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Efficacy of vancomycin impregnated deep freeze irradiated allogenic bone graft in osteoreconstructive surgery

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Abstract

Aim of study was to use the allogenic bone graft with or without vancomycin impregnation in osteoreconstructive surgery and compare the results with respect to:

- Efficacy and safety in prevention of graft related and surgical site infection.
- Effect on bone healing and osteointegration.

Materials & Methods: In our study a total of 30 patients who required allogenic bone grafting for varied indications and gave informed consent for participation in the study were included. Patients with active osteoarticular infection at the proposed surgical site and with any medical contraindication to the use of vancomycin were excluded from the study. Broadly three indications for which allogenic bone graft was used included fractures, benign osteolytic lesions and miscellaneous indications which included allograft use for lumbar spinal fusion and for augmenting acetabular reconstruction.

Observation & Result

Infection: An overall infection rate of 3.3% (1 out of 30 cases) was found in this study which is much lower than what is mentioned in the literature as infection rates ranging from 4-12% have been reported by different workers

Osteointegration: The overall success rate in terms of adequate osteointegration in our study was 83.33% (5 failure cases out of 30) with 12 cases (80%) out of 15 in study group and 13 cases (86.7%) out of 15 achieving adequate osteointegration and there was no significant difference (p value=1) between the two groups.

Bone Healing: Fractures: In cases of fractures a good overall union rate of 88.8% was obtained with 16 out of 18 patients achieving adequate union. The two failure cases brought down the union rate to about 77.7% in the study group as compared to 100% union rate in the control group but this difference was not statistically significant with p value of 0.384 Thus vancomycin impregnation was not found to affect fracture union in our study.

Benign bone lesion: A total of eight patients (3 each of SBC and GCT and 2 of ABC) were included. After random allocation five patients (2 each of SBC and GCT and 1 of ABC) came under the study group and three patients (1 patient each of SBC, GCT and ABC) under control group. The mean age of patients in the study group and control groups was 25.2 years and 34.1 years respectively and thus were comparable. There was no significant difference in terms of lesion healing between the two groups (p value= 0.684) as all the eight patients (100%) showed adequate healing as defined by Neer's classification^[1].

Keywords: Vancomycin, freeze dried allogenic bone graft, benign bone lesions, fractures

Introduction

Depleted or insufficient bone stock in primary and subsequent revision surgeries has become challenging problem in osteoreconstructive surgery. Although autologous bone graft remains the gold standard for addressing this problem but limited availability and donor site morbidity are two of its major shortcomings. Synthetic bone substitutes, though present in sufficient quantities, do not undergo any uptake process by the host bone bed and require a subsequent second surgery for removal. Allogenic bone grafts serve as an excellent solution for the above shortcomings of autologous graft and synthetic bone substitutes as it can be available in sufficient quantities without risking any donor site morbidity to the patient as well as does not

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require any second surgery for removal. But allogenic bone graft are inherently susceptible to colonization by small colony variants forms of microorganisms and thus a higher rate of infection has been found to be associated with their use. Here lies the rationale of impregnating allogenic bone graft with antibiotics. These grafts may additionally serve as good local antibiotic carriers as they get osteointegrated with host bed and, as observed in our study, any extraosseously placed graft gets resorbed, thus the chances of formation of sequestrum serving as infective focus in the future are minimal. Among the antibiotics used for allograft impregnation, the most favoured is vancomycin due to its hydrophilicity and effectiveness against staphylococcus species which is most notorious for formation of biofilm.

Materials & Methods

In our study a total of 30 patients who required allogenic bone grafting for varied indications and gave informed consent for participation in the study were included. Patients with active osteoarticular infection at the proposed surgical site and with any medical contraindication to the use of vancomycin were excluded from the study. Broadly three indications for which allogenic bone graft was used included fractures, benign osteolytic lesions and miscellaneous indications which included allograft use for lumbar spinal fusion and for augmenting acetabular reconstruction. Under fractures came patients with established nonunions, delayed unions and difficult fractures, that is relatively fresh fractures with severe comminution and bone loss. Under benign osteolytic lesions came patients with Simple Bone Cyst (SBC), Aneurysmal Bone Cyst (ABC) and Giant Cell Tumour (GCT). The patients were randomly allocated into study group where vancomycin impregnation of allogenic bone graft was carried out and in control group where non vancomycin impregnated allogenic bone graft was used. Each group had 15 patients each (n=15) with study group having 9 patients of fractures, 5 patients of Benign osteolytic lesions (2 each of SBC and GCT and 1 patient of ABC) and one patient of spinal lumbar fusion and the control group having 9 patients of fracture, 3 patients of Benign osteolytic lesions (1 each of SBC, AB and GCT), 2 patients of spinal lumbar fusion and one patient of acetabular reconstruction. The mean age in both the groups was comparable with it being 36 years in the study group while it was 44 years in the control group. The maximum numbers of patients were in the age group 21-40 years in both the cases and controls group. Both the groups were statistically comparable in terms of sex distribution. In the study group 66.7% of the patients were males while in the control group 73.3% of the patients were males, the rest being females.

The institutional bone bank had bone grafts procured from consenting patients having undergone total hip and knee arthroplasty at the institute and stored them at -76° Celsius for minimum of three months before use. The gamma irradiation was achieved by giving a dose of 25 grays of radiation at an accredited centre. The graft was manually morselized to fragment size of 0.4-0.6 cms and washed with plenty of sterile saline. The bacterial culture of the allograft were taken before implantation to ascertain sterility and all came out to be negative. In cases where antibiotic impregnated bone allograft was used, the morselized bone graft was for 1 hour kept in 20ml vancomycin solution (50 mg/ml) prepared by adding 500 mg of vancomycin powder to 20 ml distilled water. Patients were seen at 5th day for 1st wound check, then 2 weeks postoperatively at the time of suture removal and again at 6 and 12 weeks. Particular attention was given to

infection / local signs of active inflammation. Radiographs were done first at 15th day postoperatively, then every four weeks for initial four months and finally every two months till completion of follow up. A minimum follow up of seven months was there in our study. Both the groups were broadly compared in terms of occurrence of infection, healing status of the bone achieved, extent and rate of osteointegration of bone allograft. Postoperative infection was identified by using WHO Guidelines for SSI^[3], osteointegration was assessed by radiographic signs on plain x-rays as delineated by Sloof *et al.*^[2] Bone healing in fractures was assessed in terms of adequate union, defined radiographically as presence of at least three of four healed cortices and crossing trabeculae on anteroposterior and lateral radiographs and in cases of benign osteolytic lesions as attainment of stage 1 of Neer's classification^[79] and as adequate fusion seen on radiographs in cases of spondylolisthesis. In case of acetabular reconstruction, adequate new bone formation in the region of graft placement was taken as adequate bone healing. Results were assessed in terms of infection, osteointegration and bone healing.

Observation and findings

Infection

Out of a total 30 patients where allogenic bone graft was used, a single patient of Aneurysmal Bone Cyst belonging to the control group, where no vancomycin impregnation of allogenic bone graft was carried out, developed surgical site infection with serous discharge which on culture revealed growth of *Pseudomonas aeruginosa*. Thus, an overall infection rate of 3.3% (1 out of 30 cases) was found in this study which is much lower than what is mentioned in the literature as infection rates ranging from 4-12% have been reported by different workers (Lord *et al.* 1988, Haddad *et al.* 2000)^[4, 5]. There was no infection in the study group patients and an infection rate of 6.7% (1 out of 15) was observed in the control group, but this difference is statistically not significant (p value=1.00). The much lower infection rate in our study as compared to previous works involving the use of allogenic bone grafts may be attributed to use of vancomycin impregnated allogenic bone graft in half of patients (study group) and also better bone bank services with gamma sterilization of all allogenic bone grafts used. Further a single incidence of infection which was reported occurred in benign osteolytic lesion category (Aneurysmal Bone Cyst) and no infection occurred in fracture cases either in the study or control group.

Osteointegration

The overall success rate in terms of adequate osteointegration in our study was 83.33% (5 failure cases out of 30) with 12 cases (80%) out of 15 in study group and 13 cases (86.7%) out of 15 achieving adequate osteointegration and there was no significant difference (p value=1) between the two groups. The mean duration of graft uptake in the study group was 7.5 ± 1.09 months while in the control group it was 6.6 ± 1.55 months and this difference in duration to achieve adequate osteointegration was not statistically significant with p value of 0.148. Thus in our study vancomycin impregnation of allogenic bone graft did not appear to affect the time to achieve adequate osteointegration.

The period of osteointegration varied between different indications for which allogenic bone graft was used in our study. For Benign osteolytic lesions the mean time of osteointegration in the study group was 7.20 ± 1.64 months

and in the control group was slightly lesser at 5.33 ± 2.08 months but there was no statistical difference with p value of 0.206.

In cases of fractures mean time taken to achieve osteointegration in the study group came out to be 7.71 ± 0.49 months and in the control group it was slightly lesser at 7.22 ± 1.20 months. But here again no significant difference between the study and control group was there in terms of mean time period taken for osteointegration in case of fractures (p value = 0.328).

One more important finding which could be drawn in our study was that any extraosseous placement of allogenic bone graft, that is graft material placed out of the cystic cavity in lytic lesions and outside the bone defect in cases of fractures inevitably got resorbed in both the groups in an average time period of 9 weeks. Thus allogenic bone graft appears to carry a little risk, if any, of getting converted to sequestrum vulnerable to infection in the future.

In our study the time of healing of lesion and adequate osteointegration closely followed each other and varied according to the nature of lesion. In unicameral bone cysts all the three cases showed incorporation of bone within 4 months. In aneurysmal bone cysts all the cases showed graft incorporation but the time period varied within a range of 7-10 months and both cases of giant cell tumour showed adequate osteointegration within 9-11 months.

Bone healing

In our study, the patients could be broadly divided into three categories depending on the indication for which allogenic bone graft was used. The first and the largest category comprised of patients having fractures with comminution, bone loss, delayed union, non unions and other difficult to heal fractures. In these patients healing was assessed in terms of union achieved which was radiographically defined as presence of at least three of four healed cortices and crossing trabeculae on anteroposterior and lateral radiographs. A total of 18 patients with this indication were included in the study with 9 patients being in the study group and 9 patients in control group. A further ramification of diagnosis revealed that 4 cases were of delayed union, 9 cases of frank non union and 5 cases of difficult fractures, that is relatively fresh fractures with comminution and bone loss. An overall union rate of 88.8% was obtained with 16 of 18 patients achieving adequate union. The two failure cases were in the study group which brought down the union rate to about 77.7% in the study group as compared to 100% union rate in the control group but this difference was not statistically significant with p value of 0.384. Thus, vancomycin impregnation was not found to adversely affect fracture union in our study.

The two failure cases in the study group comprised of one established non union of mid-diaphysial tibial fracture in 30 year old male patient and one case of delayed union of fracture midshaft radius and ulna in a 31 year old male patient. All the patients belonging to difficult fracture subgroup achieved union in both study and the control group. As both the failure cases belonged to old fractures, that is established non union / delayed union, with hampered healing potential it appears that in such situations use of allogenic bone alone does not suffice and some osteogenic potentiator is also required to boost the already sluggish healing process. The failure case of tibial non union was further subjected to fracture site freshening, external fixation with JESS (Joshi External Stabilisation System) and bone marrow aspirate infiltration. Intraoperative findings were suggestive of

increased vascularity at the fracture site with complete resorption of allograft and presence of bone defect. These findings are suggestive of allogenic bone graft being able to induce an inflammatory reaction at the fracture site which may aid in healing process but is not sufficient to bring about fracture union as graft resorption occurs at around 4 to 5 months.

The second major indication for which allogenic bone graft was used in this study was benign osteolytic lesions such as Simple Bone Cyst (SBC), Aneurysmal Bone Cyst (ABC) and Giant Cell Tumour (GCT). Intralesional curettage was undertaken along with allogenic bone grafting in all these patients. A total of eight patients (3 each of SBC and GCT and 2 of ABC) were included. After random allocation five patients (2 each of SBC and GCT and 1 of ABC) came under the study group and three patients (1 patient each of SBC, GCT and ABC) under control group. The mean age of patients in the study group and control groups was 25.2 years and 34.1 years respectively and thus were comparable. There was no significant difference in terms of lesion healing between the two groups (p value= 0.684) as all the eight patients (100%) showed adequate healing as defined by Neer's classification^[1].

The overall mean time of adequate healing in these lesions in the study group and the control group were 7.62 ± 1.45 months and 6.93 ± 1.53 months respectively and were comparable with a p value of 0.239. The time for adequate healing varied according to the nature of lesion with all three cases of Simple Bone Cyst healing earliest at an average time of 5.33 months and the three Giant Cell Tumour cases taking the longest average duration of 8.33 months for adequate healing. The 2 cases of Aneurysmal Bone Cyst cases took an average time of 6 months to heal completely.

Vancomycin impregnated allogenic bone graft appears to be safe and effective filler, without any systemic and local adverse effects, for bone defects secondary to benign osteolytic lesions and relatively fresh fractures with comminution and bone loss as graft osteointegration and bone healing does not get adversely affected as well as prophylaxis against infection is also gained by its use. The use of allogenic bone graft in established non unions and delayed unions may require augmentation with osteogenic potentiators to expedite the already sluggish healing process in these cases. This study may serve as a basis for further studies assessing the use of vancomycin impregnated allogenic bone graft as a local antibiotic delivery system in controlled osteoarticular infections.

Conclusions

In this study patients who underwent allogenic bone grafting could be broadly classified into three groups:

Fractures: Which included cases of established nonunions, delayed unions and difficult fractures (relatively fresh fractures with severe comminution and bone loss).

Benign Osteolytic lesions: Included cases of Simple bone cyst (SBC), Aneurysmal Bone Cyst (ABC) and Giant Cell Tumour (GCT).

Miscellaneous: Three cases of spinal lumbar fusion and one case of acetabular reconstruction.

The allograft used was impregnated with vancomycin in the study group (n=15) and non vancomycin impregnated allograft was used in the control group (n=15). The

conclusions are drawn with respect to infection, graft osteointegration and healing status of bone.

Infection

A very low infection rate of 3.33% (1 out of 30) was observed in our study which can be attributed to better bone bank services with gamma irradiation and use of vancomycin impregnated of allogenic bone graft in half of the patients. A single instance of infection occurred in the control group and the cultured organism was *Pseudomonas aeruginosa* which may have occurred as graft related or surgical site infection. This organism was not sensitive to vancomycin. Although no statistical difference was observed in infection rate between the study and control group (p value = 1.000), but a very low overall infection rate points that vancomycin impregnation of allogenic bone graft can be a safe and effective measure in prophylaxis of allograft related and surgical site infection.

Any extraosseously placed allogenic bone graft, that is graft material placed out of the cystic cavity in lytic lesions and outside the bone defect in cases of fractures, inevitably got resorbed in both the study and control groups in an average time period of 9 weeks. Allogenic bone graft appears to carry a little, if any, risk of getting converted to sequestrum vulnerable to infection in the future. Thus allogenic bone grafts impregnated with antibiotics may also be used in active osteoarticular infection as there are less chances of the remaining graft serving as dead necrotic bone aiding in persistence of infection.

Bone healing

All the 8 cystic lesions in the study healed with the use of allogenic bone graft. Thus no difference in terms of healing of Benign osteolytic lesions (Simple Bone Cyst, Aneurysmal Bone Cyst and Giant Cell Tumour) was noted in the study. Thus vancomycin impregnated allogenic bone graft can serve as an excellent filler for augmenting healing in Benign osteolytic lesions of bone. In cases of fractures a good overall union rate of 88.8% was obtained with 16 out of 18 patients achieving adequate union. The two failure cases brought down the union rate to about 77.7% in the study group as compared to 100% union rate in the control group but this difference was not statistically significant with p value of 0.384 Thus vancomycin impregnation was not found to affect fracture union in our study.

The mean duration of fracture union was also not found to be adversely affected by vancomycin impregnation. The two failure cases in the study group comprised of one established non union of mid-diaphysial tibial fracture in 30 year old male patient and one case of delayed union of fracture midshaft radius and ulna in a 31 year old male patient. All the patients belonging to difficult fracture subgroup achieved union in both study and the control group. As both the failure cases belonged to old fractures with hampered healing potential, that is established non union/ delayed union, it appears that in such situations use of allogenic bone graft alone does not suffice as some osteogenic potentiator is also required to boost the already slow healing process.

Osteointegration

An overall good rate of osteointegration was achieved in our study with 83.33% (25 out of 30) of patients achieving satisfactory osteointegration of the allograft with host bone bed. Vancomycin impregnation did not adversely affect the allograft osteointegration as well as the time taken to achieve it. Thus allogenic bone graft impregnated with vancomycin

can osteointegrate satisfactorily without any systemic and local complication.

In this study, the time of healing and consolidation of Benign osteolytic lesion and adequate osteointegration closely followed each other and varied according to the nature of lesion. In simple bone cysts all the three cases showed incorporation of bone allograft within 4 months. In aneurysmal bone cysts all the cases showed graft incorporation but the time period varied within a range of 7-10 months while both cases of giant cell tumour showed adequate osteointegration within 9-11 months.

Vancomycin impregnated allogenic bone graft appears to be safe and effective filler, without any systemic and local adverse effects, for bone defects secondary to Benign osteolytic lesions and relatively fresh fractures with comminution and bone loss as graft osteointegration and bone healing does not get adversely affected as well as prophylaxis against infection is also gained by its use. The use of allogenic bone graft in established non unions and delayed unions may require augmentation with osteogenic potentiators to expedite the already sluggish healing process in these cases. This study may serve as a basis for further studies assessing the use of vancomycin impregnated allogenic bone graft as a local antibiotic delivery system in controlled osteoarticular infections.

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