

Masquelet's procedure and bone morphogenetic protein in congenital pseudarthrosis of the tibia in children: a case series and meta-analysis

Bruno Dohin · Remi Kohler

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Abstract

Purpose A type 2 recombinant human bone morphogenetic protein (rhBMP2) and Masquelet's procedure were used in three children presenting with congenital pseudarthrosis of the tibia (CPT). Recent studies on CPT suggested the presence in situ of pathologic tissues promoting pseudarthrosis. The authors hypothesized that large segmental resection of pseudarthrosis could improve prognosis of the CPT. Masquelet's procedure and rhBMP2 have been advocated for the treatment of long bone defect.

Method The authors report three cases of CPT in children treated with Masquelet's procedure and application of rhBMP2. They analyzed all published cases of CPT similarly treated.

Results In the present study, Masquelet's procedure did not improve the results in the treatment of CPT, but segmental bone reconstruction was possible. Bone healing was obtained in three out of the five applications of rhBMP2. In one case, the patient's parents asked for leg amputation. Analysis of the 33 published cases with the application of BMP in CPT points to a 62 % healing rate in this pathology.

Conclusion The authors confirmed that segmental bone reconstruction is possible in CPT using Masquelet's procedure. In the literature, the success rate of the application of rhBMP in CPT appears to be lower than the healing rate usually reported without BMP. Nevertheless, the strict

selection of patients, limited number of cases, and their heterogeneity make interpreting the results difficult. However, the theoretical risk which the children are exposed to during the use of BMP makes rigorous selection of the indications necessary. Finally, the interest of rhBMP2 application in Masquelet's procedure remained to be proven.

Keywords Bone morphogenetic proteins · Induce membrane · Congenital pseudarthrosis · Neurofibromatosis · Child

Introduction

Bone morphogenetic proteins (BMPs) have been in clinical use in adults for several years in clearly defined indications: long bones pseudarthrosis, treatment of fresh open fractures, and anterior intersomatic spine arthrodesis or lumbosacral arthrodesis [1, 2]. BMPs are members of the large family of the transforming growth factors (TGF β). They induce mesenchymal cells proliferation and differentiation into osteoblasts [3–6]. Two of the numerous identified BMPs are used for clinical applications: rhBMP2 and rhBMP7 (human recombinant BMP2 and human recombinant BMP7, respectively). They have been studied in animals and their healing improvement activity is well documented [7, 8]. Nevertheless, little is known about these proteins implicated in the tumor process (especially for long-term follow-up), and, in the absence of specific studies, the principle of caution applies [9, 10]. The use of BMPs in children is, as yet, not allowed, and reported cases are compassionate. Such a lot is at stake in congenital pseudarthrosis of the tibia (CPT) that the outcome could be an amputation [11]. The results obtained using BMPs in

B. Dohin (✉)
Pediatric Surgery Department, North Hospital, Jean Monnet
University of Saint Etienne, 42055 Saint Etienne, France
e-mail: bruno.dohin@chu-st-etienne.fr

R. Kohler
Pediatric Orthopedic Surgery Department, HFME Hospital,
University of Lyon 1 Claude Bernard, 69500 Bron, France

adults, particularly in the case of pseudarthrosis of long bones, have opened up the perspective of applying these proteins to children in certain highly complex situations. A few authors have reported their experience in compassionate indications, especially CPT [12–18].

CPT in children is one of the most challenging pathologies in pediatric orthopedics. Numerous procedures have been described in this treatment, with varying degrees of success [19–29]. Moreover, the knowledge of the phenomena altering the physiological bone tissue or the periosteum in neurofibromatosis type 1 (NF1) is not yet complete and has improved even more recently. The studies of Cho et al. [30], Schindeler and Little [31], and Ippolito et al. [32] led us to make the hypothesis that a large resection of pathologic bone and periosteum is required in this disease to improve results. The procedure described by Masquelet et al. [33, 34] (also call “induced membrane procedure”) seemed to be an appropriate procedure for bone reconstruction in this disease. This study reports on and analyses the results of the application of rhBMP2 in addition to or following Masquelet’s procedure in three clinical cases of CPT in children. Two patients were treated twice with BMP. We also analyzed the results of all published cases of CPT in children treated with the application of BMP.

Patients and methods

The limited number of observations made on children led us to envisage analyzing the total number of cases already published and treated with other procedures. To our knowledge, few authors have reported experience (Table 1). We have tried to analyze all the available published cases whilst adding our own experience.

The criteria studied were: indication of the use of BMP, type of BMP used, number of bone sites treated, treatment technique used, number of healed bone sites, time taken to heal, length of follow-up, and possible complication or relapse (fracture or pseudarthrosis). In the cases presented

by the authors, radiological healing was considered to be reached when at least three out of four bone cortexes of the tibia presented evidence of bone bridging on the two orthogonal X-rays.

The BMPs used in the presented cases and published cases were the two available types: rhBMP2 (InductOs[®], Wyeth Europa LtdTM, MetronicTM, France) and rhBMP7 (Osigraft[®], Stryker BiotechTM, Hopkinton, MA, USA). The application technique for rhBMP2 used a sponge of a purified bovine collagen soaked in a reconstituted solution of the active drug. The sponge was then applied to the bone site (with or without a bone graft). In the present cases, only rhBMP2 was used. For rhBMP7, the application technique was somewhat different: the base consisted of powdered purified bovine collagen which was soaked in a reconstituted solution of the active drug and had the consistency of dank sandy dough which was applied to the bone site.

Masquelet’s procedure consists of two surgical procedures [33, 34]. First, a large resection of pathologic tissue was performed and a spacer made of prosthetic cement was put in place of pathologic bone and stabilized with osteosynthesis. Second, 6 weeks later, the spacer was removed, exposing a bone defect surrounded by a new vascularized membrane. The defect was filled with cancellous bone graft and a sponge soaked in a reconstituted solution of rhBMP2 was additionally laid on the bone graft in one case (case 3). The membrane was closed on the bone graft.

In the presented cases, parental consent was requested for application of the rhBMP2, as well as for the exploitation of the medical charts for scientific ends.

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Clinical cases

Case 1—Q.R. was born in June 2000 and had a congenital bow (CB) of the right tibia (Crawford type II). He presented NF1 with a pseudo-tumoral glioma of the optic nerve. In December 2003, he broke his right leg and

Table 1 Reported cases of applications of bone morphogenetic proteins (BMPs) in children in the literature

Authors	Year	Number of cases	Indications	BMP type
Fabeck et al. [12]	2006	1	Cg Ps T	rhBMP7
Anticevic et al. [13]	2006	1	Cg Ps T	rhBMP7
Lee et al. [14]	2006	5	Cg Ps T	rhBMP7
Kujala et al. [15]	2008	1	Cg Ps T	Native bovine BMP
Burkhart and Rommens [45]	2008	1	Tibial Ps after tumoral resection	rhBMP7
Dohin et al. [16]	2009	10	Cg Ps T	rhBMP7
Richards et al. [17]	2010	7	Cg Ps T	rhBMP2
Spiro et al. [18]	2011	5	Cg Ps T	rhBMP2

Ps pseudarthrosis, *Cg* congenital, *T* tibia, *rhBMP7* human recombinant bone morphogenetic protein 7, *rhBMP2* human recombinant bone morphogenetic protein 2

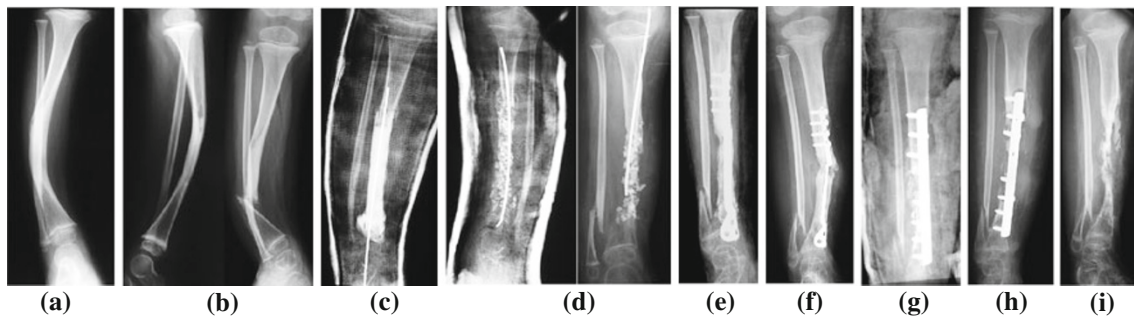


Fig. 1 Observation 1, Quentin: **a** Congenital bow of the tibia in neurofibromatosis type 1 (NF1), **b** fracture, orthopedic treatment with casting failed, **c** Masquelet's procedure, **d** pseudarthrosis relapses, **e** first application of human recombinant bone morphogenetic protein 2 (rhBMP2), healing within 14 weeks (distal screws were removed

early in order to protect the growth plate), **f** 1 year follow-up, fracture of the plate, **g** second application of rhBMP2 and bone grafting, **h** in situ infection with bone absorption, **i** radiological result when parents asked for amputation

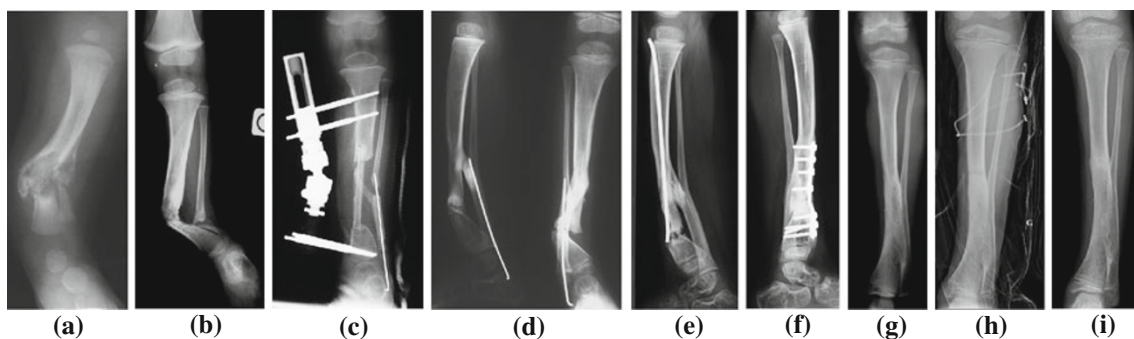


Fig. 2 Observation 2, Loris: cystic congenital pseudarthrosis of the tibia (CPT), **a** 2 months old, **b** worse evolution despite orthopedic treatment, **c** first treatment with vascularized autogenous fibula graft and external frame, **d** pseudarthrosis relapses, **e** third pseudarthrosis

despite performing a Masquelet's procedure, **f** third treatment with the application of rhBMP2 leading to bone consolidation, **g** result in July 2008, **h** fracture in March 2010 with orthopedic treatment, **i** result at final follow-up in May 2011

presented a pseudarthrosis after orthopedic treatment (Fig. 1b); an “induce membrane” (Masquelet's procedure) was carried out in June 2004 (Fig. 1c). The bone graft was subsequently partially and spontaneously reduced. Finally, a pseudarthrosis developed distally. A second operation, adding a bone graft, some rhBMP2, and an osteosynthesis with a plate, was carried out in January 2005. Healing was achieved in 14 weeks (Fig. 1e) but the plate snapped 1 year later. Yet another graft was carried out in March 2006 with a second application of rhBMP2 and a new osteosynthesis with a plate (Fig. 1g). During post operative care, the surgical area became swollen and severely inflamed with phlyctena and osteolysis of the graft (Fig. 1h). A deep infection with identification of *Pseudomonas aeruginosa* surrounded and the plate was removed. At the request of the parents, a below-knee amputation was performed in December 2006 (Fig. 1i). At final follow-up (May 2011), Quentin was in good health, using a leg prosthesis.

Case 2—L.K. was born in May 2000 with a cyst shape congenital pseudarthrosis of the left tibia (CPT) (Crawford

type III) (Fig. 2a). He walked aged 1, but despite the use of a brace, his leg gradually became misshapen (Fig. 2b). Surgery was necessary with excision of the pseudarthrosis, followed by an autogenous vascularized fibular graft (Fig. 2c) and osteosynthesis using a mono-lateral external fixator. Healing did not occur and the pseudarthrosis set in again (Fig. 2d). In February 2004, an operation using Masquelet's procedure was performed, but pseudarthrosis continued on the distal part (Fig. 2e). A further excision followed by a bone graft, osteosynthesis with a plate, and application of rhBMP2 was carried out in September 2005. Union was obtained in 28 weeks (Fig. 2f, g). In March 2010, he presented a midshaft fracture of the tibia (Fig. 2h). The orthopedic treatment led to healing and the tibia was still sound at the final follow-up in May 2011 (Fig. 2i).

Case 3—A.C. was born in October 2003 with a CB of the tibia (Fig. 3a) in NF1 (Crawford type III). She broke her leg in September 2006 (Fig. 3b). A Masquelet's procedure was applied in November 2006; the second procedure used a tibial cortical bone graft and an iliac cancellous

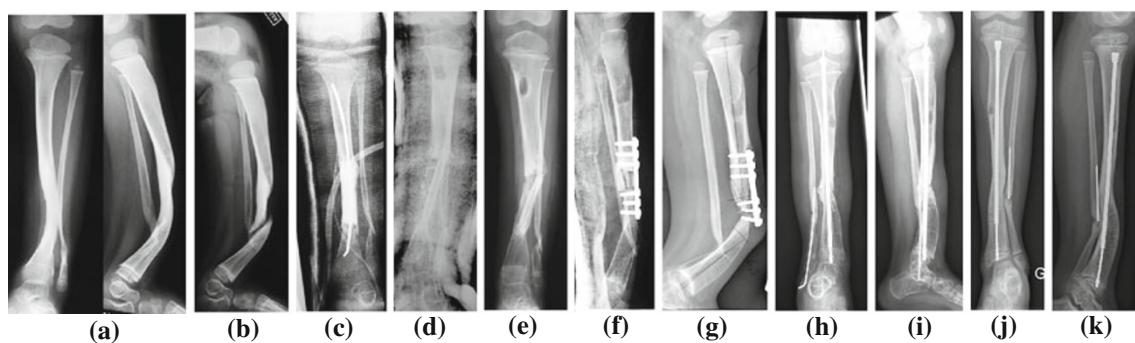


Fig. 3 Observation 3, Alicia: **a** congenital bow of the tibia in NF1, **b** fracture at 3 years old, **c, d** first procedure (Masquelet's) and application of rhBMP2, **e** 7 months follow-up, pseudarthrosis relapses, **f** second application of rhBMP2 and bone grafting,

g pseudarthrosis relapses, **h** third procedure with intramedullary nailing (Fassier–Duval nail) and bone grafting (May 2008), **i** bone consolidation (October 2008), **j, k** result at final follow-up (May 2011)

bone graft associated with rhBMP2 (Fig. 3c, d). In June 2007, a pseudarthrosis was still present proximally to the bone graft (Fig. 3e). When excision of the pseudarthrosis was done (September 2007), a second application of rhBMP2 was made with an iliac cortico-cancellous bone graft (Fig. 3f). Later, a gradual curve appeared in April 2008 and the bone broke underneath the plate with relapse pseudarthrosis (Fig. 3g). In May 2008, another graft with Fassier–Duval nailing was carried out and, by October 2008, finally, the tibia had healed without complication (Fig. 3h, i). At the final follow-up in May 2011, the tibia was still sound (Fig. 3j, k).

Results

The results obtained for these three patients are presented in Table 2. Masquelet's procedure allowed bone rebuilding after large resection of the pathologic tissues in the three patients. Nevertheless, we noted a pseudarthrosis in every case at one's extremity of the grafted area. Three of the five pseudarthroses treated with rhBMP2 healed up. In the successful cases, the average healing time was 18 weeks, whereas the average follow-up lasted 24 months. It is to be noted that one of the healed bones broke again after a year, leading to infection after he was re-operated and, eventually, at the parents' request, to amputation.

Analysis of cases reported in the literature (Table 3) highlight the fact that most of the observations concern patients who, despite numerous operations, have not got better. Surgical treatment used internal or external devices in the three presented cases. We performed three procedures described by Masquelet et al. [33, 34]. The similarity of the severe condition and the good results reported in this technique encouraged us to adapt the procedure in CPT. In the three present cases, bone segmental resection was totally rebuilt, but we noted persistence of a

pseudarthrosis at one out of the two extremities of the segmental bone resection. Osteosynthesis techniques used in the literature were various; nevertheless, nailing and external osteosynthesis with an Ilizarov device have been preferred by several authors, sometimes in combination (Table 4; Fig. 4). Nailing appears to be the procedure with which consolidation has been obtained in most of the cases.

About the use of BMP in CPT, all reported cases and these three present cases are characterized by heterogeneous types of surgical procedure after the application of BMP, depending, in most cases, on the authors' preference. Furthermore, in most of the cases, procedures were performed for re-operations. These facts must be taken into account when interpreting results. The BMP used varied from one author to another, and the criteria for this choice were not specified. Thirty-three cases of the use of BMP in pseudarthrosis of the tibia in children have been reported to date. Out of a total of 44 applications, 19 were rhBMP2 and 24 were rhBMP7. In one case, the authors used native bovine BMP [15]. The overall success rate (26/33) was 79 % (Table 3). The success rate falls to 66 % when only successful applications of BMP are considered (29/44). The rate of positive results depending on the type of BMP used revealed a significant difference for rhBMP2 (Yates' Chi-square test, $p < 0.2$): 13 successes out of 24 applications (54 %) for rhBMP7 and 15 out of 19 (79 %) for rhBMP2. Overall, the average follow-up lasted 34 months. The time taken to heal in successful cases was 22 weeks (with the exception of Fabeck et al.'s observation, in which the healing time was not clearly specified [12]).

Apart from the deep infection which we reported in this series, there was another serious complication (Spiro et al. [18]): compartment syndrome. No other author witnessed any local swelling. There were no secondary effects or complications directly linked to the use of BMP in the cases reported. From a purely orthopedic point of view,

Table 2 Summary of the three cases reported in this study: three procedures used Masquelet's procedure, five anatomic sites were treated with the application of human recombinant bone morphogenetic protein 2 (rhBMP2), and three anatomic sites healed

Patients	Number of previous surgeries	Number of treated anatomic sites	Result of Masquelet's procedure	Number of healed anatomic sites after rhBMP application	Surgical technique of rhBMP application	Follow-up (months)/ complications	Delay for consolidation (weeks)
1A	1 (Masquelet's procedure)	1	Healing proximally and pseudarthrosis distally Total bone rebuilding	1	Screwed plate and bone grafting	12 (fracture)	14
1B	2	1	–	0	Screwed plate and bone grafting	9 (infection and resorption of bone graft)	– (amputation)
2	2 (1 Masquelet's procedure)	1	Healing proximally and pseudarthrosis distally Total bone rebuilding	1	Screwed plate and bone grafting	65	28
3A	0	1 (Masquelet's procedure)	Healing distally and pseudarthrosis proximally Total bone rebuilding	1 (1 extremity)	Bone grafting and cast immobilization	4 (pseudarthrosis at 1 out of 2 extremities)	– (1 extremity: 12)
3B	1	1	–	0	Screwed plate and bone grafting	31 (fracture)	– (pseudarthrosis: nailing and bone grafting, healed 24 later)
Total/ mean		5	Three bone rebuilding Three pseudarthrosis	3		24 months	18 weeks

four repeated fractures were observed and there was one recurrence of a bow.

Discussion

CPT is a rare pathology occurring in between 1/140,000 and 1/250,000 births and is one of the most complex orthopedic situations in pediatrics. In more than 50 % of cases, this occurs in a context of NF1 [19]. The numerous treatment approaches proposed in the literature goes to show the difficulties encountered to obtain healing. The results reported in the literature in the treatment of congenital pseudarthrosis with usual techniques noted a healing rate of 60–85 %. However, in most of the cases, numerous operations were needed, either because of frequent non-unions either or repeated fractures in a short delay. Nowadays, the most commonly used techniques applied either individually or in combination are nailing,

vascularized bone graft, and Ilizarov-type circular external frame [20, 22, 23, 25–29, 35–42].

Technique

The surgical technique initially used in the three patients was in accord with the literature. Plates were used in re-operation in the three cases after the first failed procedures with the aim to obtain tibiofibular fusion. This type of osteosynthesis could be open to criticism regarding the three other options recommended in the literature; nevertheless, the results could be argued: in case 1, we preserved ankle mobility with a plate, but the first plate broke when bone reconstruction was obtained, and then infection surrounded; in case 2, we preserved ankle mobility with a plate and obtained bone healing; in case 3, bone grafting healed but pseudarthrosis recurred beneath the plate. We considered that all therapeutic options must be discussed in these dramatic situations. Such therapeutic difficulties go to

Table 3 Summary of the published cases and mean delay for consolidation and complications reported by the authors

	Delay for consolidation (average)/follow-up	Number of cases and successful cases	BMP	Surgical technique	Complications and outcome
Fabeck et al. [12]	112 weeks (first radiological signs from 5 weeks)/ns	1 case, 1 success	rhBMP7	Nailing and bone grafting	–
Anticevic et al. [13]	24 weeks/45 months	1 case, 1 success (6 applications, 1 success)	rhBMP7	Ilizarov	–
Lee et al. [14]	24 weeks/14.5 months (12–18 months)	5 cases, 1 success	rhBMP7	External devices associated with nailing	1 local sterile discharge
Richards et al. [17]	29 weeks (17–37 weeks)/72 months (48–108 months)	7 cases, 5 successes (8 applications and 6 successes)	rhBMP2	Nailing and bone grafting	1 fracture (1 amputation)
Kujala et al. [15]	24 weeks/24 months	1 case, 1 success	Native bovine BMP	Ilizarov and biocoral	–
Dohin et al. [16]	20.9 weeks (8–60 weeks)/29.5 months (3.5–74 months)	10 cases, 9 successes (16 applications and 10 successes)	rhBMP7	4 external devices, 8 nailing and 1 cast (5/13 procedures without bone grafting)	1 recurring tibia bow, 1 fracture, 2 pins infections
Spiro et al. [18]	14.2 weeks (12–16 weeks)/31 months (10–48 months)	5 cases, 5 successes (6 applications and 6 successes)	rhBMP2	Nailing with or without Ilizarov	1 pins infection, 1 compartment syndrome, 2 fractures
Present study 2012	18 weeks/24 months (4–40 months)	3 cases, 3 successes (5 applications)	rhBMP2	3 Masquelet's procedures, 4 plates with grafting, 1 cast with grafting	1 local inflammatory reaction, 1 infection (1 amputation), 1 fracture
	33 weeks (22 weeks except for the case reported by Fabeck et al.)/average 34 months	33 cases and 26 successes (44 applications and 29 successes)			

ns not specified

show why additional treatments such as electromagnetic stimulation, bisphosphonates, and, more recently, BMP have been tried out [43, 44].

Application of BMP

First described by Urist [3, 4] in 1950, the proteins isolated from a demineralized bone matrix known as BMPs are part of the large family of TGF β . They are secreted by the bone marrow cells, bone, muscle, periosteum, and endosteum cells, and stored in the mineralized bone matrix. Their defining principle activity is osseous-induction; that is to say, the capacity to induce cellular differentiation in order to synthesize the mineral matrix, even aside of the bone tissue itself or on a heterotypical site. They ensure the differentiation of the mesenchymal stem cells, which are recruited, multiplied, and shunted toward the cartilaginous stock (chondroblasts) and bone stock (osteoblasts). They play an inductive and regulatory role. A second important activity is their angiogenesis capacity. There are over 30 of them, but only two have been developed for application in

mankind and produced by genetic engineering: the recombining BMP2 and BMP7. The use of rhBMP in pseudarthrosis of the tibia seems promising in the light of initial observations published about children [12–18, 45] and the results obtained in adults [1, 2]. In children, the question arises as to the early and long-term side effects. The potential influence of these proteins on growth has not been documented. The possibility of triggering or development of tumors (one BMP was identified in certain tumorous pathologies [9]) remains unconfirmed for several authors and no cases of malignant tumors have been reported when safety recommendations are followed [9, 46, 47]. Steib et al. [10] reported a case of malignant tumor when rhBMP was used in an NF1 patient (who presented with scoliosis), but the authors could not follow the safety recommendations for the use of the drug (contraindication in the presence of tumor process) because of the severity of the case. The appearance of heterotypical calcifications may have been at the origin of complications, which are closely monitored nowadays. The possibility of a paradoxical effect of bone resorption has been reported in spine surgery. The local

Table 4 Analysis of the literature regarding results and osteosynthesis

	Total of cases	Total of procedures	Total of applications	Successes	Failures	Cast	Plate	Nail	Iliizarov	Nail + Iliizarov	Monolateral external device	Nail + monolateral external device	Elastic nailing	Iliizarov + vascularized bone graft
Fabeck et al. [12]	1	1	1	1	0			1/1						
Anticevic et al. [13]	1	1	1	1	0				1/1					
Lee et al. [14]	5	6	6	1	5			0/1	0/1			1/3		
Richards et al. [17]	7	8	8	6	2			6/8						
Kujala et al. [15]	1	1	1	1	0				0/1					
Dohim et al. [16]	10	13	16	10	6	1/1		6/7 (+2)	1/2	1/1		0/1	0/1	1/1 (+1)
Spiro et al. [18]	5	6	6	6	0			1/1		5/5				
Dohin-Kohler (present study)	3	5	5	3	2	1/1	2/4							
Total	33	41	44	29	15	2/2	2/4	14/18 (+2)	2/5	6/6	0/1	1/3	0/1	1/1 (+1)

a/b number of healed cases/total number of procedures, (+n) number of cases with two healed sites

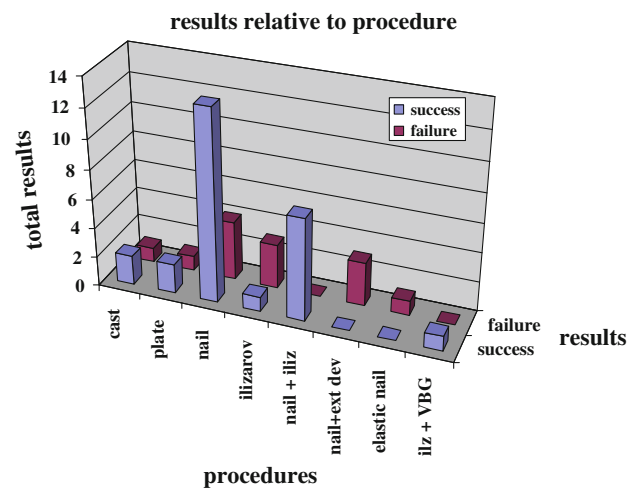


Fig. 4 Results presented relative to the procedure used for stabilization after the application of bone morphogenetic protein (BMP)

overdosage of the drug could play a role in resorption. The induction of antibodies observed has, so far, not led to any description of complications and seems to be transitory [1, 2, 12, 14, 48–50]. Despite these uncertainties and in the absence of any serious complications described in the previously published cases, we considered the benefit/risk ratio to be favorable and put forward a few indications for exceptional cases. We used rhBMP2 in the three presented cases because of its earlier activity in the bone formation process and its lower cost compared to rhBMP7. The first application we carried out in 2005 seemed encouraging and led us to continue using this drug. Two patients had repeated application and one patient had application of rhBMP2 from the onset. We justified these indications by patients' status as challenging diseases. The analysis of the three cases reported in this article points to a low success rate. Although only two cases gave good results in the long term, nevertheless, the relatively short initial healing delay must be underlined (18 weeks).

Literature analysis brings up other questions and comments: the conditions in which reported procedures were carried out are often unclear and most cases described are complex and dramatic clinical situations. BMP is only used as an associated treatment and its efficacy could depend on the osteosynthesis, the procedure itself, and the time the rhBMP is applied (carrier, dosage, half-life of the drug, associated bone graft). Finally, the type of BMP used could play a role. In this analysis of the literature, we noted a significant difference between a 54 % success rate for rhBMP7 (13 out of 24) and 79 % for rhBMP2 (15 out of 19 applications) (Yates' Chi-square test, $p < 0.2$). Nevertheless, this result must be analyzed regarding the small size of the studied groups.

The use of BMP in children raises an important ethical problem. The theoretical risks involved in using BMP for a

growing person and the uncertainty of the long-term effects of these products are still not yet documented. The classical adverse effects observed and described in our patients (local swelling [18, 51], heterotopic calcifications [52–54]) are rare, but already reported in children. We observed in one case a severe local inflammatory reaction without complication. Swelling could be consecutive to excessive bone grafting (in volume) or absence of drainage to prevent suction of the drug during the immediate post operative period; conversely when there was an absence of logical cause, the drug could be in question. We did not note any heterotopic calcification; among the explanations, the use of the drug in a stuffy area could limit drug spreading in surrounding soft tissues. The presence of antibodies developed against the BMP or the carrier seems to be transitory and with no further effect: for this reason, we did not check for the presence of antibodies in our patients. Out of the 44 applications of BMP in children with CPT reported in the literature, we noted 14 incidents or complications (31 %). The cases which could possibly be directly connected with the use of BMP were early local inflammatory reactions (case 1) in the present series and compartment syndrome reported by Spiro et al. [18]. Nevertheless, fracture or recurrent bow leg are part of the possible incidents following the treatment of CPT, more in relation with poor mechanical conditions than default for consolidation. Three fractures are reported in the literature and one underwent treatment in the presented cases. If these fractures healed without surgical procedure, one can consider delayed fractures as benign complications. Analysis must take into account that this pathology presents a high potential risk for repeated fractures. Regarding this risk, the question remains as to whether another fracture occurring after healing obtained by BMP can be considered as a failure of this drug and not a failure of the procedure (i.e., osteosynthesis technique or resection of the pathological tissues).

Otherwise, the infection reported in this study cannot be clearly linked to the use of BMP and could have surrounded without the use of the drug. It was the only failure we observed, the severe infection leading to resorption of the bone graft (case 1). In this case, the parents were discouraged and asked for amputation. To date, this child is well and has settled well with his leg prosthesis. Even if, to date, no long-term effect has been reported, all these risks call for extreme caution in using BMP in children and its application must be limited to rare or exceptional situations with a severe prognosis, as in the case of CPT. It is to be remembered that, up till now, the use for BMPs for children is not officially allowed, their application coming under compassionate indications.

Finally, it is by clinical analogy with pseudarthrosis that other authors have tried using BMP in children, in particular for CPT. The reasons for choosing a particular type of

rhBMP were not reported by the authors. An overall analysis of the results obtained in the literature (Table 3) showed a success rate of 78 % (26 cases out of 33), which is not higher than other treatment described so far in this pathology. Moreover, the success rate related to the number of drug applications has decreased to 66 % (26/44), which could be considered as the real efficacy rate of rhBMP. The time to consolidation is not mostly improved following the application of BMP (22 weeks).

Osteosynthesis and Masquelet's procedure

This disease brings up the question of the local conditions required to obtain healing. Several parameters can, indeed, come into play, such as the vascular or tissue state of the soft surrounding area or the absence or presence of residual pathological bone tissue at the interfaces with the bone graft. However, certain observations showed good results even in the absence of bone excision or in multi-operated patients whose surrounding soft scar tissue had been previously modified by surgery on numerous occasions. It must also be underlined that most of the operations included a bone graft, which could influence the result obtained. Moreover, certain patients were treated right from the first operation with BMP without a bone graft, and some of these cases gave a positive result. Encouraged by previously published successes in Masquelet's procedure and believing in the responsibility of the status of the local soft tissues (either soft scar tissue or pathologic hamartoma tissue) [30, 31, 33, 34, 55, 56], we decided to apply the procedure to congenital pseudarthrosis. Moreover, in one patient, we used Masquelet's procedure in association with rhBMP2 application (case 3). Bone rebuilding was obtained but pseudarthrosis persisted even in the presence of rhBMP2. We cannot make any conclusions about the efficacy of Masquelet's procedure in congenital pseudarthrosis, but we demonstrated that such a procedure allowed a large resection of pathologic bone and reconstruction of the wide long bone diaphyseal defect in this disease. We believe that Masquelet's procedure must take a place in the therapeutic solutions in the treatment of congenital pseudarthrosis as reported previously [55]. To our knowledge, it is the first time Masquelet's procedure is reported in CPT.

Overall, the surgical techniques described in the literature were very varied, depending largely on the teams' habits, and while the results could be influenced by the choice of technique, it was difficult to draw any conclusion on this score (Table 4). It should be highlighted that, under no circumstances, can BMP make up for poor surgical techniques and that their usage must respect the principles of a stable osteosynthesis and as favorable an environment as possible from a vascular and bone point of view.

Analyzing the results regarding osteosynthesis (Table 4; Fig. 4) is delicate. The heterogeneity of the procedures used following the application of rhBMP and the high heterogeneity of cases' histories with previous treatments make conclusions hazardous. Nevertheless, as previously noted [20–22], intramedullary nailing (isolated or associated with an Ilizarov device) appears to be the preferred method with the highest rate of success.

Limitations

This study was limited by the small number of patients, relatively short follow-up, and retrospective nature. Moreover, the literature review is based on reports of individual experiences with a low level of evidence. Further studies are mandatory, but the heterogeneity of surgical procedures and patient populations will represent a great difficulty in the evaluation of BMP in CPT.

Conclusion

It is not easy to know how innocuous bone morphogenetic proteins (BMPs) are and to draw conclusions about the interest of BMPs in children. Conversely, the clinical use of BMPs in children in the case of congenital pseudarthrosis of the tibia (CPT) seems to be a logical indication, in theory at least. An analysis of the literature and reported cases do not provide conclusive evidence but only a possible benefit. A better understanding of the way different BMPs act should make it possible to progress in the method for the application of these drugs and especially in CPT. Today, it appears essential to explore this therapeutic process in optimal analytical conditions and security for young patients.

The knowledge of the phenomena altering the physiological bone tissue or the periosteum in neurofibromatosis type 1 (NF1) hamartoma is not yet complete. Even if consolidation could be obtained without large resection of pathologic tissues, we advocate Masquelet's procedure in order to improve local conditions in the treatment of CPT. The first results are encouraging, despite the fact that reoperations were needed. Interest in the association of Masquelet's procedure and human recombinant BMP2 (rhBMP2) application remains to be proven.

Conflict of interest None.

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