Masquelet technique for the treatment of infected segmental long-bone defects

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ABSTRACT

Introduction: Infected segmental bone defects are challenging conditions which require a complex treatment. The Masquelet technique is an alternative for these cases. The aim of this retrospective, multicenter study was to show the clinical and radiological outcomes achieved with the use of this reconstruction technique in infected femoral and tibial segmental defects in order to characterize the defects treated and describe different aspects of this surgical approach. **Materials and Methods:** We analyzed 24 patients (14 men and 10 women; average age 36.16 years [range 18-67]) treated with the Masquelet technique between 2011 and 2016. The average follow-up was 16.5 months (range 12-27) from the second surgical stage. We analyzed the affected bone, defect length (cm), consolidation time and infection control. **Results:** Average length of bone defects was 5.7 cm (range 3-12), exceeding 4 cm in 50% of the cases. The largest segmental bone defect was 12 cm at the tibia and 10 cm at the femur. Bone consolidation was achieved in all cases on an average of 4.5 months. One patient presented a recurrent infection 12 months after successful consolidation. **Conclusions:** The Masquelet technique, or induced membrane technique, offers a feasible and simple alternative to a highly challenging problem such as infected segmental bone defects, achieving a consolidation rate of over 90% even in difficult cases.
Key words: Segmental bone defect; infected bone defect; femur; tibia; Masquelet technique.
Level of evidence: IV

Defectos óseos segmentarios infectados en huesos largos: tratamiento con técnica de Masquelet

RESUMEN

Introducción: Los defectos óseos segmentarios infectados son entidades de complejo tratamiento. La técnica de Masquelet representa una alternativa para estos casos. El objetivo de este estudio retrospectivo multicéntrico fue mostrar los resultados clínicos y radiográficos obtenidos con esta técnica de reconstrucción en defectos óseos segmentarios infectados de fémur y tibia, caracterizar los defectos tratados y describir los diferentes aspectos de la técnica quirúrgica. **Materiales y Métodos:** Analizamos a 24 pacientes (14 hombres y 10 mujeres; edad promedio 36.16 años [rango 18-67]) tratados con la técnica de Masquelet, operados entre 2011 y 2016. El seguimiento promedio fue de 16.5 meses (rango 12-27) desde el segundo tiempo quirúrgico. Se analizaron el hueso afectado, la longitud del defecto (en cm), el tiempo de consolidación y el control del proceso infeccioso. **Resultados:** La longitud del defecto óseo tratado fue, en promedio, de 5,7 cm (rango 3-12), fue superior a 4 cm en el 50% de los casos, el defecto óseo segmentario de mayor tamaño en la tibia fue de 12 cm y de 10 cm en el fémur. Se logró la consolidación ósea, en todos los casos, en 4.5 meses. Un paciente presentó una recidiva del proceso infeccioso a los 12 meses de la consolidación. **Conclusiones:** La técnica de Masquelet o de la membrana inducida ofrece una alternativa razonable y sencilla para un problema altamente desafiante como son los defectos óseos segmentarios infectados. La tasa de consolidación es superior al 90% aun en casos complejos.
Palabras clave: Defecto óseo segmentario; defecto óseo infectado; fémur; tibia; técnica de Masquelet.
Nivel de Evidencia: IV

INTRODUCTION

Segmental bone defects (SBD) are among the most challenging conditions an orthopedic surgeon can face in his practice. The complexity of these cases relies on the fact that their management requires long-term treatment and multiple surgical procedures, and results in a significant complication rate[1-5].

Among the most widely used approaches for this type of bone reconstruction are autologous iliac crest grafts or morcellised allografts[6], callotasis[2, 5, 7-10], and vascularized bone grafts[11]. All these are defined as high-demand approaches, sometimes being unpredictable and resulting in complications.

The Masquelet technique was first used on the late 1980s, but it wasn't reported until the year 2000. It is a relatively simple technique that allows to reconstruct diaphyseal and metaphyseal SBD of multiple causes and sizes, without the need for microsurgery skills or high-complexity hospital infrastructures[12-14].

It is based on the placement of a polymethylmethacrylate (PMMA) cement spacer, which causes a foreign body reaction and subsequent formation of an *induced biological membrane*. In a second surgical stage, the spacer is removed, and the cavity (covered by the biological membrane) is filled with a bone graft, preferably an autologous graft. The biological membrane prevents graft resorption and formation of fibrous tissue at the bone-cement interface and secretes growth factors that promote bone consolidation[15-18].

This approach is currently used in adult and pediatric patients to treat infected and non-infected long-bone nonunions[17], reconstructive procedures in cancer patients[19-21], and birth defects[21, 22].

This retrospective, multicenter study aimed to show the clinical and radiological outcomes resulting from this reconstructive approach in infected femoral and tibial SBD, to characterize the type of defects treated, and to describe the particulars of the surgical approach.

MATERIALS AND METHODS

This was a retrospective, multicenter study in patients undergoing infected SBD reconstruction, treated with the Masquelet technique at three high-complexity Orthopedic Surgery institutions in Buenos Aires between March 2011 and December 2016.

The inclusion criteria were: 1) patients >18 years old; 2) tibial or femoral SBD; 3) clinical or microbiological diagnosis of defect infection; and 4) >12-month-follow-up as from the second surgical stage.

Our series was comprised of 24 patients (14 men and 10 women) with an average age of 36.16 years (range 18-67). The mean follow-up time was 16.5 months (range 12-27) as from the second surgical stage.

Defects were located on the tibia in 13 cases (54%) and on the femur in 11 cases (46%). Sixteen patients (66.6%) had open fractures. Most common fracture type was Gustilo subtype IIIB, present in 7 cases (29%). Eight patients (33.3%) had closed fractures (Table 1).

The average time elapsed from the injury and the treatment of the SBD with Masquelet technique was 9 months (range 1-24). All defects were infected, as confirmed clinically or microbiologically.

Preoperative evaluation of the SBD was carried out with AP and lateral X-rays of the target bone (Figure 1). The Bone Reconstruction Index (BRI) was expressed according to Gouron's description[22] (bone defect length/total bone length).

All patients were operated on by surgeons skilled in lower limb trauma following the same treatment guidelines in two surgical stages, as described by Masquelet[12].

Surgical approach

The basis of the surgical approach is to elicit an inflammatory reaction to a foreign body by placing a PMMA cement spacer, around which a biologically-active membrane is created.

First surgical stage: aggressive debridement is carried out, resecting all devitalized tissue affected by the underlying infection following the principles of oncologic resection. This way, we were able to restrict the risk of persistent infection. Debridement was carried out down to bleeding cortical bone and drilling of the medullary canal was performed to create bleeding sites. Then the bone was stabilized by the most adequate osteosynthesis technique for each case (as per the attending specialist judgment), followed by placement of a PMMA tubular-shaped antibiotic-spacer within the SBD (Figure 2). PMMA was mixed with antibiotic agents and molded by hand. If any pathogen was identified before surgery, a specific antibiotic was used. If tegumental coverage was needed, appropriate procedures were also carried out at this point.

Second surgical stage: carried out after 6 weeks from the first stage, once humoral titers and patient's condition were stable. The induced membrane was identified and opened longitudinally, the cement spacer was removed by

Table 1. Detailed description of the patients included in the series.

Patient/ Age/Gender	Segmental bone defect location	Length (cm)/ BRI (%)	Fracture type (Gustilo)	Time elapsed since the onset of the segmental bone defect (months)
1/56/M	Tibial shaft	12/35	IIIB	12
2/43/M	Distal tibia	7/20	IIIA	2
3/39/M	Femoral shaft	9/20	Closed	9
4/51/M	Distal tibia	4/15	IIIA	4
5/18/M	Distal tibia	4/12,5	IIIB	4
6/37/F	Proximal tibia	3/12,5	Closed	15
7/48/M	Distal tibia	3/10	IIIB	12
8/38/M	Distal tibia	3/7,5	IIIB	4
9/19/F	Femoral shaft	8/20	Closed	18
10/26/M	Tibial shaft	8/25	IIIB	1
11/27/M	Tibial shaft	6/25	IIIC	5
12/30/M	Femoral shaft	6/15	IIIA	3
13/29/F	Tibial shaft	4/15	IIIB	1
14/67/F	Femoral shaft	7/20	Closed	22
15/41/M	Distal femur	4/15	II	12
16/64/F	Femoral shaft	4/15	Closed	24
17/43/F	Distal femur	7/20	Closed	12
18/18/F	Distal femur	8/19,5	Closed	18
19/23/F	Tibia distal	3/10	IIIA	1
20/29/F	Tibial shaft	4/15	IIIB	1
21/28/M	Femoral shaft	8/20	II	4
22/32/M	Femoral shaft	3/10	Closed	3
23/43/F	Distal tibia	4/15	II	12
24/19/M	Femoral shaft	10/30	IIIA	9

BRI: Bone Reconstruction Index.

Figure 1. A 19-year-old man with a history of open femoral fracture (Gustillo IIIA). **A.** Fistula in the middle third of the affected thigh 9 months after the fracture. **B.** 10 cm-long segmental bone defect.

fragmentation, being careful to avoid further damage to the SBD and especially the membrane. Bleeding points were created at cortical bone level to improve blood flow at the nonunion. The cavity was then filled with a morcellised iliac crest autograft, chosen for its osteoconductive, osteoinductive and osteogenic properties (Figure 3). If this was not enough, a bone substitute or morcellised/structural allograft can be used, not to exceed a 1:3 ratio (substitute:autograft)[5, 12, 16, 22].
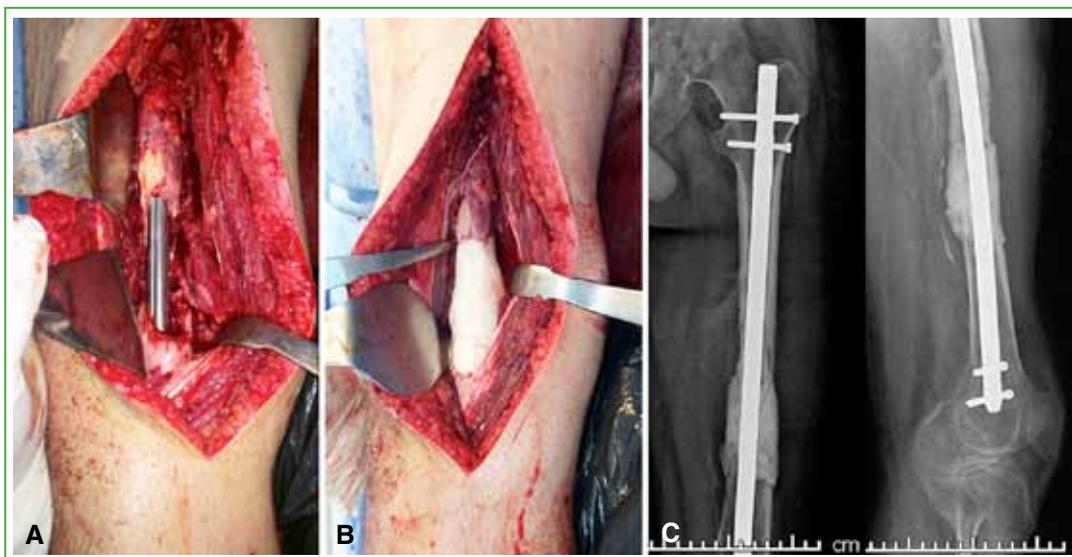

Figure 2. A. 10 cm-long segmental bone defect after debridement and stabilization with an intramedullary rod. **B.** Placement of polymethylmethacrylate plus an antibiotic agent (vancomycin). **C.** Postoperative follow-up after placement of the cement spacer and the intramedullary rod.

The implant chosen for bone fixation during the first stage was an intramedullary rod (IMR) in 20 cases, an external hybrid fixator in one patient, a plate in two patients, and an external fixator plus an IMR in another one. They were chosen as per the surgeon's judgement, according to the location of the SBD. During the second stage, the primary fixation method was preserved in 18 patients and changed in 6 of them. Replacements were made due to material failure (breakage of the cement or the rods) in some cases, and, in others, due to loosening of the osteosynthesis.

The antibiotic agent used was chosen before cell isolation and culture. In 21 cases, it was vancomycin and, in 3 of them, gentamicin.

The graft used for reconstruction was an autologous iliac crest graft in 6 patients and an allograft in the rest of them. In 8 cases, it was combined with a morcellised allograft from a bone bank; in 2 cases, with a more structural morcellised allograft; in 3 cases, with a bone substitute and, in 5 cases, the RIA system (reamer, irrigator, aspirator) plus a femoral allograft was used (chosen according to the size of the SBD and the availability of the different types of allografts at the three Orthopedic Surgery institutions). Growth factors were unnecessary in all cases (Table 2).
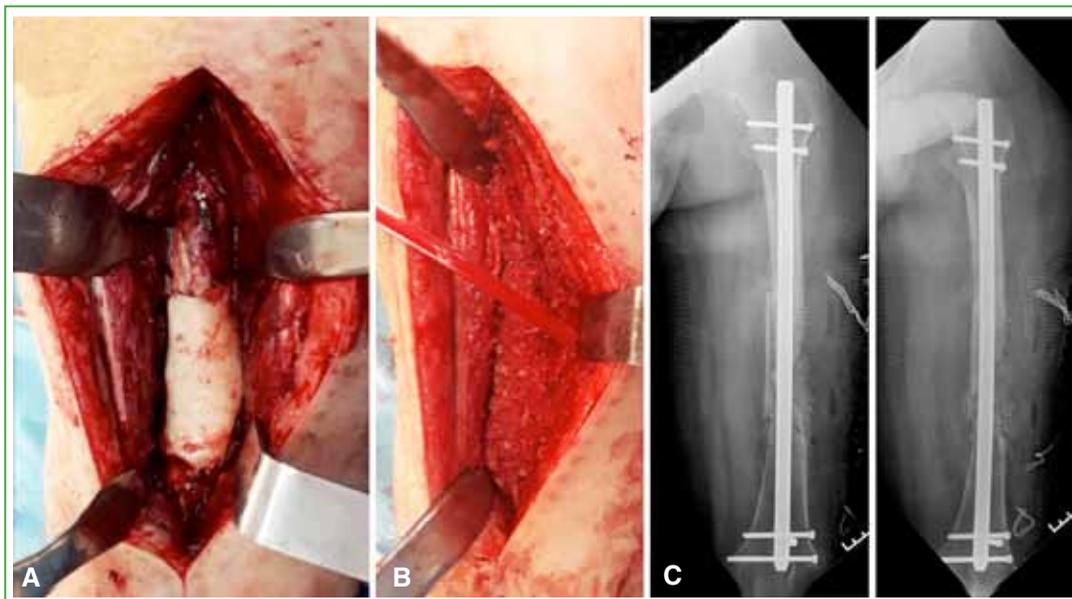

Figure 3. Second surgical time 11 weeks after the first one. **A.** Polymethylmethacrylate spacer placed after the longitudinal opening of the membrane. **B.** Filling defect with an iliac crest autograft plus morcellised allograft and structural allograft. **C.** Radiographical control showing the structural allograft marrow on the medial side.

The surgical wound was monitored after one week. In the third week, the stitches were removed. Follow-ups were then carried out at weeks 4, 8 and 12, and monthly thereafter until bone consolidation. Follow-ups confirmed progressively increased ability to stand on both feet.

The postoperative evaluation consisted in the review of the medical records and radiological follow-ups of the 24 patients. We recorded complications, need for surgical corrections and the time elapsed until the patient regained the ability to stand on both feet without assistance.

For the radiological evaluation, AP and lateral X-rays of the affected segment were taken and used for determining time to bone consolidation, interpreting it as the presence of radiographical consolidation of at least three cortical bones. In addition, the presence of graft resorption, fractures of the graft marrow or signs osteosynthesis fatigue was evaluated (Figure 4).

Table 2. Time elapsed between surgical stages, antibiotic agent used on the spacer, graft type, time to regaining ability to stand on both feet, and time to consolidation for each patient.

Patient/ Age/ Gender	Fixation	Time elapsed between both surgical stages	Spacer	Graft	Time to regaining ability to stand on both feet (months)	Time to consolidation (months)
1/56/M	EF/IMR	7	Vancomycin	RIA + BS	4	6
2/43/M	IMR	5	Vancomycin	IC	3	3
3/39/M	IMR	6	Vancomycin	RIA + BS	4	5
4/51/M	Placa	8	Vancomycin	IC + BS	3	3
5/18/M	IMR	12	Vancomycin	IC + BS	2	4
6/37/F	Hybrid EF	8	Vancomycin	IC + BS	3	7
7/48/M	IMR	20	Vancomycin	IC	2	5
8/38/M	IMR	12	Vancomycin	IC	2	4
9/19/F	IMR	8	Vancomycin	IC + allograft	1	5
10/26/M	IMR	8	Vancomycin	IC + allograft	2	8
11/27/M	IMR	6	Vancomycin	IC + allograft	2	1.5
12/30/M	IMR	16	Vancomycin	IC + allograft	2	6
13/29/F	IMR	6	Gentamicin	IC	1.5	6
14/67/F	IMR	10	Gentamicin	RIA + IC	4	6
15/41/M	Plate	9	Vancomycin	RIA	3	5
16/64/F	IMR	12	Vancomycin	IC + allograft	3	5
17/43/F	CEM	9	Vancomycin	IC + allograft	2	4
18/18/F	CEM	9	Vancomycin	IC + allograft	4	6
19/23/F	CEM	6	Vancomycin	IC	3	5
20/29/F	CEM	6	Gentamicin	IC + allograft	2	3
21/28/M	CEM	8	Vancomicina	IC	2	3
22/32/M	CEM	12	Vancomicina	IC + allograft	2	3
23/43/F	Placa	8	Vancomicina	IC + allograft	3	4
24/19/M	CEM	11	Vancomicina	IC + allograft	4	5

EF: external fixator; IMR: intramedullary rod; RIA: reamer, irrigator, aspirator system; IC: iliac crest; BS: bone substitute.

RESULTS

In the last follow-up, all patients had clinical and radiographical signs of bone consolidation. None of them was lost to follow-up. The time elapsed between the two surgical stages was, on average, 9 weeks (range 6-20).

Figure 4. AP and lateral femur X-rays. **A.** Two months after the second surgical stage. **B.** Seven months after the second surgical stage.

The length of the treated bone defect was, on average, 5.7 cm (range 3-12), which accounted for 17.5% (range 7.5-30) of the total bone length. In 50% of cases, defects were larger than 4 cm. The largest SBD was 12 cm (BRI 35%) at the tibia and 10 cm at the femur (BRI 30%).

Regarding radiological evaluation, there were no cases of massive graft resorption, fractures of the graft marrow, or major complications related to the implant (Figure 5).

Bone consolidation was confirmed at an average of 4.5 months (range 1.5-8) from the second stage. The ability to stand on both feet was regained at 3 months (range 2-4). At the end of the follow-up, none of the patients walked with assistance.

No differences were observed in the time to consolidation between patients who suffered open fractures and those with closed fractures, nor with respect to the affected bone (tibia/femur), or the type of autograft used to fill the SBD (RIA/iliac crest). These factors did not affect patients when regaining the ability to stand on both feet without assistance.

One patient had a recurrent infection 12 months after consolidation. The patient was treated by removal of the IMR, reaming, debridement, antibiotic IMR, and intravenous antibiotic therapy, after which remission of osteomyelitis was achieved.

DISCUSSION

The treatment of SBD is challenging, complex and continues to be a subject of debate. Traditionally, it required surgeons to be highly trained in microsurgery techniques, a highly complex surgical infrastructure and patients who were cooperative and tolerant to prolonged and tedious treatments, such as callotasis.

Figure 5. A 38-year-old man with a history of open fracture (Gustilo IIIB) of the left distal tibia.
A. Infected 4-month-old segmental bone defect measuring 3 cm long. **B.** Radiographical follow-up 12 months after the second surgical stage.

The induced membrane technique developed by Masquelet offers a novel, simple and effective treatment alternative for bone reconstruction. It was originally described to fill infected post-traumatic bone defects. Masquelet took 16 years to publish his technique, since the accidental findings and excellent results of his series of infected patients led him to perfect the histopathological processes of the membrane to understand the basis of the results obtained[5, 12]. Nowadays, there are literature references supporting its use in non-infected bone defects[17], oncologic reconstructions[19-21] and birth defects[21, 22].

The formation of granulomas in response to a foreign body is an essential part of tissue healing. It occurs as a result of the injury caused by a foreign material in a vascularized area[23]. The first stage is the inflammatory phase around the bruise and detritus of the foreign body, which stimulate tissue regeneration and maturation of the granulomas to form a biological membrane with proliferation potential into dense fibrous tissue, bone or any other mesenchymal lineage, culminating in the inclusion of the foreign body[23].

The membrane induced by the cement spacer is a richly vascularized structure formed by type I collagen, a dense extracellular matrix with fibroblastic cells, macrophages and a high concentration of growth factors, such as vascular endothelial growth factor, TGF-β1 and bone morphogenetic protein 2, which theoretically have the ability to differentiate mesenchymal stem cells in a specific cell lineage while increasing surrounding neovascularization[4, 5, 13, 15, 18, 24]. Increased levels of TGF-α1, a critical factor of osteoblast cell growth, were also found in the fibroblast cells of the membrane[5, 25]. The result of this favourable biological microenvironment is the enhancement of neovascularization, cell differentiation into bone lineage, and the early graft marrow incorporation and corticalization[23].

The membrane also has mechanical properties, since it prevents graft resorption and growth of soft-tissue at the defect-cement interface and serves as a barrier that prevents the passage of growth and osteoinductive factors[5, 16, 24, 26]. Woon and colleagues argued that the membrane is waterproof, hyper-vascularized and has a thickness of 0.5-1 mm[27]. Taylor and colleagues, on the other hand, argued that, at the sixth week, the membrane is 1-2 mm thick, hyper-vascularized and free from attachment to the underlying spacer[5]. It should be noted that, in the case of the IMR fixation during the first surgical stage, a second membrane is formed between the rod and the spacer. We believe that this should be preserved to maximize the potential for consolidation.

The spacer, in addition to the properties already mentioned, has the additional advantage of being able to be built with a high dose of antibiotics, which allows the gradual release of the agents to the surrounding tissues, obtaining antibiotic tissue levels that exceed several times the minimum inhibitory concentration without increasing antibiotic systemic levels or resulting in toxic effects[5, 23]. The antibiotics that are generally used are gentamicin, tobramycin, vancomycin and other cephalosporins[28-30]. The recommendation is not to exceed 8 g of antibiotic for every 40 g of PMMA, as the properties of the cement are altered, making it difficult to set and mold[31].

Karger, Masquelet and Begue proposed the use of an autologous iliac crest graft as the reference standard due to its osteoconductive, osteoinductive and osteogenic properties[12, 14, 16] and recommended using chips no larger than 1-2 mm[3]. They claimed that both iliac crests are enough to harvest a graft to fill defects of up to 15-20 cm[8, 14, 16, 32]. However, if this is not enough, a bone substitute or a morcellised allograft from a bone bank can be used, not to exceed a 1:3 ratio[5, 12, 16]. Nevertheless, this ratio is determined in a purely empirical way, since there are no studies to support it. There is even literature claiming that good results have been achieved with a 1:1 ratio[14]. In our case, using a heterogeneous sample as to the type of graft used, we reached total consolidation in all patients, since the strength of this procedure is not strictly dependant on the iliac crest morcellised autograft.

The BRI, according to Gouron *et al.*, shows that the technique allows for a successful reconstruction of bone defects of a third of the length. In cases with greater-sized defects, they use, empirically, a cortical bone allograft. In this way, they aimed to increase the stability and volume of the graft marrow[22]. Masquelet, however, states that his technique can be used in bone defects of up to 25 cm without the need for structural grafts[12, 13]. In our series, structural bone grafting was used in two patients with a SBD >30% of the length of the affected bone.

Another aspect that is still debated on the literature is the time period between the two surgical stages. A period of 6-8 weeks was described empirically as optimal, based on histopathological findings in animals[5, 12, 16, 24]. Aho and colleagues showed that vascularization of the membrane reaches its peak at the fourth week and decreases to less than 60% at the third month[23]. Specimens collected at the fourth week also showed the highest expression of vascular endothelial growth factor, interleukin-6 and type I collagen, while those collected at the second month showed less than 40% of these values[23]. Pelissier and colleagues studied the technique in rabbits and found a peak of bone morphogenetic protein 2 at the fourth week after spacer implantation, followed by a gradual decline[15]. By the sixth month after surgery, no inflammatory reaction was observed, thus losing the theoretical biological benefits of the induced membrane[5, 33, 34].

Following the findings of Pelissier and Aho, the optimal time for the second stage of the Masquelet technique is the fourth week; however, the results are still successful with a longer interval[22]. Donegan and colleagues achieved a consolidation rate of 90% when they performed the second stage at an average of 58 days (range 32-92)[35]. In the case of our series of infected SBD, the clinical and humoral resolution of the infection usually took no less than six weeks and, according to our experience, the results are still satisfactory if surgery is performed at an average of 9 weeks. In accordance with the findings of Donegan *et al.*, in one patient, a time period of 20 weeks was recorded (for non-medical reasons), in which a consolidation similar to that of the rest of the series was achieved.

The initial description of the technique recommends an external fixator as the stabilization method, and it is also the preferred method of the Société Française de Chirurgie Orthopédique et Traumatologie (SoFCOT) to treat infected nonunions[14]. However, there are other valid alternatives and, in our series, supported by the literature, we used an IMR as fixation in 20 patients, achieving a 100% consolidation rate, with only one case of recurrent infection after consolidation. We believe that it was due to the infection predating the SBD and do not attribute the recurrence to the use of the IMR. Stafford and Noris corroborate our results and argue that excellent results have been recorded using an IMR during the first surgical stage and sparing the original rod at the second stage.

With respect to the analysis focused on the length of the bone defect, we observed, like the SoFCOT, that it does not seem to affect the time to consolidation[12, 14, 23] nor the nonunion rate[14], or the time needed to regain the ability to fully stand on the limb[23]. The Masquelet technique has been used successfully in bone defects >20 cm[5]. We observed this same trend, since the progression of our greater-sized SBDs was comparable to that of smaller defects.

The literature reports a consolidation rate of 82% to 100%[4]. In 2000, Masquelet and colleagues reported the first series of 35 patients with a consolidation rate of 100% in defects of up to 25 cm[12]. Stafford and Norris achieved a consolidation rate of 90% in 27 cases, but they used a femoral graft obtained by the RIA system[7]. McCall and colleagues achieved a consolidation rate of 85% with the same technique[36]. Apard and colleagues reported a consolidation rate of 90.9% in 12 patients using an IMR as the fixation method and allowing patients to stand on both feet after four months of the second surgical stage[37]. In 2012, Karger and colleagues published, together with the SoFCOT, the largest series to date, consisting of 84 patients with SBDs >5 cm, and obtained a consolidation rate

of 90% at 14.4 months of the first surgical stage[14]. In contrast, Gouron and colleagues described a 35% rate of nonunions in pediatric reconstructions and attributed the errors to flaws in the technique and to the learning curve[22]. In the rest of the series under evaluation, no such thing was reported. In our series, we obtained results comparable to those of the international literature. We achieved consolidation in all 24 patients of the group, without variations between patients treated with iliac crest grafts or with the RIA system, or differences between those treated with a pure autograft and those treated with an allograft or a bone substitute.

The strength of our work relies on being the first of its kind within the country and its multicentric nature (3 high-complexity trauma centers in Buenos Aires), as well as dealing with a condition that has been reported in only a few international publications. The weaknesses are its retrospective nature, the low number of patients and the heterogeneity of the variables under study. However, we deem the future analysis of the variables to be promising, since we achieved adequate results in all the different cases studied. We believe it is necessary to extend this study by incorporating a greater number of cases in order to obtain findings that will allow for a treatment consensus not yet reached in the international literature.

CONCLUSIONS

The Masquelet technique, or the induced membrane technique, offers a feasible and simple alternative for a highly challenging condition such as infected SBDs. It allows, in turn, to avoid complex and demanding procedures, such as vascularized grafts or callotasis, with a consolidation rate >90% even in difficult cases.

This technique is increasingly used due to the proven properties of the membrane, which allow for a favourable environment for neovascularization, bone induction and consolidation in a previously hostile bone environment. Clinical and radiological results are quite satisfactory for a highly complex condition treated with a relatively simple and feasible procedure.

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