Acta Orthop. Belg., 2014, **80**, 196-204

ORIGINAL STUDY

Local complications of massive bone allografts : an appraisal of their prevalence in 128 patients

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Bone allografts were used in our department since twenty-five years to reconstruct segmental bone loss and our data were retrospectively reviewed to assess the complications related to the use of a bone allograft. A consecutive series of 128 patients who received a bone allograft was analyzed. The minimal follow-up was 18 months. Fracture, nonunion, infection and explantation were investigated using a multivariate analysis and logistical regression. Kaplan-Meier survival of the allograft was performed, using allograft removal as the end point. Tumour disease was excluded from this study.

Patients were followed up for an average 103 months. Bone tumour occurred in 78% of the patients whereas revision arthroplasty was the cause of implantation in 15% of them. Nonunion was the most prevalent complication, occurring in 35% of the grafts. For nonunion occurrence, the type of reconstruction was found to be a significant variable, the intercalary allograft being the most exposed. Primary bone autografting at the anastomotic site was not significant to prevent nonunion.

Fracture of the allograft was the second most frequent complication with a prevalence of 16.4%. The length of the allograft and an osteoarticular allograft were two significant variables in that occurrence. Infection of the allograft was present with a rate of 5.4% of patients.

Explantation of failed allografts occurred in 30% of them.

The duration of the frozen storage of the allograft and the donor age of the allograft were not significant on any local complication occurrence.

Bone allografts are a reliable material but a high rate of local complications must be anticipated.

INTRODUCTION

The use of structural bone allografts as a material for skeleton reconstruction has gradually emerged with the pioneered work of Ottolenghi (*25*), Parrish (*26*) and Mankin (*17*). The reliability of bone allografts as a reconstruction material in oncologic surgery was later confirmed by other clinical series (*9,18*). Massive bone allograft can be however the source of local complication such as nonunion at the anastomotic junction, fracture and infection with a highly variable reported prevalence in clinical series (*2,3,10,14,28,29,31*). A reappraisal of the

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No benefits or funds were received in support of this study.

allograft-related complication rate is warranted as bone fixation material has improved in patients who have now a longer survival than in the past. Moreover the influence of bone autografting at the anastomotic site, intramedullary fixation or plating and other variables on the complications occurrence needed to be addressed. In contrast to a metallic prosthesis, implantation of a bone allograft provides a natural surface for a bone callus formation and allows the reinsertion of tendon when applicable. An allograft can also be used in teenagers with a bone tumour as an osteoarticular segment to preserve the opposite physis.

Amongst the disadvantages of using bone allograft are the potential transmission of diseases from a tissue donor and the complications related to the bone allograft itself. Disease transmission of viruses remains a critical issue. Guidelines for tissue banks have been regularly reviewed by the American association of tissue banks (*1*). Complications related to a bone allograft have been reported (*2,3,10,14,18,28,29,31*) but long-term follow-up in a large series of patients having had a structural bone allograft remains rare and would be worth to closely outline their most appropriate indications (*15*).

The investigation was aimed at assessing the complications that were directly related to the use of a bone allograft in the appendicular skeleton : nonunion, fracture and infection and failure of an allograft. It was hypothesized that there was no favoring factor in the occurrence of bone allograft complications. The rate of bone allograft related-complication was found high. Nonunion was the most prevalent complication and occurred preferably in intercalary allograft. Fracture of the allograft was the second most frequent complication. The length of the allograft and an osteoarticular allograft were two significant variables in fracture occurrence.

MATERIAL EN METHODS

Patient series

Recipients of massive bone allografts were traced back with the registry of our tissue bank. 128 patients could be enrolled and were agreed to participate in the study. They underwent between 1985 and 2009 a complete bone resection at a limb that was reshaped with a circumferential bone allograft or an osteochondral allograft. A minimum follow up of eighteen months was observed for inclusion. Follow up was ended either at the end of 2010, at the time of explantation or at the patient death, should these events have occurred. Five patients who had an early failure of the bone allograft before the eighteen month interval were nevertheless included as the transplanted bone itself had already failed and was explanted. Table I lists the clinical data and causes of bone resection.

Table I. — Patient series

Patients (n)	128	
Mean age	36.5 + 22 years	(median : 34)
Gender	66 F / 62 M	
Mean length	14.2 + 6.3 cm	(median : 14)
Composite allograft		47/128
Osteochondral allo.		42/128
Intercalary allo.		27/128
Allo-arthrodesis		12/128
Medullary fixation		83/128
Plate fixation		45/128
Etiology	Tumor	100
	Revision arthroplasty	19
	Trauma or other	9
Upper/lower limb		39 / 89
Chemotherapy		61/128
Tissue donor age	37.6 + 13 years	(median : 37)

Definition

A *massive bone allograft* is a full segment of bone (measuring by convention at least 3 cm of length) that provides a mechanical function and that is able to resist or transmit loads (*8*). Three categories of massive bone allografts were met :

- A *composite* allograft meant the association of a metallic prosthesis with an allograft that was used to reinsert a tendon such as at the proximal femur or tibia and was implanted in 47 cases (Fig. 1).
- An *osteochondra*l allograft was a full osteoarticular hemi-joint of variable bony length and with its capsule (Fig. 2) and was performed in 42 patients. Partial reconstruction of a hemi-joint was excluded.
- An *intercalary* allograft was defined as a full bone segment used to bridge a significant metaphyseal or diaphyseal gap and was performed in 27 patients (Fig. 3). An *allo-arthrodesis* to bridge a joint resection occurred in 12 patients and was included in that category.

Fig. 1. — Composite allograft with a knee prosthesis implanted after an osteosarcoma resection in a 24 year-old patient. Lateral view of the knee in flexion at fourteen years after surgery.

Fig. 2. — A 22 cm-long osteoarticular allograft at the distal femur in a teenager. Antero-posterior view at two (A) and four years (B) after surgery for an osteosarcoma. Distal fracture at 4 years.

Nonunion was defined as the absence of any bone bridging callus at an anastomotic junction between the allograft and the host bone. The absence of a true bony contact on either part was assessed on two orthogonal x-ray views at 18 months postoperatively or later. Union was defined as new bone bridging at three or more cortices on AP and lateral radiographs. If an additional surgery was performed to achieve the union, the junction was considered not being united.

Fracture of the allograft was diagnosed as a newly appearing line of discontinuity in the bony structure of the allograft when compared to the immediate postoperative aspect.

Explantation was defined as the removal of the allograft because of a local complication and considered as the end point of the allograft survival.

Bone allograft procurement and banking

Bones were sterilely procured in an operating room in organ donors by a trained team (*6,27*). Donor selection, procurement and storage of tissues were performed according to the standards for tissue banking (*1*) in an agreed tissue bank in Belgium. The bones were deep-frozen at -80°C. They were not further sterilized by irradiation. The storage duration of the bones was limited to five years after procurement as required by the Belgian law.

Statistical methods

To determine if occurrence of a bone allograft complication could be influenced by different variables, a multivariate analysis with use of multiple logistic regressions was performed using a stepwise procedure. It was hypothesized that there was no favoring factor for a bone allograft complication to occur.

To improve clarity, variables were classified when possible, into categories (Table II). Category delineation was put forward by descriptive statistics analyzing data from a subset of patients with or without allograft com-

Fig. 3. —Tight nonunion of a proximal junction of a intercalary allograft at distal femur in a symptom-free 14 year-old patient. Lateral view at 11 years after surgery.

Table II. — list of used variables

Categorical variables	n = 128
Patient age < 30 years old	61
Patient age > 30 years old	67
Donor age < 30 years old	32
Donor age > 30 years old	96
Length of allograft : < 10 cm	36
Length of allograft : 10-20 cm	75
Length of allograft : > 20 cm	17
Type of reconstruction : composite	47
Type of reconstruction : intercalary-alloarthrodesis	39
Type of reconstruction : osteoarticular	42
Location : upper limb	39
Location : lower limb	89
Autografting with iliac bone	68
Autografting with bone from other location	36
No autografting	24
Step-cut osteotomy	50
Transverse osteotomy	78
Continuous variables	
Average storage period of the allograft	13.5 ± 12.7 months
Average follow-up period	103 ± 81 months

plications. The categorical variables that were expressed in terms of percentage and frequency were : Patient age and donor age (below and above 30 years), length of bone allograft (below 10 cm, between 10 and 20 cm and above 20 cm), chemotherapy, the types of limb reconstruction : composite allograft with a prosthesis, intercalary and osteoarticular allografts, upper or lower limb location, cancellous bone autografting at the anastomotic site, step-cut or transverse osteotomy. Continuous variables such as storage duration of the allograft and follow-up period were expressed as mean and standard deviation.

Variables that could influence allograft survival were evaluated using Kaplan-Meier curves and log-rank testing when applicable or performed with multivariate analysis and use of Cox proportional hazards. End point for survival analysis was the explantation of the allograft for any cause or amputation and expressed in months from the date of surgery with allograft implantation.

The storage period was also correlated in a pairwise fashion with variables such as fracture, nonunion, infection or explantation. The level of significance was set at $p = 0.05$.

RESULTS

Tables 1 and 2 list the main characteristics of the series. 128 patients with a massive, structural bone allograft were included and followed up for an average 103 ± 81 months (95% CI 88-117 months). There were 66 females in the series. The mean age of patients at the time of the index procedure was thirty-six years (95% CI 32.6-40.4 years of age). Every patient received a fully circumferential structural bone allograft with a mean length of 14 cm ± 6 cm (95% CI 13-15 cm). There were 47 composite prosthesis with an allograft, 42 osteoarticular allografts, 27 allografts that were intercalary whereas 12 allografts served for performing an arthrodesis. Eighty-three patients had the allograft fixed by an intramedullary material either a nail or the stem of a prosthetic material whereas forty-four patients had their allografts stabilized by at least one plate. Bone tumour was the main cause for a bone resection. Chemotherapy was given in 61 patients either pre or/and postoperatively. The main type of reconstruct was the association of a prosthetic metallic implant and the allograft. A transversal osteotomy was performed with a saw under saline irrigation in

Table III. — Multivariate analysis of factors influencing nonunion of bone allografts

Variable	odds ratio	95% CI	P value
Type of reconstruction			0.039
Intercalary or desis vs composite	3.07	1.23-7.61	0.0154
Intercalary or desis vs osteoarticular	2.34	0.94-5.81	0.065
Osteoarticular vs composite	1.30	0.51-3.30	0.57

Table IV. — Multivariate analysis of factors affecting fracture of bone allograft

Variables	Odds ratio	95% CI	P value
Allograft Length category			0.043
> 20 cm vs < 10 cm	28.01	2.94-267.2	0.0038
10-20 cm vs less 10 cm	8.61	1.059-70.11	0.044
> 20 cm vs 10-20 cm	3.25	0.98-10.76	0.053
Type of reconstruction			0.01
Osteoarticular vs composite	6.08	1.48-25.01	0.012
Intercalary or desis vs composite	3.29	0.75-14.39	0.113
Intercalary or desis vs osteoarticular	1.84	0.58-5.83	0.294

76 patients whereas a step-cut osteotomy to improve the rotational stability was made in another fifty of them. A bone autograft from the iliac crest was procured in 68 patients to promote healing at the anastomotic site. In 36 another patients, the junction with the allograft was supplemented with a non-iliac autogenous bone whereas 24 patients did not receive a bone grafting material.

Nonunion, fracture and infection were the main complications observed with a massive bone allograft (Figs 2-3). Progressive resorption of the bone allograft was not observed in this series. Out of the 128 allografts of the series, 45 had a nonunion whereas 21 fractured and seven others had infection. Thirty of them had to be explanted and were failures.

Nonunion was the most prevalent allograft complication occurring in 45 patients (35%).

Using Cox regression analysis, one variable was found to promote nonunion : the type of reconstruction. Intercalary allografts were significantly more prone than composite allograft to develop a nonunion ($p = 0.015$) but not when they were compared to the osteoarticular allografts. There was no significant difference between composite and osteoarticular allograft (Table III).

Primary autografting with iliac cancellous bone, step-cut osteotomy, chemotherapy or not, allograft storage duration were variables without significant influence on nonunion occurrence.

Fracture of the allograft was the other main complication arising in 21 patients (16.4%). Eleven of them occurred within 24 months after surgery whereas three others were observed after 8 years of implantation. From the multivariate analysis, only two variables were significant for facilitating a fracture of the allograft : the length of the allograft was a major variable and in a lesser degree, the type of reconstruction (Table IV). For the latter, osteoarticular allografts were at significant risk for fracture compared to composite allograft-prosthesis.

Other investigated variables such chemotherapy, upper or lower limb, age of the patient, age of the donor, graft storage duration were not found significantly influent. Survival curves of nonunited and united allografts were significantly different ($p = 0.00008$) as were survival curves from fractured and non-fractured allografts ($p = 0.0006$) (Figs 4-5).

Infection of the surgical site can be a devastating complication for the patient and occurred in seven of them. Only one patient retained his allograft while four of them were explanted and two others had amputation of the concerned bone segment. No variable was significantly associated with infection but this occurrence was too rarely seen for significance. Explantation of the failed allograft was observed with a prevalence of 30.4% and was very sensitive to two variables : the type of reconstruction ($p = 0.0005$) and the location at upper or lower limb ($p = 0.0011$). Any osteochondral allograft at the lower limb was found particularly exposed to failure compared to composite ($p = 0.0002$) or intercalary allografts ($p = 0.001$) (Table V). We identified a subset of osteoarticular allografts at the distal femur implanted in teenagers where six out of the eleven grafts fractured at a mean time of 26 months after surgery and were explanted. The six distal femur allografts that fractured had had a transosseous perforation for allowing a cruciate lig-

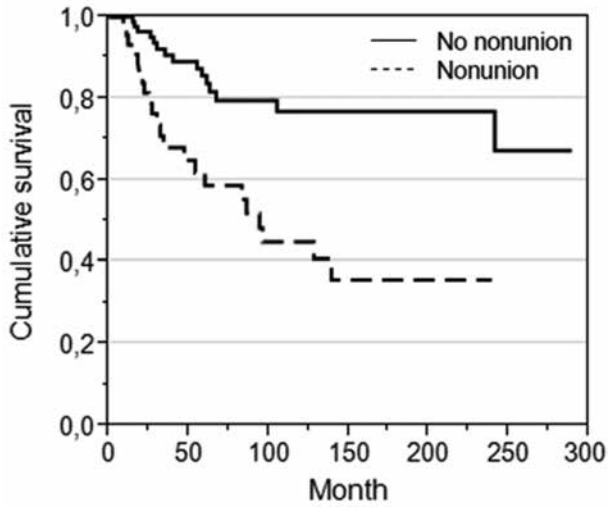

Fig. 4. — Kaplan-Meier survival curves of allografts with and without nonunion at their junctions with host bone. Curves were significantly different from each other's (p = 0.00008).

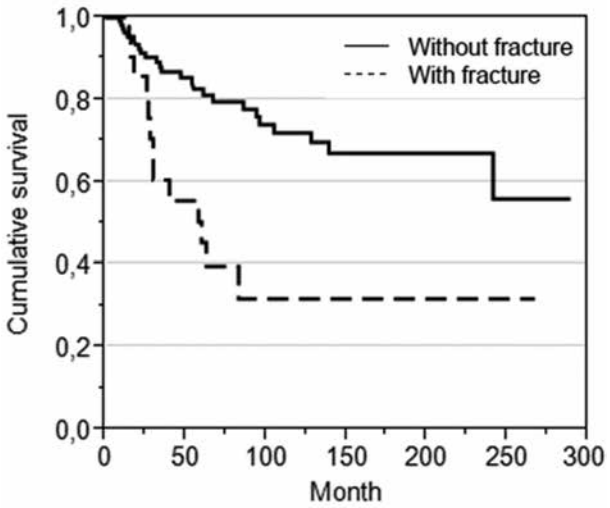

Fig. 5. — Kaplan-Meier survival curves of fractured and non fractured allografts. Curves were significantly different from each other's (p = 0.0006).

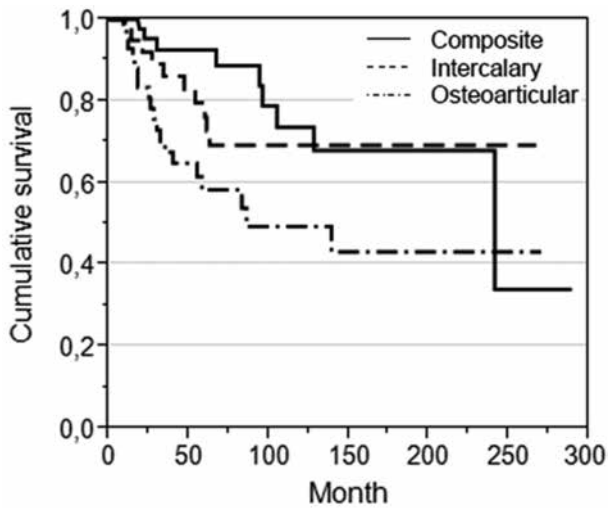

Fig. 6. — Survival curves of the three reconstruction categories according to Kaplan-Meier. Composite and osteoarticular curves were different from each other's (p = 0.011).

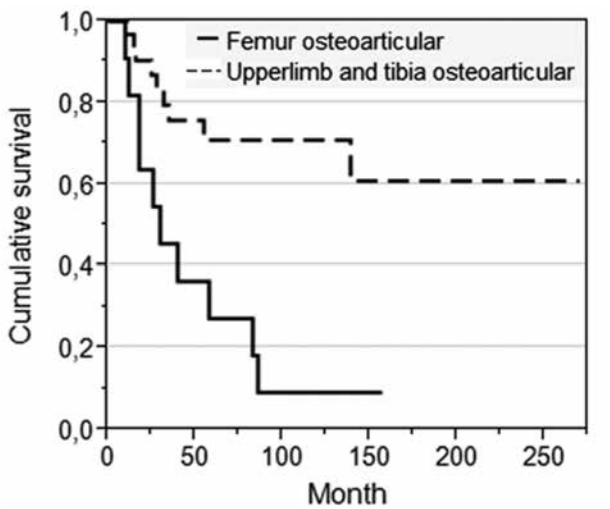

Fig. 7. — Significant shorter survival of osteoarticular distal femur allograft compared to other osteoarticular allografts at the tibia or at the upper limb (p = 0.00085).

ament substitution by a tendon allograft. Survival curves of the three reconstruction types were different but when compared in pairs, only the composite and osteoarticular allografts curves were significantly different (p = 0.011) (Fig. 6). Osteoarticular at the distal femur had a very significant shorter survival than the other osteoarticular allografts (p = 0.00085) (Fig. 7).

Storage duration of the frozen allograft could not be correlated with a complication of the allograft.

DISCUSSION

This investigation confirms that nonunion and fractures were the main local complications observed with massive bone allografts. These allo-

Table V. — Multivariate analysis of factors leading to allograft explantation

Variables	Odds ratio	95% CI	P value
Type of reconstruction			
Osteoarticular vs composite	12.26	3.34-44.92	0.0002
Osteoarticular vs intercalary or desis	8.77	2.39-32.17	0.001
Intercalary or desis vs composite	1.39	0.49-3.95	0.528
Location			
Lower limb vs upper limb	8.70	2.36-32.06	0.0011

grafts were supplied by our registered tissue bank and implanted by senior surgeons from our department.

The rate of nonunion was 35% in the present series. A lesser rate although still between 17 and 27% was reported by other authors (*10,14*). The only significant variable in the series for promoting nonunion was the type of reconstruction and in particular, intercalary allografts.

Plating an allograft has been considered as the most rigid means for bone fixation. Aponte-Tinao *et al* (*2*) observed a 15% rate of nonunion when intercalary allografts were plated whereas when nailed, a 28% rate was found. A locking nail for long bone fixation has been favored at our institution as it required less drilling than with a plate (*31*).

Chemotherapy was found to be associated with nonunion in various studies (*10,13,14,20*) but we were unable to achieve such a finding.

The supplementation of autogenous cancellous bone from the iliac crest has been supported when possible but could not influence the observed nonunion rate as already observed in other series (*23,31*). The mechanical superiority of a step-cut osteotomy could not be established at present and also in vitro when compared to transverse osteotomy (*4*).

Fracture of the allograft was not rare with a 16.6% rate which was similar in other series (*2,3,28,29*). This rate rose to 24-27% in larger series (*2,10,12)*. Multivariate analysis indicates that the length of the allograft was the most influent factor in fracture occurrence. Bone allografts measuring more than 10 cm of length and even more than 20 cm were significantly at higher risk for fracture as also observed by others (*2,10,28*). Osteoarticular allografts were particularly exposed to fracture when compared to composite allograft-prosthesis as already noted by Donati *et al* (*10*). Amongst osteochondral allografts, those at the distal femur were particularly prone to fracture as six out of eleven had this complication. Such allograft was only considered in skeletally immature patients for preserving the proximal tibial physis. Transosseous perforation had been performed in those fractured allografts. Fracture occurrence was found too high to still advocate a concomitant bone tunneling for cruciate ligament substitution in this location.

Muscolo *et al* (*22,23*) encourage the use of plated osteoarticular allograft at the distal femur as they observed a 4% of fracture. No bone tunneling for cruciate ligament substitution was made in the plated allografts. In teenagers, new options such an expanding prosthesis must be also discussed and should an osteoarticular allograft for the distal femur be considered, cruciate ligament substitution should not be attempted.

Fracture is considered as a mechanical failure and in our series, occurred at a variable range from 6 months to 8 years. As noted by Donati (*10*), half of the fracture occurred within 24 months after surgery. Late occurring fracture might be observed even after 3 years (*18,31*) and should be considered as a fatigue fracture as the allografted bone remained non vital even after years (*5,11,32*). Attempts to heal the fracture in an allograft have been rarely successful (*3,10,29*). A major drawback of fracture is that it is a sudden adverse event that is unexpected and unpredictable. Once the structural integrity of the allograft is jeopardized, replacement of the failed allograft is often necessary. Microperforations of the bone allograft could be one option to enhance the revascularization process of the bone but this also caused fracture of the allograft and was abandoned (*7*). On contrary, cementing the medullary canal of an allograft appears to be effective in decreasing the fracture occurrence (*10*). Except the length of allograft and the type of reconstruction, the other variables were non significantly related to fracture.

An infection rate of 5.4% was found in this series and can be considered as a low rate regarding the literature that reports varying rates from 8.7% to 18.7% (*10,14,16,18,19*).

In similar operation using endoprosthetic replacement, an even higher rate of infection was reported (*18,24*). To maintain contamination at a low level, the graft must be procured in an operating theatre by a dedicated team and be soaked in an antibiotic solution before freezing and after thawing (*27*).

Deep-infection is the most devastating complication related to surgery and most often it means retrieval of the implant. Bone tumor excision followed by a reconstruction time is a lengthy procedure. No variable was found significantly associated with infection in this series.

Explantation of the allograft was considered as a failure and was found to be significantly related to the use of an osteoarticular allograft when compared to a composite or an intercalary allograft. Donati *et al* had the same experience in their series (*10*). An allograft located at lower limb was more exposed to failure compared to the one at upper limb as already discussed.

This study is a retrospective review of a large series of patients treated over 20 years and without a control group. The strength of the study lies in the large number of patients reported from the same institution and followed by senior authors.

The risk of disease transmission through a human tissue is not nil but remains remote with an updated donor selection guidelines and the introduction of nucleic acid testing in donor screening procedures (*21,30*). It is the first report that demonstrates that the storage duration and the donor age of the allograft were non influent variables on local complication. Complications with massive bone allografts were high but manageable. The treatment of large bone defects is challenging and no one single method of reconstruction has emerged so far. If bone allografts are available for the patient, our data indicate that such option of managing large bone defect with a bone allograft is still valid but high complication rate must be anticipated.

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