7] external fixation[8,9] (predominantly Ilizarov apparatus), combination treatment with an Ilizarov and rodding construct[10,11] and vascularized fibula transfer[12,13] have been used to treat this disease with varying rates of success. On the basis of these approaches, the primary union rate of CPT has improved.[12,13,14] However, despite these advances, the risks of refracture and even amputation remain, thus more approaches are necessary to achieve union and prevent refracture in CPT patients.

From the *Department of Pediatric Orthopedics, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai; †Department of Orthopedics, The Third Affiliated Hospital (The Affiliated Luohu Hospital) of Shenzhen University, Shenzhen, Guangdong, China; and ‡Paley Orthopedic and Spine Institute, West Palm Beach, FL.

C.W. and G.Z. contributed equally to the work and were regarded as the common first author.

C.W. and G.Z.: manuscript preparation, performed measurements, and statistical analysis. D.W. and D.P.: study design. B.N.: study design, supervision, and validation.

None of the authors received financial support for this study.

The authors declare no conflicts of interest.

Reprints: Bo Ning, MD, PhD, Department of Pediatric Orthopedics, Children's Hospital of Fudan University, National Children's Medical Center, 399 Wanyuan Road, Minhang District, Shanghai 201102, China. E-mail: ningbo@fudan.edu.cn.

DOI: 10.1097/BPO.0000000000002138

Since 2008, we have used several approaches to treat CPT patients including vascularized fibular transfers, intramedullary rods, the Ilizarov technique, and even combinations of these surgical techniques. However, the risk of failure to achieve and maintain union and the incidence of refracture after removal of the fixators remain.

In 2002, Johnston[6] first mentioned cross-union as part of the treatment of CPT. In 2011, Choi et al[15] commended the creation of a cross-union between the tibia and fibula for CPT cases where the fibula was broken but minimally proximally migrated. They converged the 2 fibula bone ends towards the 2 tibia bone ends in what they called a "4-in-1 osteosynthesis," so all 4 proximal and distal segments of the tibia and fibula are placed in one healing mass. They used a corticocancellous sheet of the inner table of the ilium with or without its periosteum and when necessary additional cortical bone from the contralateral tibia combined with cancellous bone chips to achieve the cross-union. The cortical graft was placed posterior to the 2 bones and then cancellous chips between the bones and another layer of cortical bone anterior to the bones. Eight patients (mean age: 6.3 y) underwent "4-in-1 osteosynthesis," no refracture occurred (duration of follow-up: 7.4 y).[15]

In 2012, Paley independently[16,17] reported the cross-union technique. In Paley's technique, the tibia and fibula are both rodded straight, keeping the tibia and fibula apart by their normal interosseous distance. A telescopic growing rod is used in the tibia and the rods never cross the ankle or subtalar joints, which can decrease the occurrence rate of ankle valgus deformity and limited range of motion. Paley recommends the cross-union protocol for all types of CPT (Paley Classification of CPT, types 1 to 4). Paley also incorporates pharmacological treatment with zoledronic acid and bone morphogenetic protein (BMP) to prevent resorption of the bone graft and the CPT sites and to stimulate osteogenesis, respectively, neither of which were used by Choi et al.[15] Later, Paley used a plate combined with rodding instead of Ilizarov apparatus.[18] Using the plate eliminates the risk of pin infections, and a cast is used instead of wearing an external fixator for months. These are more convenient to most patients, families, and surgeons.

Cross-union of the tibia and fibula may enhance mechanical stability and provide a unique biological environment promoting union. The cross-union technique produces a much thicker region of bony healing which theoretically may improve refracture risk. Eventually, we chose to use this complementary approach (Paley cross-union technique) to treat CPT after several of the above treatments led to failure as subsequent refracture occurred. The purpose of this study was to evaluate the efficacy of the cross-union of tibia and fibula in the management of refractory CPT, particularly regarding bone union rate and refracture rate during a mean 4.34-year follow-up.

METHODS

Subjects

This study was approved by the Medical Ethics Committee of our hospital (IRB number No. (2021)-120), and written informed consent was obtained from the parents of all patients.

Inclusion criteria: 1. a diagnosis of CPT based on pathologic examination of the resected specimen, whether it was idiopathic or related to neurofibromatosis type; 2. surgical treatment using cross-union of the tibia and fibula; 3. all patients had undergone more than one unsuccessful procedures, including pseudarthrosis resection, intramedullary rod repair of the tibia, autogenous iliac bone grafting or Ilizarov's fixation, before management by cross-union of the tibia and fibula; 4. patients were followed up for at least 12 months. Treatment failure was defined as a nonunion at the last follow-up and/or amputation. Healing—radiographic primary union—was defined as a formation of a bridging callus across the pseudarthrosis site where there were at least 3 of 4 visible cortices on anteroposterior and lateral views.[19]

We retrospectively reviewed 33 cases of CPT patients between June 2014 and August 2020; 18 patients met the inclusion criteria and were enrolled, no patient drop out. There were 13 boys and 5 girls, with the right leg involved in 12 patients, and the left in 6. Pseudarthrosis was at the lower third of the tibia in 13 patients, middle third of the diaphysis in 4 patients, and upper third in 1one patient. The mean age at the initial operation was 5.43 years (range: 2.7 to 10) (Table 1). Because the patients with refractory CPT had undergone more than 1 unsuccessful procedures, we cannot use the Crawford/the Paley classification system to classify.

Surgical Technique

Harvesting of Autogenic Iliac Bone and Periosteum

Each patient was placed and adjusted in a supine position on the operating table. An incision was made centered over the anterior superior iliac spine. The apophysis of the ilium was split and the anterior bone surface was exposed by separating the bone and soft tissue subperiosteally. An outer rectangular cortex was then cut off the ilium, as much cancellous bone as possible was curetted and the lateral periosteum was separated from the overlying muscle and harvested using a technique described by Paley.[20] We then used a skin graft mesher to expand and maintain the size of the periosteum. The cancellous bone and periosteum were reserved for subsequent surgery.

Cross-Union of the Tibia and Fibula

A tourniquet was used before skin incision. An anterior straight incision incorporating the preexisting scar was used to expose the site of the pseudarthrosis. The anterior compartment fascia was routinely released along the length of the tibia. The interosseous membrane and the deep fascia were divided to expose the tibia and fibula. The abnormal periosteum, sclerotic bone, and surrounding pathologic soft tissues were excised. The tibial bowing was straightened and the bone ends overlapped were resected. After removal of the pseudarthrosis, a telescopic growing rod and locking compression plate (LCP) system was used to immobilize the tibia. An appropriate length and diameter telescopic growing rod was inserted and the male end locked with a wire into the distal epiphysis and the female end screwed into the proximal

TABLE 1. Summary of Patient Characteristics

Patient No.	Age (y)/sex	Number of Previous Surgeries Before Cross-Union	Bone Union (mo)	Follow-up (y)	Complications (LLD, Refracture, Deformity)
1	6/M	2	2.8	6	None
2	4/M	1	2.6	4	None
3	5/M	2	3.2	5.25	LLD (3 cm)
4	7/F	1	3	6	None
5	3/M	1	2.2	3	None
6	2.67/M	1	2.7	4.42	None
7	6/M	1	3	6	None
8	7/M	2	2.8	4	LLD (2 cm)
9	6/F	1	3.2	5.25	None
10	10/F	3	3.5	6.25	None
11	4/M	1	2.3	5.58	None
12	6/M	2	2.8	6	None
13	3/F	1	2.2	4.42	None
14	5/M	1	2.3	5.25	None
15	5/M	1	4.1	1.5	None
16	6/M	1	4	2.08	None
17	5/M	1	3.5	1.08	None
18	6/F	1	3	2.08	None

F indicates female; LLD, limb-length discrepancy, may be ascribed to the CPT itself, the acute shortening at the time of pseudarthrosis resection, or previous surgeries, not a complication; M, male.

epiphysis. The telescopic growing rod never crossed the ankle or subtalar joints. The LCP prevents rotation of the tibia, maintaining tibial stability, instead of Ilizarov apparatus. If the fibula is malformed, even forms pseudarthrosis, we would remove abnormal periosteum, sclerotic bone, and surrounding pathologic soft tissues of fibula. An appropriate length and diameter intramedullary Kirschner wire was used to fix the fibula. The periosteal graft covered the area surrounding the resection site of the pseudarthrosis in both tibia and fibula.

The previously harvested cortex was then grafted posterior to the site between the tibia and fibula to separate the implanted bones and the neurovascular bundles behind. The cancellous bone grafts were placed onto the surface of the grafted cortex between the tibia and fibula. Collagen sponge impregnated with BMP-2 was placed between the cancellous bones and then another layer of cortex was applied anterior to the cancellous bone. BMP-2 significantly enhances guided bone regeneration. During all operations care was taken to avoid damaging the neurovascular bundles (Fig. 1).[17]

Postoperative Management

Each patient was immobilized with a plaster slab after surgery and swelling was relieved by intravenous infusion of mannitol to avoid the development of compartment syndrome.[21] The plaster slab was replaced by a plaster cast at the time of hospital discharge to guarantee reliability of immobilization. The plaster cast was removed when an obvious callus was visible on radiographs. The patient began to do careful functional exercises, stand and walk, without brace protected.

All patients were followed up monthly with a re-examination of X-rays to check on bone quality for the first 3 months and then every 1.5 months for the next 3 months until radiographic union was achieved. Afterwards, the patients were followed every 3 months until skeletal union. Because fibular intramedullary Kirschner wire usually irritates skin, we often remove kirschner wire half a year after operation. We do not remove the tibial telescopic growing rod. If the patient want to remove the tibial LCP, we will remove the LCP.

Outcome Evaluation

We assessed the bone union rate and the frequencies of refracture after taking cross-union of the tibia and fibula as clinical outcomes. We also assessed pain, limb-length discrepancy (LLD), and the status of the fibula. Bone union was defined based on both clinical and radiographic data. The patients can bear full weight on the extremity and function was restored without activity limitations. Evidence of bridging callus across at least 3 of 4 visible cortices on anteroposterior and lateral views and no visible fracture line was achieved on radiographs.[22]

Refracture was also defined based on clinical and radiographic data. Pain at the site of pseudarthrosis with evidence of a reliable fracture as a new visible fracture line on a radiograph following the primary bone union.

RESULTS

A total of 18 patients with CPT were enrolled from June 2014 to August 2020. Each patient was treated by cross-union of the tibia and fibula and written informed consent was provided by the parent or guardian before taking part in the study. We did not undertake any blood transfusions, because we put a tourniquet on the patient's thigh to reduce the bleeding and get the surgery done as quickly as possible during the operation.

The mean follow-up was 4.3 years (13 mo to 6.25 y). Radiologic and clinical healing of the pseudarthrosis occurred in all patients at a mean of 2.96 months (2.2 to 4.1 mo) after primary surgical treatment. They were all pain-free and active. The mean age of the patients at surgery was 5.4 years (2.6 to 10 y). All (100%) of the 18 patients achieved primary bone union at the site of the pseudarthrosis, 2 (11.2%) patients had an average 2.5 cm LLD, and of the 18 cases who obtained initial bone union of pseudarthrosis, none (0%) had refracture which needed cast immobilization or secondary surgery (Table 2) (Fig. 2, 3). We experienced complications such as infection, breakage of internal fixation in other methods to treat CPT, however we did not experience any complications apart from LLD in these patients with refractory CPT, using cross-union of the tibia and fibula. The patients said they were all pain-free, and we saw them move actively.

DISCUSSION

More than 100 years have passed since CPT was first described, yet its treatment remains extremely challenging. Numerous surgical treatments for CPT have been recommended. Internal fixation with an intramedullary rod

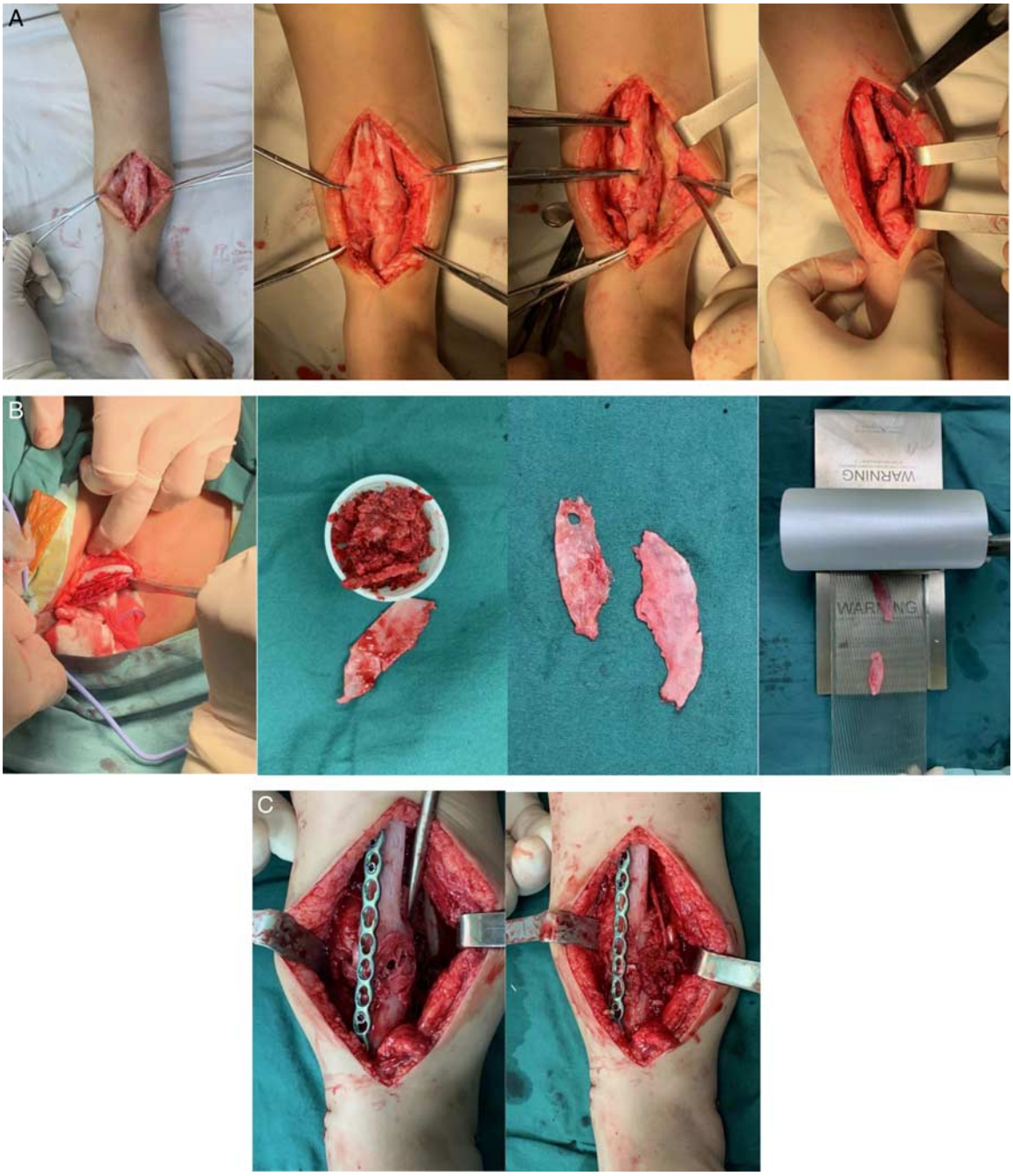

FIGURE 1. A, Exposure of the tibia, interosseous membrane and fibula; resection of the membrane under direct vision; circumferential resection of the tibial fibrous hamartoma at the planned length of the cross-union. B, A periosteal graft was harvested from the undersurface of the iliacus muscle. It was then expanded by passing it through the skin graft mesher. C, An appropriate length and diameter intramedullary rod and locking compression plate system were used to immobilize the tibia; the periosteal graft was wrapped around the congenital pseudarthrosis site and bone morphogenic protein-2 collagen sponges were inserted over the posterior muscles behind the tibia and fibula (left). The cancellous bone was inserted between the tibia and fibula (left center). Bone morphogenic protein-2 sponges were placed over the bone graft (right center).

and external fixation with Ilizarov apparatus have both been shown to have the probability of achieving definite union without refracture.[7,23,24] Adjunctive treatment with BMPs or bone marrow cells, frequently also involving internal or external fixation with or without bone grafting, has been shown to improve clinical outcomes in achieving primary union.[25,26] However, the bone union rate for CPT remains low. For comparison of these surgical methods, Paley defined success as an unequivocal radiographic union of the tibia achieved with the index procedure, without

TABLE 2. Patient Results

Parameters	Total Sample (N = 18), n (%)
Sex	
Male	13 (72)
Female	5 (28)
Side	
Right	12 (67)
Left	6 (33)
Pseudarthrosis	
Lower third of the tibia	13 (72)
Middle third of diaphysis	4 (22)
Upper third of diaphysis	1 (6)
Mean age at surgery	5.4 y (range: 2.6 to 10 y)
Follow-up	4.3 y (range: 1.5 to 6.25 y)
Limb-length discrepancy	2 (11.1%) had average 2.5 cm LLD
Primary bone union	18 (100)
Refracture	0

LLD indicates limb-length discrepancy.

subsequent refracture [union rate×(1-mean refracture rate)]. The average probability of achieving unequivocal union with the index procedure with no subsequent refracture was 50.7% (12% to 80%). A success rate of 50% is not very reassuring to a parent whose child has CPT.[17]

The treatment of CPT is a surgical challenge, in terms of both achieving and maintaining union. Refractory CPT poses a severe problem for the orthopaedic surgeon. For refractory CPT, repeated surgical treatments are sometimes inevitable; and unacceptable outcomes still occur or in more severe cases the condition leads to amputation. Currently, the best surgical treatment for CPT remains controversial for there is no widely accepted surgical technique to successfully treat CPT of all types and presentations. Regardless of the reconstruction technique used, for a better union, realignment of the tibial segment and stable internal fixation are essential, and bone healing and leg alignment must be considered jointly.[27,28] The reconstruction technique used should be adapted to the type of pseudarthrosis and the extent of the bone defects.

Like Paley, we used BMP at the time of surgery. In more recent studies, there has been an increase in the use of biological intervention with administration of BMP.[29] RhBMP-2 has been shown to induce bone formation and resorption in nonhuman primate models.[30] In a similar manner, BMP is used to induce osteogenic formation in combination with traditional fixation methods to decrease time to initial union.[29] In these ways, the Paley technique results in almost twice as large a cross-sectional area of healing as calculated using the relative cross-sectional area of Choi and colleagues (0.46 vs. 0.27).[17] Preliminary results of intentional tibiofibular cross-union from Choi and colleagues and Paley report a probability of primary union without refracture of 100%.[31] This cure rate of CPT is much higher than in traditional methods.

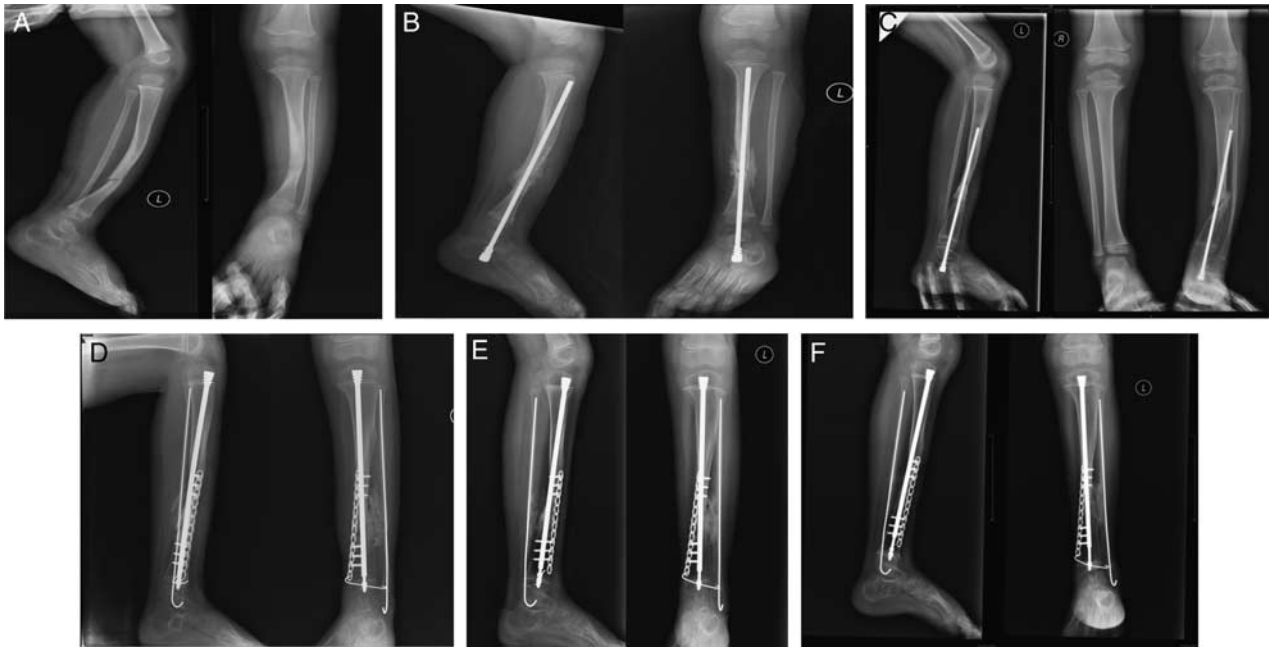

FIGURE 2. Case 1. A child aged 5 years and 1 month with congenital pseudarthrosis of the tibia, had been treated by traditional surgery with pseudarthrosis resection, autologous iliac bone allografting, and intramedullary nail fixation before treating by cross-union of the tibia and fibula. The first procedure was a failure with bone nonunion and lower limb deformity. Three years later, we treated the child by cross-union of the tibia and fibula. Nearly 2.3 months after the second surgery, we found that the child had obtained initial bone union of the pseudarthrosis. One year after the second surgery, we found the child recovered well without lower limb deformity. Anteroposterior (right) and lateral (left) radiographs of (A) preoperation, (B) 4 days after the first surgery, (C) 3 years after the first surgery, (D) treating by cross-union of the tibia and fibula, (E) 2.3 months after the second surgery, (F) 1 year after the second surgery.

FIGURE 3. Case 2. A child aged 5 years and 2 months with congenital pseudarthrosis of the tibia, had undergone traditional surgery twice with pseudarthrosis resection, autologous iliac bone allografting and intramedullary nail fixation before treating by cross-union of the tibia and fibula. The first 2 surgeries were failures with bone nonunion and lower limb deformities. We treated the child with the cross-union of the tibia and fibula procedure. Nearly 3.2 months after the third surgery, we found that the child had obtained initial bone union of the pseudarthrosis. Seven months after the third surgery, we found the child lower limb deformity with 2 cm limb-length discrepancy. Anteroposterior (right) and lateral (left) radiographs of (A) preoperation, (B) the first surgery, (C) 4 months after the first surgery, (D) the second surgery, (E) 2 years after the second surgery, (F) the third surgery, (G) 3.2 months after the third surgery, (H) 7 months after the third surgery.

Since 2013, we have chosen to use Paley's technique for the cross-union of the tibia and fibula, but without zoledronic acid administration, for treating refractory CPT after several failed treatments. Bisphosphonates was not allowed to use in our hospital, we did not have experience in using bisphosphonates in treating CPT. In the present study, 18 patients with CPT were treated by the cross-union of the tibia and fibula procedure and 18 (100%) of the patients achieved initial union at the site of pseudarthrosis. During a mean of 4.3 years follow-up, the primary union rate and the refracture rate in our patients were comparable to those reported in the literature[16,18,31]: 100% union; no refractures.

However, some residual deformities such as LLD still existed. An average of 2.5 cm LLD in 2/18 cases (11.2%) was observed in our study. The LLD following successful union may be ascribed to the discrepancy of limb-length preoperation and the acute shortening at the time of pseudarthrosis resection. Either epiphysiodesis of the contralateral side or tibial lengthening of the involved side could be used to equalize the limb length.[26] Literature reviews show that proximal tibial lengthening may be considered when the LLD is more than 4 cm in younger children after primary union of CPT.[13] Other problems such as proximal tibia valgus and ankle valgus appear relatively minor and attention should be paid to management to correct these deformities in the future if happened. For CPT, the most difficult problem which needs to be dealt with is the nonunion of the tibia fracture. After initial union at the site of pseudarthrosis has been achieved and maintained, any residual deformities can be treated later.

Cross-union of the tibia and fibula, autogenic iliac bone grafting and reliable fixation were evaluated as an effective protocol for the treatment of refractory CPT in our study. The present study still has some limitations. During follow-up, the patients said they were all pain-free, and we saw them move actively. No gait analysis was performed, and we do not evaluate these by pediatric outcomes data collection instrument, visual analog scale. In the future, we will consider to perform gait analysis, use pediatric outcomes data collection instrument, visual analog scale to measure functional outcome, pain score. We experienced ankle valgus in CPT treated by other methods. In these cases, we did not find ankle valgus, maybe the follow-up time is not long enough to present ankle valgus. The sample size was small and we did not document the real incidence of other residual deformities with this combined approach, including proximal tibial valgus or ankle valgus. In the future, larger-scale prospective studies need to be designed to investigate the efficacy of the combined technique.

CONCLUSIONS

The combined technique was evaluated and found to be an effective treatment for managing the refractory pseudarthrosis of the tibia with excellent radiologic outcomes. However, it is necessary to increase the number of subjects and pay more attention to other residual deformities to evaluate the long-term outcome.

REFERENCES

1. Hefti F, Bollini G, Dungl P, et al. Congenital pseudarthrosis of the tibia: history, etiology, classification, and epidemiologic data. *J Pediatr Orthop B*. 2000;9:11–15.
2. Richards BS, Anderson TD. rhBMP-2 and intramedullary fixation in congenital pseudarthrosis of the tibia. *J Pediatr Orthop*. 2018;38: 230–238.
3. Vander Have KL, Hensinger RN, Caird M, et al. Congenital pseudarthrosis of the tibia. *J Am Acad Orthop Surg*. 2008;16:228–236.
4. Crawford AH, Schorry EK. Neurofibromatosis in children: the role of the orthopaedist. *J Am Acad Orthop Surg*. 1999;7:217–230.
5. Cho TJ, Seo J-B, Lee HR, et al. Biologic characteristics of fibrous hamartoma from congenital pseudarthrosis of the tibia associated with neurofibromatosis type 1. *J Bone Joint Surg Am*. 2008;90:2735–2744.
6. Johnston CE II. Congenital pseudarthrosis of the tibia: results of technical variations in the charnley-williams procedure. *J Bone Joint Surg Am*. 2002;84:1799–1810.
7. Dobbs MB, Rich MM, Gordon JE, et al. Use of an intramedullary rod for treatment of congenital pseudarthrosis of the tibia. A long-term follow-up study. *J Bone Joint Surg Am*. 2004;86:1186–1197.
8. Ohnishi I, Sato W, Matsuyama J, et al. Treatment of congenital pseudarthrosis of the tibia: a multicenter study in Japan. *J Pediatr Orthop*. 2005;25:219–224.
9. Paley D, Catagni M, Argnani F, et al. Treatment of congenital pseudoarthrosis of the tibia using the Ilizarov technique. *Clin Orthop Relat Res*. 1992;280:81–93.
10. Agashe MV, Song SH, Refai MA, et al. Congenital pseudarthrosis of the tibia treated with a combination of Ilizarov's technique and intramedullary rodding. *Acta Orthop*. 2012;83:515–522.
11. Shabtai L, Ezra E, Wientroub S, et al. Congenital tibial pseudarthrosis, changes in treatment protocol. *J Pediatric Orthop B*. 2015;24: 444–449.
12. Weiland AJ, Weiss AP, Moore JR, et al. Vascularized fibular grafts in the treatment of congenital pseudarthrosis of the tibia. *J Bone Joint Surg Am*. 1990;72:654–662.
13. Grill F, Bollini G, Dungl P, et al. Treatment approaches for congenital pseudarthrosis of tibia: results of the EPOS multicenter study. *J Pediatr Orthop B*. 2000;9:75–89.
14. Joseph B, Somaraju VV, Shetty SK. Management of congenital pseudarthrosis of the tibia in children under 3 years of age: effect of early surgery on union of the pseudarthrosis and growth of the limb. *J Pediatr Orthop*. 2003;23:740–746.
15. Choi IH, Lee SJ, Moon HJ, et al. "4-in-1 osteosynthesis" for atrophic-type congenital pseudarthrosis of the tibia. *J Pediatr Orthop*. 2011; 31:697–704.
16. Paley D. Congenital pseudarthrosis of the tibia: combined pharmacologic and surgical treatment using biphosphonate intravenous infusion and bone morphogenic protein with periosteal and cancellous autogenous bone grafting, tibio-fibular cross union, intramedullary rodding and external fixation. In: Zorzi A, ed. 2012: 91–106. Available at: https://www.intechopen.com/books/bone-grafting/treatment-of-congenital-pseudarthrosiswith-periosteal-and-cancellous-bone-grafting-.
17. Paley D. Congenital pseudarthrosis of the tibia: biological and biomechanical considerations to achieve union and prevent refracture. *J Child Orthop*. 2019;13:120–133.
18. Paley D. Congenital pseudarthrosis of the tibia. In: Johari A, Waddell J, eds. *Current Progress in Orthopaedics*. Mumbai: Tree Life Media; 2017:318–348.
19. Gilbert A, Brockman R. Congenital pseudarthrosis of the tibia. Long-term followup of 29 cases treated by microvascular bone transfer. *Clin Orthop Relat Res*. 1995;314:37–44.
20. El-Rosasy MA, Paley D, Herzenberg JE. Congenital pseudarthrosis of the tibia. In: Rozbruch SR, Ilizarov S, eds. *Limb Lengthening and Reconstruction Surgery*. New York, NY: Informa Healthcare; 2007: 485–493.
21. Nesaraj J, Varghese VD, Boopalan PR, et al. Intravenous Mannitol reduces intracompartmental pressure following tibia fractures: a randomized controlled trial. *Chin J Traumatol*. 2021;24:109–112.
22. Nicolaou N, Ghassemi A, Hill RA. Congenital pseudarthrosis of the tibia: the results of an evolving protocol of management. *J Child Orthop*. 2013;7:269–276.
23. Joseph B, Mathew G. Management of congenital pseudarthrosis of the tibia by excision of the pseudarthrosis, onlay grafting, and intramedullary nailing. *J Pediatr Orthop B*. 2000;9:16–23.
24. Kim HW, Weinstein SL. Intramedullary xation and bone grafting for congenital pseudarthrosis of the tibia. *Clin Orthop Relat Res*. 2002;405: 250–257.
25. Anderson DJ, Schoenecker PL, Sheridan JJ, et al. Use of an intramedullary rod for the treatment of congenital pseudarthrosis of the tibia. *J Bone Joint Surg Am*. 1992;74:161–168.
26. Lehman WB, Atar D, Feldman DS, et al. Congenital pseudoarthrosis of the tibia. *J Pediatr Orthop B*. 2000;9:103–107.
27. Pannier S. Congenital pseudarthrosis of the tibia. *Orthop Traumatol Surg Res*. 2011;97:750–761.
28. Cho TJ, Seo JB, Lee HR, et al. Biologic characteristics of fibrous hamartoma from congenital pseudarthrosis of the tibia associated with neurofibromatosis type 1. *J Bone Joint Surg Am*. 2008;90:2735–2744.
29. Richards BS, Oetgen ME, Johnston CE. The use of rhBMP-2 for the treatment of congenital pseudarthrosis of the tibia: a case series. *J Bone Joint Surg Am*. 2010;92:177–185.
30. Seeherman HJ, Li XJ, Bouxsein ML, et al. rhBMP-2 induces transient bone resorption followed by bone formation in a nonhuman primate core-defect model. *J Bone Joint Surg Am*. 2010;92: 411–426.
31. Packer DRJ, Liu R, Robbins C, et al. Combined pharmacologic and biological treatment of congenital pseudoarthrosis of the tibia; 100% union; no refractures!. *J Child Orthop*. 2016;10:S19–S20.