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ORIGINAL ARTICLE

Induced membrane technique for reconstruction after bone tumor resection in children: A preliminary study

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Summary
Aim: Segmental long-bone defect due to tumor resection remains a challenge to treat. The induced membrane technique is a new alternative for biological reconstruction. During the first stage, a cement spacer is inserted after bone resection and stabilisation. The cement spacer is removed during a second stage procedure performed after chemotherapy, and cortico-cancellous bone autograft was placed in the biological induced chamber. The aim of this study was to assess preliminary results in eight children.
Patients and methods: This prospective study included six girls and two boys, with a mean age of 12.1 years (range 9.5 to 18) and treated for a mean 15 cm defect (range 10 to 22 cms) due to resection of osteosarcoma ($n = 4$), Ewing sarcoma ($n = 3$) and low grade sarcoma. All patients except one, were given pre- and postoperative chemotherapy. Surgery was performed for three patients with a distal femur tumor, two patients with a proximal tibial tumor and three patients who had proximal humerus, shaft of humerus and fibular tumors. Fixation was mainly performed with locking compression plate ($n = 4$) and locked nail ($n = 2$). The mean operating times for first and second step procedures were 4.8 and 4 h respectively. The healing process was radiologically assessed.

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Results: After a mean follow-up of 21.6 months (15 to 30), all patients were free of disease and seven had bony union. For the lower limb reconstructions, full weight bearing was possible after a mean of 116 days (range90 to 150) following the second stage. Mean time to bone union was 4.8 months (1.5 to 10). The early Musculoskeletal Tumor Society (MSTS) score was 25.2/30 (range 20—30). Complications were: non-union ($n = 1$), paradoxical graft resorption ($n = 1$) requiring graft revision.
Conclusion: This two stage procedure reduces the operating time during the first stage and it also reduces early complications. Rapid bone union is objectively obtained despite major bone resection and the patients receiving chemotherapy.
Significance: The induced membrane technique could be an excellent alternative for biological reconstruction after tumor resection in children.

Introduction

Segmental long-bone defect due to trauma, infection or tumor resection remains a challenge as it requires complex reconstructive surgery. Multiple surgical procedures had been reported with varying results [1—7].

The French technique of bone-grafting within induced membranes, otherwise known as Masquelet technique [8—10] is an alternative technique and it has recently become more popular [11—16]. This procedure is a two-stage procedure. During the first stage, stabilisation is performed following the bone resection and a cement spacer is inserted followed by soft tissue repair. The second stage is performed a few weeks later, with removal of the spacer, bone decortication and use of cancellous bone graft in the biological induced membrane. Previous experimental studies in animals reported that these membranes possessed a rich capillarity network and have a high concentration of growth and osteoinductive factors [17—20]. This technique was used mainly in the post-traumatic or post-infection diaphyseal defects in adults [10,14,15,20,21].

Biau et al. reported this technique for reconstruction of a diaphyseal bone defect following bone tumor resection in a child [11]. More recently Villemagne et al. have studied a series of 12 cases after 6.2 years follow-up [12]. The purpose of this study was to assess preliminary results of the Masquelet technique in a series of eight children or adolescents treated for metaphyseal or meta-diaphyseal bone tumors. We hypothesized that the technique was safe, led to fewer complications and allowed rapid bone healing.

Patients and method

Patients

A prospective study of induced membrane technique for reconstruction after excision of primary bone tumors was started in September 2008. Inclusion criteria were metaphyseo-diaphyseal and juxtaphyseal malignant bone tumors of long bones in children.

Preoperative assessment of the tumor extension to the epiphysis through the growth plate was assessed using MRI scans at time of diagnosis and after preoperative chemotherapy [22]. Exclusion criteria were patients who were older than 18 years, epiphyseal or intra-articular extension of the tumor, patients with poor prognosis for whom biological reconstruction was not recommended.

Between September 2008 and April 2011, 13 consecutive children or adolescents had induced membrane technique performed in our unit. One patient had poor response to chemotherapy and had developed lung metastases after the first stage surgery and the second stage surgery was not performed. Four other patients were excluded due to short (less than one year) follow-up.

Results in eight patients were included in this preliminary study (Table 1). The mean age at time of resection was 12.1 years (range 7.5 to 18). All patients had pre and post-operative chemotherapy according to the current protocols (OS 2006 for osteosarcoma and EuroEW99 for Ewing sarcomas) [23]; except one patient who had a low-grade periosteal osteosarcoma.

Masquelet procedure

The procedure of the tumor resection was performed according to principles of management of malignant bone tumors. The biopsy tract was excised in continuity with the tumor specimen. The mean bone resection was 15 cm (40% of the length of the long bone). For juxtaphyseal tumors ($n = 3$), the resection was performed through the epiphysis using wires placed under fluoroscopic control to guide the cuts [3]. The osteosynthesis was performed using a LCP plate® or intra-medullary nail (Table 2). A high viscosity polymethylmetacrylate cement spacer (PALACOS Gentamicine LV+ G, Heraeus, Haneau, Germany) was placed in the bone resection defect.

Particular attention was provided to cover the bone-cement junction with the cement, except for the first patient (learning curve). Thermal effect of cement polymerization was minimized with the use of plastic syringes and continuous irrigation with cold saline solution. After careful hemostasis, the wound was closed with a suction drain. The mean operating time for this first stage was 288 min (range 168 to 438 min) (Table 2). Prophylactic antibiotics were given according to the protocol, and anticoagulation therapy was not routinely used. Patients who had lower limb surgery were allowed partial weight bearing for the first 2 weeks followed by full weight bearing

Table 1 Series of patients treated with induced membrane for bone defect due to bone tumor resection.

Patient	Sex	Age[a]	Diagnosis	Location	Level/growth plate	Bone resection (cm- %)	Growth plate preservation
1	F	18	OS	L Prox Humerus	Metaphyseal	15–33	–
2	F	9	Ewing	R Prox Tibia	Juxtaphyseal	11–34	No
3	F	12	OS	L Distal Femur	Metaphyseal	19–47	Yes
4	M	14	Ewing	R Distal fibula	Juxtaphyseal	16.5–26	No
5	F	9	OS	L Distal Femur	Metaphyseal	22–66	Yes
6	F	14	OS Periosteal	R Prox Tibia	Metaphyseal	11–32	–
7	M	13.5	OS	L Distal Femur	Juxtaphyseal	17–37	No
8	F	7.5	Ewing	R Distal Humerus	Metaphyseal	8–40	Yes

F: female; M: male; OS: osteosarcoma; Prox: proximal; L: left; R: right.
[a] Age at first stage surgery.

until the second stage procedure. Adjuvant chemotherapy was started 15 days after the first stage surgery.

In contrast to the Masquelet recommendation for traumatic or infection bone defects, the second stage was delayed to more than 6 weeks in order to minimise the adverse effect of chemotherapy. It was performed one month after the completion of postoperative chemotherapy (6 to 7 months after the first stage) except for patients 4 and 6. Patient 6 (low grade periosteal osteosarcoma) did not receive post-operative chemotherapy and had the second stage surgery 2 months following the first stage procedure.

Patient 4 had a fibular tumor with multiple metastases at the time of diagnosis; the first stage was performed as a definitive local management procedure. Because of event free survival after 18 months, the patient was offered the second stage procedure. As the patient had excellent function with unrestricted sporting ability, the offer of second stage surgery has not been accepted by the patient to date (Table 2).

The second stage was performed under general anaesthesia combined with epidural anaesthesia for patients 5 to 8 and local administration of analgesia on the graft donor site for the other patients. Patients were positioned prone in order to harvest a large bilateral posterior cortico-cancellous iliac crest autograft. After the wound closure without a drain, the patients were placed in a supine position and the reconstruction surgery was performed using the previous incision. The induced membrane was carefully opened along the spacer and the first few centimetres on the adjacent bone, and the cement spacer was easily exposed with minimal dissection. The cement was removed after fragmentation with osteotomes. The adjacent bone—cement junctions were decorticated and freshened for a cm until bleeding bone was obtained. The medullary canal was reamed. Morcellised cortico-cancellous graft was placed into the biological chamber. For patients 5 and 7, demineralized bone matrix injected with bone marrow aspirate was used (in a proportion of 10% around) with the cortico-cancellous autograft in order to have full filing of the biological chamber. The membrane was closed without a drain. The mean operating time for this second stage was 242 min (range 165 to 350 min) (Table 2).

Intermittent passive mobilization was started immediately after surgery as was touch weight-bearing mobilisation for lower limb resections.

For the patients who had lower limb resections, partial weight-bearing with 50% of the weight was allowed until 45 days and it was increased by 10% each week thereafter. The weight bearing was also tailored according to the DEXA assessment [24,25].

Assessment

Oncology follow-up was done at three monthly intervals for the first year and six monthly intervals until 3 years. The surgical margins were histologically negative for tumors in all patients (R0 according to UICC classification). The response to chemotherapy was 100% for patients 1, 3, 4, 7, 8; less than 1% of residual tumor for Patient 2 and 7% of residual tumor for patient 5 (no chemotherapy for case 6).

Bone healing was assessed using antero-posterior (AP) and lateral radiographs.

Each patient was evaluated by an independent observer not involved with the care of the patients. Functional results were assessed using the Musculoskeletal Tumor Society Score (MSTS score) at the last follow-up visit [26]. Joint range of motion, strength, muscular atrophy and lower limb length discrepancy were also assessed at the follow-up visits.

Results

Patients were followed for a mean period of 21.6 months (range 15 to 30). All patients were free of disease at time of last follow-up. Technical details, time of each surgical stage, complications and results are reported in Table 2. Six out of eight patients had bony union after the second stage procedure. Patient no. 1 required a third procedure due to non-union which could be partly attributed to the technical error (learning curve of the method). Patient no. 5 had difficult recovery with inability to weight-bear. It was noted that there was progressive, massive resorption of the graft. Further surgery was performed using new auto graft and revision fixation. Patient no. 3 had screw removal after 10 months following the second stage in order to dynamize the locked nail; this surgery resulted in bony union. No infection was reported after the first stage of reconstruction. Following the second stage of reconstruction, patient no. 1 who was obese (BMI = 42.5 kg/m^2) had a superficial infection of the posterior iliac crest site, which resolved without further surgery or antibiotics.

Table 2 Management procedures and results.

No.	Op Time [a] first stage (mn)	Internal fixation	Op Time [a] stage II (mn)	Time to full WB/S2	Time to bone union/S2 (months)	Healing Complication Or Surg n°3	Follow-up/S1 (months)	MSTS/score	Mobility
1	280	Plate	240	—	11	Non union—graft revision	33	25	F: 110 Abd 90
2	285	LCP plate®	210	90	3	0	27	23	Full mob
3	240	Loocked Nail	165	120	4	Screw removal	27	20	0-120
4	168	Wire + scew	—	—	—	—	21	30	Full mob
5	438	Loocked Nail	247	>250	—	Graft Resorption-waiting new graft	18	—	0-90
6	274	LCP plate®	174	105	3.5	0	16	26	Full mob
7	330	LCP plate®	312	150	6	0	16	—	15-0-120
8	—	LCP plate®	350	—	1.5	0	15	27	20-140

Time to full WB/S2: time in days to full weight bearing following the second stage of induced membrane; MSTS: Musculoskeletal Tumor Society.
[a] Operating time.

After the second stage, early partial graft resorption at the periphery was noticed in the radiographs of all patients (Fig. 1). After exclusion of case 5 (waiting new graft), mean time to bone union was 4.8 months (1.5 to 10). Three patients who had intraepiphyseal resection and growth plate resection will require further surgery to correct secondary limb length discrepancy.

Discussion

Despite major bone resection (40% of the bone length) and aggressive chemotherapy, seven out of eight patients treated in this study achieved rapid bone healing with low rate of complications. The method failed in one patient for whom a massive and progressive graft resorption occurred.

Masquelet had developed a two-stage procedure to reconstruct long bone defects in 1986 [8—10,13]. Clinical, experimental, and fundamental studies have shown that the foreign body-induced membrane can be used to promote the consolidation of a conventional cancellous bone autograft for reconstruction of long bone defects [17,18]. The main properties of the membrane are to prevent the resorption of the graft and to secrete growth factors [8,17,18].

This technique has been used for many other indication [10,15,16,21], and we believe that its application in orthopaedic oncology is a novel but effective application.

The adverse effect of chemotherapy on bone healing

The adverse effect of chemotherapy on bone healing prompted the modified Masquelet procedure; the second stage was not performed after 6 weeks but delayed after the end of chemotherapy. Despite this adaptation, two patients in this study did require a revision surgery because of healing problems; both of them had osteosarcoma; and both had Methotrexate used during the treatment. Methotrexate's adverse effect had already been highlighted after bone reconstruction with vascularized fibula in sarcomas [6]. Our observations could suggest that adverse effect of chemotherapy on bone healing was observed even 1 month following the end of chemotherapy.

Bone loss

Moreover, bone loss secondary to oncologic surgical resection is usually massive. In our series, the mean bone defect was 15 cm and it was 40% of the bone length. A percentage of bone length resection is preferable than an absolute value in cm in order to compare adult and pediatric series. Long diaphyseal resection or meta-diaphyseal resection required a large cancelous graft and both posterior iliac crests were routinely harvested in this series. Posterior crest allows more important bone graft with lower morbidity than anterior crest [27,28]. Two patients with very long and large bone defects due to meta-diaphyseal resection (patients 5 & 7), the graft did not fully fill the gap and it was combined with demineralised bone matrix. The only donor site morbidity in all eight cases was one case of superficial sepsis (patient 1).

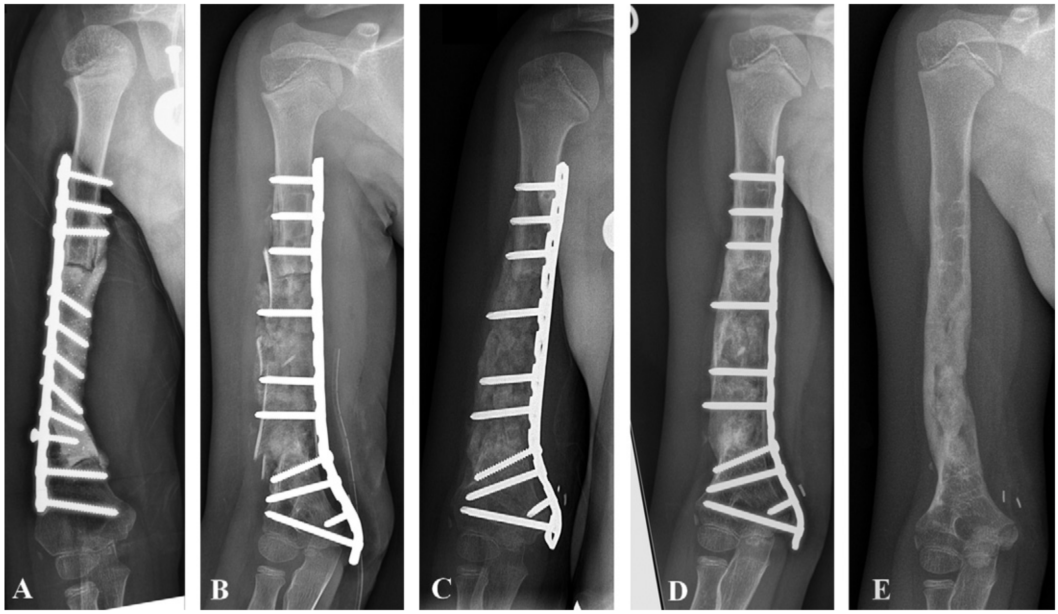

Figure 1 Patient 8: Ewing sarcoma of the right humerus in a 7.5 year-old girl. Radiologic appearance after first stage performed in another country (A), postoperative radiograph after second stage (B), 45 days after second stage: remodelling and peripheral bone resorption (C), 5 months after second stage: corticalisation (D) and 1 year follow-up after second stage (plate remove after 9 months) (E).

There was minimal cosmetic change due to the posterior scars.

Intra-epiphyseal resection

Bone sarcomas are mainly located in the metaphyseal area; sometimes very close to the growth plate which can act as a barrier to the epiphyseal extension. Intra-epiphyseal resection and biological reconstruction is an alternative to endoprosthestic reconstruction; it should be performed only in selected patients with good prognosis [22]. Care must be taken when determining surgical margins and tumor should not cross the growth plate for option of epiphyseal preservation [3,22].

Intraepiphyseal resection is also associated with growth plate sacrifice, and will require additional surgery in order to manage further limb length discrepancy. Because of very low morbidity, percutaneous curettage of the controlateral physis can be performed when provisional lower limb discrepancy is between 2 to 4 cm [29]. This procedure can be delayed and combined with the second stage of induced membrane technique rather than later in order to avoid a third procedure. For younger children, the percutaneous epiphysiodesis procedure can be combined with bone lengthening after skeletal maturity (no patient in this series).

Choice of osteosynthesis

Of course, the level of resection impacts the choice of osteosynthesis. This choice could play a role in the healing process; the stabilization was performed with a nail when epimetaphyseal bone was sufficient to achieve a good fixation. When resection was intraepiphyseal, an LCP plate® was used (Fig. 2). Too rigid fixation with a strong nail should probably be avoided. On the contrary, unstable fixation is not recommended. Villemagne et al. reported recently a similar study to the present one with longer follow-up [12]. Twelve patients had induced membrane technique for segmental reconstruction of long bone after malignant tumor resection. Elastic stable intramedullary nailing (ESIN) was used eight times out of 12 during first stage and four times during the second stage. This paper, in our opinion, should suggest avoiding ESIN fixation in such indication, as none of the patients in this study had spontaneous normal healing. All needed repeat grafting procedures except one who did require a femoral osteotomy for varus deformity...

MSTS score

The tumor location affects the final results and the MSTS score. In our study, tibial resection was associated with a full range of motion recovery and highest MSTS score. After femoral resection, knee flexion was often restricted because of quadriceps adherence to the induced membrane. Further procedures for knee joint release may be necessary after femoral reconstructions. Moreover, intraepiphyseal distal femoral resection required the sacrifice of posterior condylar structures and gastrocnemius muscle insertions; patient 7 had tumor resection which led to a moderate knee recurvatum despite attempts to obtain reinsertion of the posterior structures.

The unexpected evolution of patient 5 with a complete and progressive graft resorption could be due to association of multiple factors; use of Methotrexate (osteosarcoma), femoral location with a major bone defect which required additional demineralized bone matrix in order to fill the bone defect, and use of a rigid fixation with a locked nail.

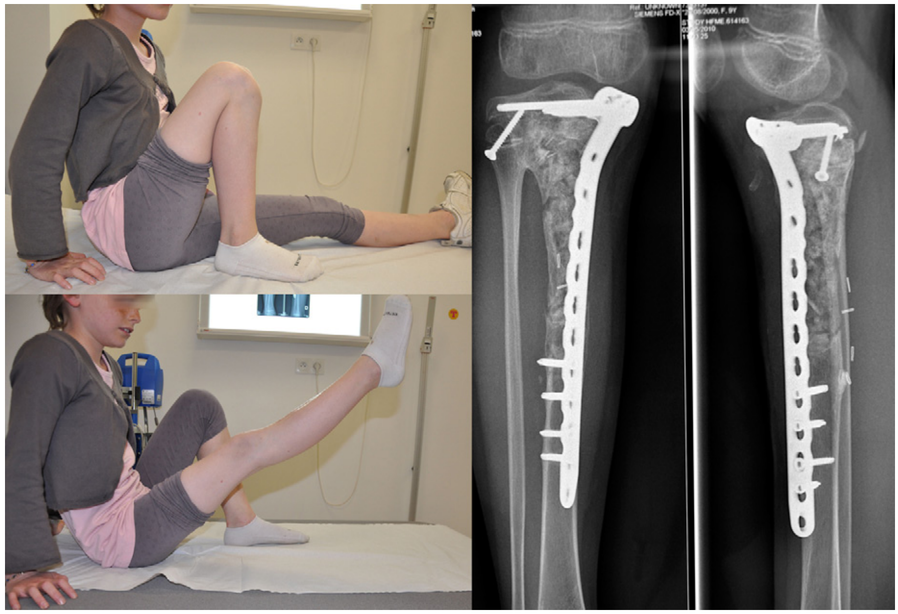

Figure 2 Patient 2 after 9 months following second stage. Knee mobility in flexion and active extension after intraepiphyseal tumor resection preserving the chondral anterior tuberosity (left). X-ray AP and lateral view (right).

Moreover, weight-bearing was delayed because of psychological difficulties. However, other biological processes in the biological chamber could have also contributed to this unexplained graft resorption.

The induced membrane method

Compared to others alternative of biological reconstructions, the main advantage of induced membrane method is the simplicity; no major technical expertise is required. Contrary to vascularized fibular graft [5,6,30,31] or hybrid reconstruction described by Capanna et al. [7], this method can be used in centres without access to microsurgery. Another advantage of the induced membrane technique is the low morbidity of the graft donor site using the posterior iliac crest. Only one superficial infection was noted in our series. Classical complications associated with vascularized fibular graft reconstruction in children are: retraction of the Hallux flexor (1 to 3%), paresis of the common fibular nerve (4 to 5%), and ankle valgus deformity (2 to 3%) [32—35]. These complications reached 36% in Hariri study with a similar population to those of the present study [6].

It can be argued that the disadvantage compared to vascularized fibular reconstruction is the necessity of two-stage surgery. Hariri et al. in a recent study about vascularized fibula noticed that the mean number of reoperations was 2.02 (0 to 5) per patient. In the later study, 50% of patients required secondary iliac crest autogenous grafts and 26% needed an osteotomy for malunion [6]. Only two patients in our study required a third procedure in order to achieve bone union. Capanna et al. described a primary reconstruction with vascularized fibular autograft in association with massive allograft. This reconstruction provides early mechanical stability, protecting the fibula from fracturing and allowing axial loading of healing bone [7].

Operating time and infection

In our experience, the first stage is simplified and the operating time was reduced in comparison to the fibular graft reconstruction. The mean operating time was 3.8 h in our study, it was 4.8 h in Villemagne et al. study [12], compared to 9 h in Lafosse study [5] and 12.9 h in Zaretski study [30]. There is no need of two-team approach when using the induced membrane technique. Also, a lower rate of complication during the period where the patient is vulnerable due to the effects of the chemotherapy could be expected. Our series is too small to draw conclusions regarding complications. Nevertheless, both Villemagne and our study, have not observed any infection at the site of reconstruction. While the rate of deep infection after vascularized fibular graft is between 10 to 18% [5,6,30,31], and 7.5% in Capanna et al. series with mixed adult and children patients [7].

Time to full weight-bearing and bone union

Time to full weight-bearing in lower limb reconstruction is important as it impacts on the quality of life. The induced membrane technique used for lower limb reconstructions could reduce time to full weight-bearing when compared with vascularized free fibular graft reconstruction. In our study, except patient 5 (graft resorption), mean time to full weight-bearing was 116 days or 3.8 months years (3 to 5). Time to weight bearing was similar: 4 months (0.2 to 14.2) in Villemagne et al. study [12]. Hariri, in a similar population using free fibular vascularized graft, found the mean time to full weight-bearing was 11.4 months (1.6 to 41.4) [6]. When using Capanna technique in children, full weight bearing was achieved in a mean of 5.5 months [36].

Time to bone union was found short 4.8 months in our study, compared to Villemagne et al. study, where it was found to be 11.5 months. It was achieved in 16 months in seven cases of intercalary resection reconstructed with vascularized fibula in Lafosse et al. study and 21.4 months in Hariri et al. study with the same technique. The adjunction of allograft as described by Capanna allows decreasing time to bone union to 9 months in Moran study [37].

The weakness of our study is a short follow-up and comparison with long or mid-term follow-up study using other biological methods. But comparison was mainly done for pre- and intraoperative data and early complication and bone union rate. Moreover when bone healing is achieved, the result is usually stable after biological reconstruction, contrary to endoprosthesis or allograft replacement.

Short follow-up

Despite a short follow-up (incompatible with full return to sporting activities), a 25.2 points mean MSTS score in the present study is similar to the mean MSTS score reported after vascularized fibula [6,31,38] or Capanna method [7] applied in pediatric oncology (between 23 to 27 according to literature).

Conclusion

These preliminary results are encouraging as the induced membrane technique simplifies the first stage procedure performed during the critical period reducing the rate of infection and the donor site complications. Early full weight-bearing and rapid bone union is objectively obtained even after major bone resection and concurrent chemotherapy. The ideal indication for induced membrane technique in children could be intercalary resection of the tibia for Ewing sarcoma. Further studies with longer follow-up and larger population will be needed to validate this preliminary study.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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