International Orthopaedics (SICOT) (2014) 38:1987–1992
DOI 10.1007/s00264-014-2361-7

ORIGINAL PAPER

Effectiveness of recombinant human bone morphogenetic protein-7 in the management of congenital pseudoarthrosis of the tibia: a randomised controlled trial

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Received: 9 April 2014 / Accepted: 14 April 2014 / Published online: 15 May 2014

Abstract
Purpose Despite the popularity and an increased use of bone morphogenetic protein to improve bone healing in patients with congenital pseudoarthrosis of the tibia (CPT), no previous study has compared its efficacy against any other procedure.
Methods We randomised 20 consecutive patients (mean age 4.1 years) with CPT (Crawford type IV) associated with neurofibromatosis type 1(NF1) and no previous history of surgery into two groups. Group 1 received recombinant human bone morphogenetic protein-7 (rhBMP-7) along with intramedullary Kirschner (K)-wire fixation and autologous bone grafting; group 2 received only K wire and grafting. Outcome measures were time to achieve union, Johnston grade, tibial length and the American Orthopaedic Foot and Ankle Society (AOFAS) score, which were evaluated preoperatively and at five year follow-up.
Results Study results showed that patients in group 1 achieved primary bone union at a mean of 14.5 months [standard error (SE) 5.2], whereas group 2 took a mean of 17.11 months (SE 5.0). However, the log-rank test showed no difference in healing times between groups at all time points (P=0.636). There was a statistically significant pre- to post operative improvement (P<0.05) within groups for the other outcome measures.
Conclusion In a five year follow-up, these results suggest that rh-BMP-7 and autologous bone grafting is no better than autologous grafting alone.

Keywords Congenital pseudarthrosis · Tibia · Bone morphogenetic proteins · Bone wires · Grafting

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Introduction

Congenital pseudarthrosis of the tibia (CPT) is a rare disease with varied clinical presentations, and half the people with CPT have neurofibromatosis type 1 (NF1) [1]. The reported incidence of CPT varies between one in 140,000 and 250,000 live births [2]. CPT becomes evident usually during the first year of the life as the child starts to stand and walk [3, 4], and it has a tendency to refracture until skeletal maturity. CPT is one of the most challenging problems in pediatric orthopaedics due to the difficulty in achieving and maintaining bone union. Results of current surgical approaches for CPT consisting of vascularised bone grafting, intramedullary stabilisation and external fixation is only average [5, 6].

In our 15 years of clinical experience, we achieved long-term satisfactory results using intramedullary Kirschner (K) wire. The cost of the implant is another factor favoring K wire over others in the developing world. Hung [7] reported satisfactory long-term functional outcome in CPT using an intramedullary K wire accompanied by excision of the pseudarthrosis and autologous bone grafting. We were unable to find other studies in the literature that report long-term results using K wire.

Bone morphogenic protein (BMP) is a naturally occurring member of the β protein superfamily [2, 8] and plays a key role in transforming mesenchymal cells into bone and cartilage [9]. Clinical studies show that recombinant human BMPs

(rhBMPs) have significant osteoinductive properties and are used to treat a variety of bone-related conditions, including spinal fusions and nonunions, as a graft substitute [10, 11]. BMP [12–18] is increasingly being used to improve bone healing in patients with CPT. Despite its popularity, reported results are short term and anecdotal [12, 13, 19–23].

The primary outcome measure and interventions reported in all previous studies is the time taken to achieve bone union or survival time (time-to-event of discrete occurrence) in patients with CPT. As the events (fracture in CPT) may occur at any time, data do not correspond to normative distribution, and using conventional statistical tool or qualitative description may lead to false interpretation of results. The efficiency of BMP is also not fully known, as no study has compared its effect against any other procedure. This formed the focus of the study, and our aim was twofold: to determine the effectiveness of intramedullary K wire and autologous bone grafting on fracture healing and compare the combined effectiveness of rh-BMP-7 and surgery over a control group that had received only surgical intervention over a duration of five years in patients with CPT.

Materials and methods

This prospective randomised trial comprised 120 patients who reported for CPT management between 2002 and 2007 and were screened for NF1 and type of pseudoarthrosis. NF1 was diagnosed by the presence of pseudoarthrosis of the tibia and six or more café-au-lait spots of ≥0.5 cm diameter, fulfilling the US National Institutes of Health (NIH) diagnostic criteria [24]. Pseudoarthrosis of the tibia was classified radiologically as per Crawford's criteria [25, 26].

Twenty patients (seven boys and 13 girls) who fulfilled our criteria of CPT Crawford type IV (Fig. 1a), presence of NF1 and no previous surgery were recruited and randomised into two groups by consecutive sampling. Mean age at the time of surgery was 4.1 years (range two to seven years). Pseudoarthrosis was located on the distal third of the tibia in all patients. Associated fibular pseudoarthrosis was found in six patients (four in group 1 and two in group 2).

Group 1 [two boys and eight girls, mean age 4.2 (range two to six years), four left and six right tibia) underwent excision of bone and fibrous tissue at the site of pseudoarthrosis. The site was then packed with an autologous tibial graft taken from the opposite side, along with 3.5 mg of rhBMP-7. The tibia was fixed internally with a K wire. Group 2 [five boys and five girls, mean age 4.1 years (range 2.4 to seven years), eight left and two right tibia] underwent the same procedure except that no rhBMP was administered.

Outcome measures

Time taken for healing Survival time is defined in the context of this study as the time required to attain a well-defined endpoint, i.e. bone union and no recurrent fracture for a period of five years.

Johnston grade Non-weight-bearing anteroposterior and lateral radiographs of the involved extremity were evaluated pre-operatively and after surgery as per Johnston's criteria [27].

Tibial length Tibial length was measured from the most prominent portion of the medial condyle of the tibia to the tip of the medial malleolus. Readings were compared with the contralateral leg pre-operatively and at five years.

American Orthopaedic Foot and Ankle Society (AOFAS) score The gold-standard score for foot and ankle is regarded as the AOFAS score [28–31]. The score was evaluated pre-operatively and at the end of follow-up.

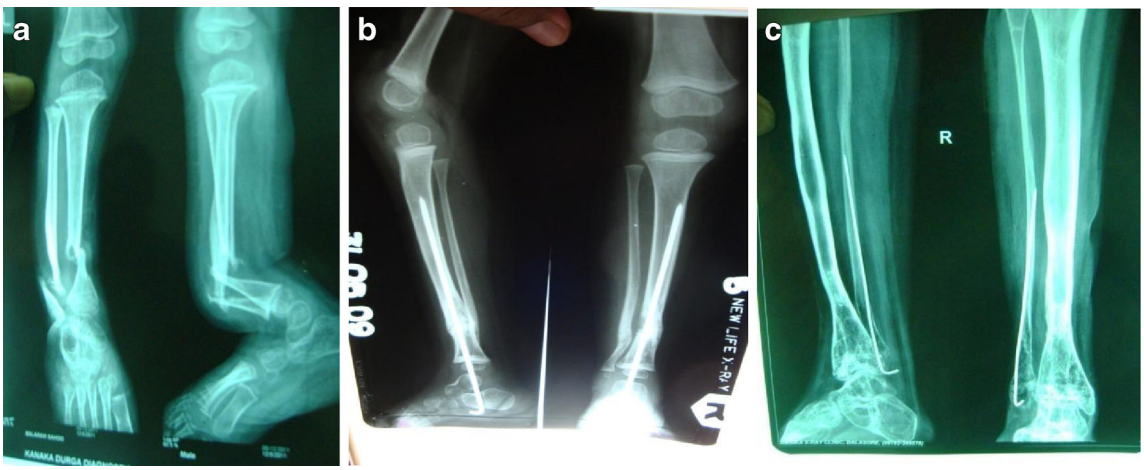

Fig. 1 **a** Pre-operative radiograph of a child with congenital pseudoarthrosis of the tibia (CPT) Crawford type IV). **b** and **c** Postoperative radiographs showing a Johnston grade 1 union

Procedure

The patient was positioned supine on the operating table, and the affected tibia was exposed through an anterior incision over the site of the pseudarthrosis. Bone and fibrous tissue at the site were excised completely to the normal bone of the tibial shaft. The tibia was internally fixed with the K wire, which was passed distally from the sole of the foot, calcaneus, subtalar joint, talus and tibia. Its distal end was folded and pushed up to the plantar surface of the calcaneum. When there was fibular pseudarthrosis, it was resected, and an intramedullary small-diameter k-wire fixation was done (Fig. 1b, c). If not, a fibular osteotomy was carried out. Cortical bone graft and bone marrow was harvested from the opposite tibia and placed alongside the pseudarthrosis site along with rhBMP-7. The subcutaneous tissue and skin were closed. Bilateral above-knee cast was applied to protect both lower limbs. After three weeks, the cast and stitches were removed. The duration of immobilisation and the type of cast (weight-bearing or non-weight-bearing long or short leg cast) were applied on the basis of healing noted during clinical and radiographic examinations. Fiberglass synthetic casts (Scotch cast, Opticast) was used, as follow-up X-ray did not need cast removal. Prolonged orthotic protection was recommended when ankle transfixation had been performed, and a knee-ankle-foot orthosis was prescribed until the patient reached skeletal maturity.

The K wire was removed when solid clinical and radiographic union was apparent. Repeated radiographs were carried out at the follow-up visits until osseous union was achieved and then every six months thereafter. Refracture and nonunion were retreated by operation or cast. Union was considered 'primary' when it united after the intervention without any need for secondary surgeries and as 'secondary' when additional surgery was required to obtain union.

Statistical analysis

Data were analysed with SPSS 16 .0. Time to union was analysed using Kaplan–Meier survival analysis. Tibial length and AOFAS scores were analysed using repeated-measures analysis of variance (ANOVA). *P* value was set at 0.05.

Results

Time taken for union, and Johnston grade Twenty patients with CPT Crawford type 1V and NF1 were randomised in to two groups. Group 1 received rhBMP-7 and excision of pseudoarthrosis; group 2 was treated surgically only. Both groups had a preintervention Johnston grade of 3, and time to union is shown in Table 1. Three patients in group 1 reported refracture: one after trauma to the lower leg after ten months, and the other two after six and seven months. Four patients in group 2 had an episode of fracture within the five year follow-up (range four to eight months) (Table 2). The K wire broke in all patients who had refracture, and none of these patients were Johnston grade 1 after the first intervention. Of those who reported refracture, two patients in each group remained in the cast; the rest were reoperated with K-wire fixation. Two patients in total, one from each group, did not achieve union at the time of final follow-up and were graded Johnston grade 3.

Table 1 Time to union following first intervention

Range	Group 1 (n=7)	Group 2 (n=6)
4.1–5.0	1	0
5.1–6.0	1	2
6.1–7.0	4	2
7.1–8.0	1	0
8.1–9.0	0	0
9.1–10.0	0	1
10.1–11.0	0	0
11.1–12.0	0	0
12.1–13.0	0	0
13.1–14.0	0	1

Kaplan–Meier survival analysis (Fig. 2) showed that patients in the group 1 achieved primary bone union at a mean time of 14.5 months [standard error (SE) 5.2], whereas the control group achieved union at 17.11 months (SE 5.0). However, the log-rank test showed no statistically significant difference in healing times between groups at all time points (P=0.636) (Table 3).

Tibial length

Tibial length deficit reduced from 3.8 cm (range 2.5–5 cm) to 2.8 cm in group 1 (range 2–3.4 cm) and 3.2 cm (range 2–4.2 cm) to 3.0 cm in group 2 (range 2–3.5 cm) (P=0.004)., with no statistically significant difference between groups.

AOFAS score

The AOFAS score improved from 34 (range 20–42) to 64 (range 48–78) in group 1 and from 38 (range 20–48) to 62

Table 2 Time to union and Johnston grade 2 after second intervention

Range	Group 1 (n=2)	Group 2 (n=3)
16.1–17.0	1	1
19.1–20.0	1	1
29.1–30.0	0	1

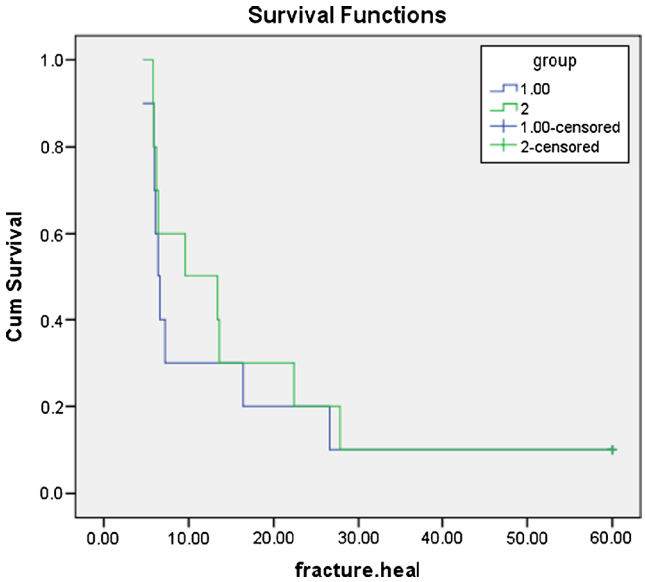

Fig. 2 Kaplan–Meier survival analysis showing healing times in both groups

(range 50–75) in group 2 (p=0.00), with no statistically significant difference between the groups (P=0.821).

Discussion

The treatment method for CPT is controversial and the majority of literature reports are usually case studies and series that are small, noncomparative and composed of heterogeneous groups of patients [32]. To our knowledge, this is the first randomised controlled trial on CPT with a homogenous patient group with identical baseline scores. Results show that adding rhBMP-7 to K-wire fixation was no better than K wire alone in patients with Crawford type IV CPT and NF1 over the longer term. However, addition of rh-BMP helped in early primary fracture healing in patients who responded in group 1 but was of no statistical significance. We chose rhBMP-7 over BMP-2, as BMP-2 was found to be less efficient for promoting new bone formation in NF1-deficient mice [33]. Our results show that all patients greater than three years (four in group 1 and five in group 2) achieved primary fracture healing and a Johnston grade 1 after surgery, which contradicts the consensus of the European Pediatric Orthopedic Society [34] that surgery should be avoided before the third year of life.

Managing CPT requires three steps: excision of the pseudarthrosis surrounding the hamartomatous tissue, autogenous bone grafting and adequate fixation. In this study, we excised bone and fibrous tissue at the site of pseudarthrosis to the extent that all visibly thick periosteum was removed and normal bone was visible. No adjacent neurovascular structure was traumatised during the procedure by maintaining excision extent to the essential. It is now accepted that some form of bone graft is required to facilitate union [35–37]. We chose tibial graft over others sites, as harvesting the tibial cortical graft is associated with minimal morbidity and is more resistant to osteoclastic resorption [36, 38]; cancellous bone graft from the metaphyseal area of the tibia ensured high osteogenic potential and vascularity across the fracture site.

Our results are consistent with that of Hung [7]. The distally folded K wire ensured rigid fixation across the fracture site and prevented distal migration during bone growth. Further, packing the excised area with bone graft increased the cross-sectional area of union, eliminating angulations at the pseudoarthrosis site. This approach ensured that the pathology of the CPT was adequately addressed.

Patients packed with rhBMP-7 had union at 6.1 months compared with the control group, who achieved union at 7.8 months. However, extrapolation of results must be done with caution, as with interpretation of results, as they are may lead to type-1 error. There was a 70 % success rate in group 1; the remaining patients had another episode of fracture. The lack of primary union in the three patients in group 1 may be attributed to many factors. Packing with rhBMP-7 does not govern the entire fracture-healing process and may even assist in modifying mechanical properties at the psueudoarthrosis site but not the biological environment. Where NF1 and CPT coexist, cells have high levels of receptor activator of nuclear factor κ-B ligand (RANKL) and low levels of osteoprotegerin [39]. Limb-length discrepancy in CPT is primarily due to bone resorption, abnormal inclination of the proximal tibia, posterior bowing of the proximal diaphysis, growth abnormalities of the distal fibular physis and excision of pseudoarthrosis. It

Table 3 Means and medians for survival time

Group	Mean				Median			
	Estimate	Standard error	95 % confidence interval		Estimate	Standard error	95 % confidence interval	
			Lower limit	Upper limit			Lower limit	Upper limit
1	14.580	5.212	4.365	24.795	6.400	.395	5.625	7.175
2	17.110	5.051	7.209	27.011	9.600	5.534	.000	20.447
Overall	15.845	3.640	8.711	22.979	6.600	.894	4.847	8.353

has been advocated that patients who undergo early surgery have less growth disturbance [40]. Another potential problem with using distally folded K wire is transfixation of subtalar and ankle joints and distal tibial growth plate. We overcame this issue by removing the K wire after satisfactory clinical and radiological union.

There was statistically significant improvement in AOFAS score in both groups, but neither group was better than the other. We think the development of ankle stiffness and valgus is a potential drawback using K wires, necessitating their early removal after fracture union. Early removal to maintain active ankle range of motion must be compensated for with an orthosis. However, a study by Dobbs et al. [41] showed that temporary transfixion of the tibiotalar and subtalar joints did not negatively affect the long-term functional result. Despite an increase in AOFAS score, the majority of patients who attained fracture union never participated in outdoor sports.

There are many potential drawbacks in this study. Follow-up was limited to five years and not skeletal maturity. The dosage of rhBMP-7 was not calculated for individual patients. We did not measure new bone growth across fracture site using a bone scan. Patients who reported refracture in group 1 were fixed with a K wire alone and no rhBMP-7. We did not add bisphosphonate to rhBMP-7. The study violated the collective judgment of not removing intramedullary fixed instruments after union.

No patient developed side effects to rhBMP-7. One patient in the control group developed wound swelling and another infection, which was treated successfully with antibiotics. Three patients in the experimental group had problems with wound drainage, which resolved after three months. Future studies are recommended to examine the role of different variety of bone proteins or to study the effect of bone proteins in CPT patients without NF1, as well as using other types of intramedullary rods and nails.

Conclusion

Based on our results, we conclude that K-wire fixation along with grafting is a safe method with satisfactory results. We recommend using K wires in younger populations with small-diameter bones. K wires may be preferred to other implants, as complications are fewer and it is cost effective. We prefer not to combine bone proteins with K-wire fixation, as added benefits were limited.

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