Original research article

The Use of Bone Grafts for Local Antibiotic Delivery in Bone Reconstruction Surgery: Recent Advances

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Abstract

Background: One of the main problems in bone and joint surgery is still infection related to bone implants. In both the treatment and prevention of these infections, antibiotic-impregnated bone transplants appear to hold promise. Nonetheless, this field of research is characterized by a wide range of methodologies. An overview of the published literature is provided in this essay.

Method: The Medline database was searched, and articles were chosen based on pre-established exclusion criteria.

Results: The synthesis contained 45 papers. Studies were conducted on issues such as the type of bone graft, graft operations, elution profile, bacterial inhibition, oestotoxicity, incorporation, unique impregnation techniques, clinical use, and storage. From a therapeutic standpoint, large initial concentrations seem suitable for eliminating biofilm. It appears possible to treat an infection caused by a bone implant in a single step. When employing antibiotic-impregnated bone grafts, the literature suggests a reduction in postoperative infections as a preventative measure.

Conclusion: Both therapeutically and preventatively, local antibiotic treatment can be applied to bone grafts.

Keywords: infections, impregnation, supply of antibiotics, and bone transplants

Introduction

One of the main problems in bone and joint surgery is still infection. From 2000 to 2009, the rate of osteomyelitis increased from 11.4 cases per 100000 person-years in the years from 1969 to 1979 to 24.4 cases per 100000 person-years [1]. Device-related infections in prosthetic surgery cause up to 20% of revisions after knee arthroplasty and up to 12.8% of revisions after hip arthroplasty [2]. When comorbidities rise, it is anticipated that prevalence would rise [3]. Periprosthetic joint infection will be one of the most significant long-term consequences, with annual joint arthroplasties in the USA and the UK estimated to reach 800000 and over 4 million annually by 2030, respectively [4]. Fracture-related infections in

open fracture cases can reach up to 30% in musculoskeletal trauma surgery. In situations of open fracture during musculoskeletal trauma surgery, fracture-related infections can reach up to 30%. Permanent loss of function or amputation are examples of outcomes that can change your life [5].

Biofilm development is a significant issue with infections of bones and implants. High quantities of bactericidal antibiotics can't kill bacteria entrenched in biofilms, which results in treatment failure and infection recurrence. To eliminate biofilm-associated illnesses, local antibiotic dosages well above the minimum inhibitory concentration (MIC) are necessary [6]. For an accurate measurement of antibiotic action, new pharmacodynamic measures, such as the minimal biofilm eradications concentration (MBEC), are required [7]. As the MBEC is not attained, it has been demonstrated that systemic antibiotic treatment alone cannot produce the local concentrations needed for biofilm eradication [7].

Operative treatment for infections frequently involves two stages. Radical debridement and the removal of implants are part of the initial stage. Dead space management involves temporarily filling them with antibiotic-laced, non-biodegradable cement spacers. To restore skeletal continuity, a second stage surgery involves removing the cement spacer and inserting fresh implants [8]. However, during the first few days after implantation, bone cements generally stop serving as an antibiotic elution device [9].

They are susceptible to bacterial colonisation and re-infection of the surgical site because to their avascular nature and combination [10]. Additional drawbacks include the requirement for a second surgery to remove the biodegradable component and a constrained selection of antibiotics as a result of the heat generated during stiffening [11].

The best way to address the aforementioned issues is to deliver an antibiotic locally using a biodegradable material that has an appropriate elution profile. This would increase local antibiotic levels, enabling the removal of biofilms without causing systemic side effects and maybe allowing the treatment of bone implant-related illness in a single step [12]. Bone grafting is a method that could be able to satisfy these requirements.

The use of bone grafting in bone insufficiency following infection has been viewed as contraindicated because the avascular grafts are prone to re-infection, despite the fact that it is already common in reconstructive orthopaedic surgery [13]. It has been proposed that antibiotic-loaded bone grafts are an effective complement to systemic prophylaxis for preventive purposes [14].

Although the potential use of antibiotic-loaded bone transplants in orthopaedic surgery is obvious on paper, practical evidence is still lacking. It is challenging to draw conclusions because of the variety in approach, including the type of grafts, antibiotics, impregnation method, and dose. This study provides a summary of the published information on the therapeutic and preventive usage of bone transplants with antibiotic impurities.

METHODS:
Study Design: This was a systematic review carried out in SCB Medical College, Cuttack from August 2021 to July 2022

Methodology: The Medline article was chosen. In January 2020, the most recent search information was included. Search terms were: "Bone Transplantation" [Mesh] and (Local

antibacterial agents OR Vancomycin OR Gentamicin OR Tobramycin), Antibiotic impregnated bone grafting, Bone cell toxicity and Antibiotics and Local delivery, Osteoblast and Local antibiotics, Cancellous bone and Vancomycin, Lyophilized bone and Antibiotics, Iontophoresis and Bone and Antibiotics. By analyzing the complete text, eligibility was again checked.

Sample Size:
The compilation contained 45 papers.

Inclusion Criteria:
In-vitro, animal, and clinical research were also included. Based on the title and abstract, a first screening was conducted

Exclusion Criteria:
Papers older than 1990, review papers, case reports, expert opinions, papers from which the full text analyzing be retrieved, or papers written in a language other than English, were excluded (from title or abstract). In addition, papers discussing tuberculosis or using demineralized bone matrix were also excluded.

RESULTS:
There were 500 items in total found based on the search criteria. 52 articles passed muster after the initial review. Seven further items were disqualified in a second full-text screening. In the end, 45 papers in total were included in our analysis. 41 of the 47 articles were bone transplant experiments. Three trials that examined toxicity, as well as bone grafts, were therefore included. The following factors were examined based on these articles: bone type, manipulations, impregnation techniques, elution kinetics, osteotoxicity, incorporation, storage, and recent clinical data.

Body Type
Uptake capacity and elution profile determine whether cancellous or cortical bone grafts are suitable for impregnation. Most research employs cancellous bone transplants [Figure 1]. There are 5 studies [15–18] that use cancellous bone as an antibiotic carrier and specifically state that the in vitro elution was sufficient. The use of cortical bone alone for impregnation is only described in 4 investigations [19–21]. When four different antibiotics were implanted into cortical bone, the elution profile showed a high release within the first 24 hours. Rats with Staphylococcus aureus-induced intramedullary infections were totally cured by using grafts impregnated with netilmicin, vancomycin, and rifampicin [22].

Using vancomycin and tobramycin impregnation, a direct comparison of cancellous and corticalbone grafts was carried out [23]. Initial elution concentrations after vancomycin impregnation were substantially lower for cortical bone than for cancellous bone. At day 8, there was no longer a discernible difference in the concentrations between the two transplant types. Cortical bone had a much lower overall vancomycin release. Cortical bone grafts released tobramycin at a lower initial concentration than cancellous bone grafts did. For cortical transplants, concentrations decreased to below the minimum inhibitory concentration (MIC) at day 22, whereas cancellous bone grafts were remained significantly over the MIC at day 28 [23].
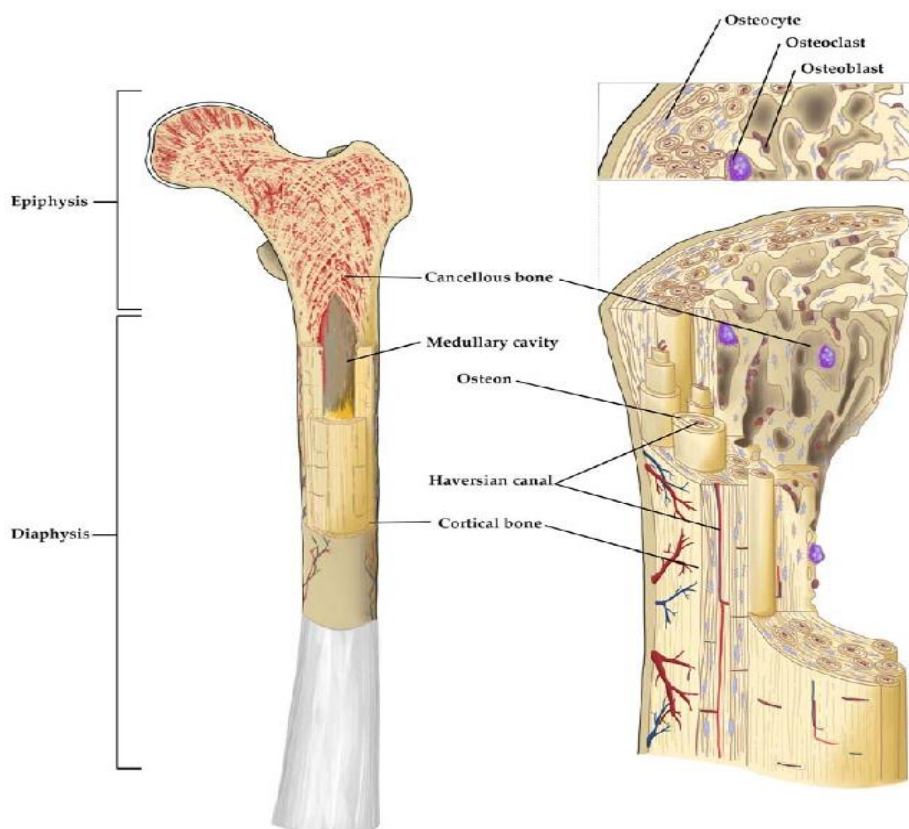
Figure 1: Cancellous bone Transplant

Allografts were employed in most investigations. No study did a direct comparison of allo- and autografts. Vancomycin elution from cancellous human allografts and bovine xenografts was comparable, although tobramycin elution from bovine cancellous bone was marginally (not statistically tested) higher [23]. The femoral head is the most common origin for bone grafts, though there are other origins as well. While cancellous autografts are more frequently extracted from the iliac crest, cancellous allografts, which are used in half of studies, come from the femoral heads. The femoral or tibial diaphysis is the source of cortical grafts.

Bone particle size varies from 0.01 to 6 mm between studies and within them. On antibiotic elution, the impact of bone fragment size was investigated [24]. Vancomycin or netilmicin were applied to finely and coarsely morselized cancellous bone, and the elution was monitored for 14 days. Vancomycin showed no discernible change, although netilmicin's elution was higher from fine particles [25].

Manipulation
The most researched grafts are newly frozen ones. Further adjustments can be made to enhance storage properties and/or lessen immunogenicity. Of the 45 research, 11 touches on the manipulation of bones. Grafts were subjected to a freeze-drying procedure in 5 investigations [Figure 2]. In two studies, gentamicin powder was used with both lyophilized and freshly frozen bone grafts [26]. By day 4, the release from freshly frozen bone decreased from an initial 10000 g/ml to 300 g/ml. From the first to the third day, lyophilized grafts displayed a release rate that ranged from 4000 to 400 g/ml. These concentrations were higher than S. aureus' MIC [26]. In another investigation that contrasted freeze-dried and fresh frozen bone grafts, gentamicin and vancomycin elution kinetics were shown to be similar [27].
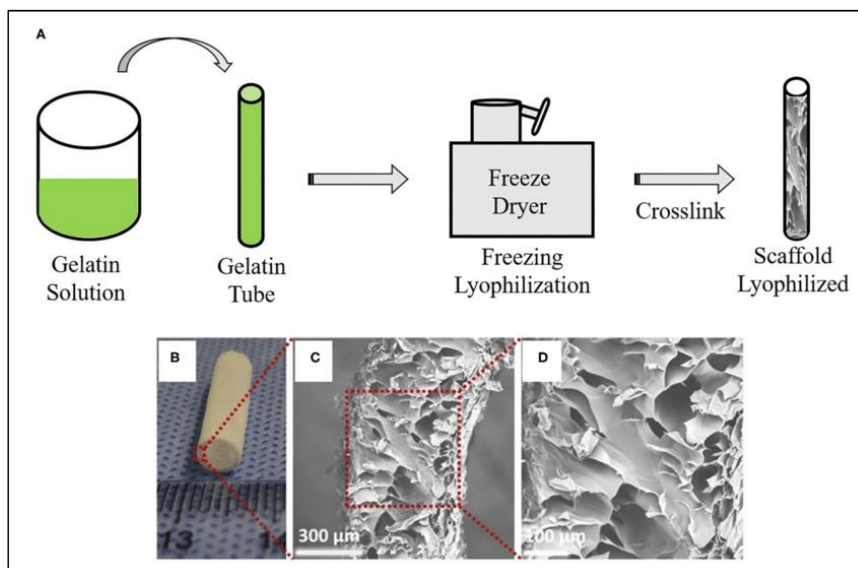
Figure 2: Grafts subjected to freeze drying

A graft was freeze-dried, vancomycin-impregnated, and then again freeze-dried in a twofold lyophilization step, although this process had no discernible impact on elution [28]. Although the elution was not delayed by freeze-drying the graft while it was still immersed in the antibiotic solution, the total amount of antibiotic released was higher [29]. Additional bone graft procedures for decellularization and/or sterilisation included pulse lavage with regular saline [30], sonication, irradiation, and combinations thereof, as well as chemical cleaning treatments using detergents [21] or solvents [28,29]. Bone graft cleaning by washing as opposed to detergent treatment and sonication had no discernible effect on gentamicin impregnation [31].

Techniques for impregnation

The majority of sheets impregnate themselves using an antibiotic solution or a dry powder mixture. Several techniques for impregnation have been considered, though. Non-traditional methods of impregnation are covered in 8 out of 45 articles. Iontophoresis is a method that uses an electric potential to speed up how quickly certain antibiotics diffuse into bone. Gentamicin or flucloxacillin was applied by immersion or iontophoresis to sections of sheep or human tibial diaphysis [24; Figure 3]. A greater zone of inhibition was seen in the specimens treated with iontophoresis compared to those that had been soaked [24] Vancomycin elution from sheep tibial diaphysis may be controlled by adjusting voltages, iontophoresis duration, and concentrations [25].
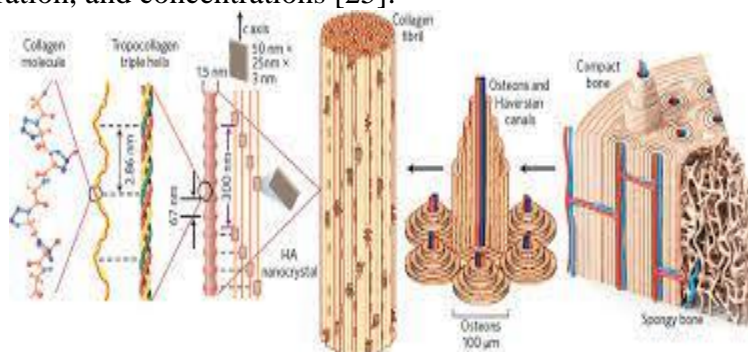

Figure 3: vancomycin drug delivery system

For autologous cancellous bone transplant, a vancomycin drug delivery system made of natural bee wax and glycerin was described, resulting in a long-acting (3–4 weeks) antibiotic-impregnated bone graft. With no adverse effects on integration, this combination was successful in curing rats of an artificially produced S. aureus osteomyelitis [33].

Kinetics of elution

The elution kinetics of a bone graft as an antibiotic carrier is its most crucial component. This property is influenced by both the antibiotic and the carrier. When the antibiotic is released from the impregnated graft, the local concentrations should be higher than the MIC (for prophylaxis) or MBEC (for therapy), respectively, for a sufficient period of time. Elution kinetics are covered in 11 out of 48 publications. For cancellous fresh frozen bone grafts combined with vancomycin powder (1% w/w), elution kinetics were characterized. Elution for S. aureus was well over the MIC for 15 days, peaking at 499.7 g/ml on day 1–3 [22]. In a different investigation, vancomycin (100 mg/ml)-impregnated highly purified cancellous grafts attained initial concentrations as high as 20,000 g/ml [28]. Vancomycin-impregnated grafts, however, did not completely cure a rat osteomyelitis caused by S. aureus in vivo. 41 In contrast, a generated S. aureus osteomyelitis in rats was successfully treated using bone grafts combined with a vancomycin-enriched wax [34; Figure 4]. Fresh frozen grafts treated with a moxifloxacin solution released 3846.9 g/ml on the first day and went over the MIC for 42 days [20].
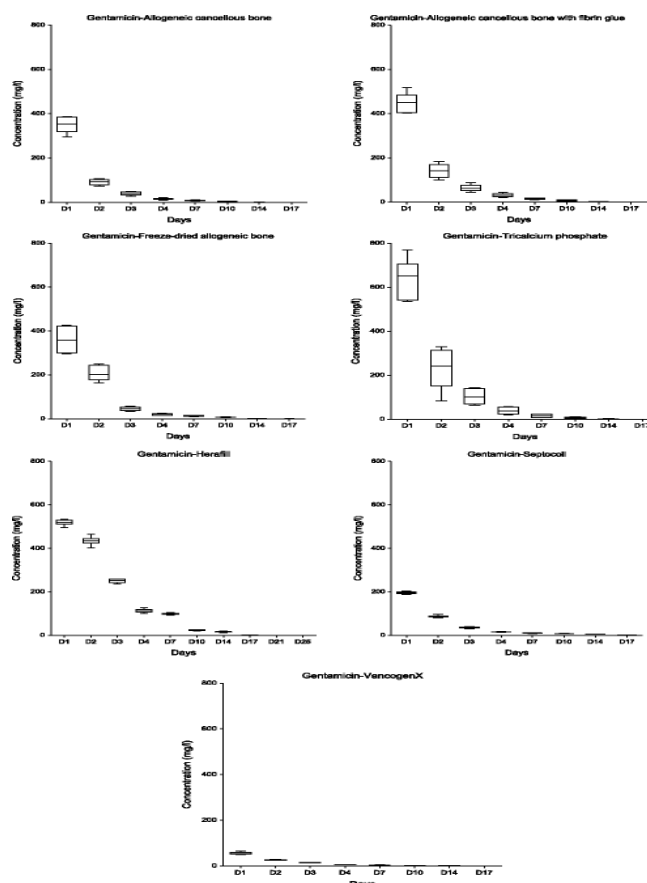

Figure 4: Elution Kinetoc of Vancomycin

Cancellous bone grafts impregnated with tobramycin solution (80 mg/ml) immediately released 10,000 g/ml and continued to release more than the MIC for 28 days [28]. Gentamicin was released rapidly from gentamicin solution-impregnated grafts over the first two days, exceeding 1000 g/ml. On day 4, half of the antibiotic that was absorbed was eluted.

For 14 days, the overall drug concentrations were higher than the MIC. 21 Gentamicin-sulfate was found to release gentamicin much more than a gentamicin-sulfate/palmitate mixture [35]. By exposing fresh, morselized bone to solutions of various antibiotics, including benzylpenicillin, dicloxacillin, cephalothin, netilmicin, vancomycin, ciprofloxacin, clindamycin, and rifampicin, release rates were studied [18]. The first three (beta-lactams) displayed extremely high values that quickly declined after 7 days. Within 14 days, netilmicin, vancomycin, ciprofloxacin, and clindamycin were made available. For a period of 21 days, only rifampicin was greater than the MIC [18]. The intramuscular implantation of rats provided in vivo confirmation of these findings. The bacteriostatic effect of bone impregnated with clindamycin, netilmicin, vancomycin, and rifampicin lasted for 7 days, ciprofloxacin for 3 days, and benzylpenicillin and cephalothin only for 1 day [19]. Investigations have been conducted on the impregnation fluid, impregnation time, and pH of the impregnation fluid.

Vancomycin and moxifloxacin benefited from the timing of cancellous bone impregnation but netilmicin elution was unaffected, indicating a difference in absorbance kinetics [20,35]. Netilmicin or vancomycin release increased by 252% or 125%, respectively, when the impregnation concentration was multiplied by four [29,36]. Gentamicin released substantially more over the first two days when it was impregnated at a rate of 10 mg/ml compared to 1 mg/ml, but by day four, elution concentrations were comparable [21,37]. When compared to bone impregnated at pH 7, antibiotic levels eluted from bone at pH 3 or pH 5 substantially less frequently [29]. Cortical bone impregnation time was also researched [27]. The total amount of released netilmicin, vancomycin, and rifampicin increased by three to four fold when the impregnation time was increased from one to ten hours. A further increase in impregnation time to 100 hours resulted in a 6–10 fold increase of antibiotic discharged. This effect was less noticeable for ciprofloxacin, with a 2-3 fold rise [27].

Bone cement has more benevolent elution kinetics when compared to bone cement coated with antibiotics For the first three days, cannulated bone produced much higher antibiotic concentrations, and the duration of detectable elution was comparable. Moreover, compared to allogeneic bone grafts, the cement still included a sizable dose of antibiotics [31].

Osteotoxicity
Antibiotic application at levels toxic to osteoblasts may impede bone resorption. As a result, antibiotic discharge shouldn't go beyond the bone toxicity limit. 45 articles were reviewed, and 9 of them examined how antibiotics affected cell lines. In a comparative research, osteoblasts were cultured with solutions containing one of various antibiotics at concentrations ranging from 0 to 5 mg/ml [39] The quantity of cells and osteogenic activity were calculated. The least cytotoxic antibiotic was discovered to be vancomycin, and amikacin and tobramycin also worked well. Rifampin, minocycline, doxycycline, nafcillin, penicillin, ciprofloxacin, colistin methanesulfonate, and gentamicin were the antibiotics that caused the most cell toxicity. Concentrations below 200 g/ml of these antibiotics already had a deleterious impact on the number of cells [40].

The results for preosteoblasts and prechondrocyte cell lines were comparable [41]. After 48 hours of treatment to ciprofloxacin at 100 mg/ml and vancomycin and tobramycin at 2000 mg/ml, proliferation was significantly hampered. In a different study, 10000 g/ml vancomycin triggered cell death in an osteoblastic cell line, but 1000 g/ml had no impact, and this lethal dosage of vancomycin was also described [42]. Similar to this, tobramycin levels

of 400 g/ml and higher inhibited osteoblast cell multiplication and led to cell death, respectively [43].

Osteoblastic cell growth was limited or unaffected by cefazolin concentrations up to 100 g/ml, while growth was inhibited at 1000 g/ml [44]. Cell decrease on mesenchymal stromal cells was observed at dosages of less than 250 g/ml for 24 hours or even less than 50 g/ml when sustained for 72 hours [45]. Below 100 g/ml, the cephalosporin cefuroxime had minimal impact on the growth of human osteoblasts. Proliferation was even increased at concentrations of 250 and 1000 g/ml When the concentration of 1000 g/ml was maintained for more than 48 hours, cytotoxicity was noted [46].

With gentamicin, preosteoblast cell number was unaffected by exposure up to 800 g/ml for 48 hours [49]However, lengthier exposure (5–10 days) at concentrations below 250 g/ml had a detrimental effect on the growth of rat osteoblasts [21].

At 10 and 25 g/ml, clindamycin caused human osteoblasts to produce more calcium, but 50 g/ml caused the opposite. At 500 ng/ml for 72 hours, proliferation dropped off in a dose-dependent manner, reaching 3.5% of control samples [47]. Notably, carriers can affect proliferation independently of antibiotic loading; freeze-dried bone inhibited mesenchymal stem cell proliferation in comparison to fresh-frozen grafts [31; Figure 5].
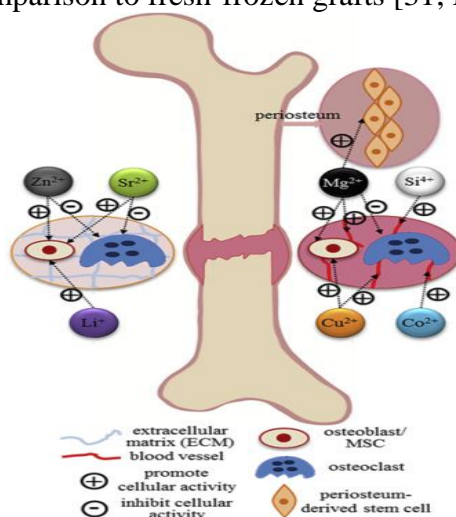

Figure 5: Bone repair using stem cells

Incorporation

The incorporation of bone graft into the host bone in vivo is even more important than the in vitro evaluation of osteotoxicity. Incorporation was covered in 13 out of 45 articles. Dogs were used as test subjects for the incorporation of tobramycin-impregnated bone grafts (impregnation doses up to 800 mg/ml) [50]. After 4 weeks of integration, histomorphological testing revealed no discernible difference between low and high drug concentrations [51]. Results that were equivalent to ordinary bone grafts were reported for cancellous bone impregnated with tobramycin powder [52]. This incorporation was assessed radiographically, microscopically, and biomechanically.

Bone healing was unaffected even after bone grafts were impregnated with vancomycin. In a pig tibial deformity, grafts with or without vancomycin were implanted. Radiography, histopathology, and immunohistology did not reveal any changes between the two groups [53]. Vancomycin-impregnated grafts had no effect on bone mineral content or density when osteomyelitis was present [41]. Goats were used to study the incorporation of cefazolin-

impregnated cancellous bone allografts. No discernible histomorphometric alterations could be identified between an antibiotic-impregnated graft and a control graft after 12 weeks [35]. The incidence of nonunion did not rise when it was clinically used in fracture surgery since the total incidence of nonunion remained within normal limits [54]. Bone samples were equal to those in allografts without vancomycin 14 and 20 months after revision of a total hip arthroplasty with vancomycin-impregnated bone grafts [55]. While employing antibiotic-impregnated autografts in the reconstruction of infected tibial nonunions, no recurrent nonunion was seen in contrast to unmodified cancellous autografts where one nonunion occurred [51]. Vancomycin and tobramycin impregnated graft integration was comparable to traditional grafting in a stage revision of periprosthetic infection [34].

Storage
As compared to newly generated samples, bone chips impregnated with gentamicin, cefazoline, or vancomycin and stored for 1-6 months at -20°C or -80°C all retained the same antibiotic activity [56].

Clinical support for the use of prophylaxis
Prophylactic usage was covered in 3 out of 45 papers. Allografts with vancomycin preservative were studied as a preventative intervention in an aseptic one-stage revision of total hip arthroplasties[52]. Impaction grafting was used to treat patients, employing allografts soaked with vancomycin powder and PMMA as the fixation. It was either PMMA alone or PMMA combined with gentamicin or tobramycin. Vancomycin was able to reach 1400 g/ml in the local environment without causing nephrotoxicity. Up to 48 hours after implantation, vancomycin-supplemented bone allografts reached local concentrations 20–300 times higher than the MIC for S. aureus without compromising renal function. The bactericidal effect of the cement was improved by the addition of tobramycin or gentamicin [50]. Vancomycin-impregnated allografts and plain PMMA were assessed on 75 patients who were getting a revision hip arthroplasty in a follow-up study.

Infection rates were examined and contrasted with information from conventional impaction grafting using antibiotic-loaded cement. One post-operative infection was the outcome, which is comparable to the prevalence of antibiotic-loaded cement [47].

A retrospective study on 220 patients with cerebral palsy who had spinal fusion surgery investigated the clinical efficacy of the prophylactic use of gentamicin powder-impregnated bone grafts. The other 66 individuals had bone transplants free of antibiotics, whereas 154 youngsters underwent fusion with gentamicini-impregnated bone grafts. Compared to 15.2% of patients without antibiotics, only 3.9% of bone graft recipients who were impregnated with gentamicin experienced deep wound infections [54].

31 individuals undergoing revision arthroplasty or limb-salvage surgery have employed iontophoresed cortical allografts as a preventative measure [Figure 6]. Using gentamicin and flucloxacillin, grafts were iontophoresed. The mean serum antibiotic levels were low, and the postoperative antibiotic levels in the drain fluid were significantly higher than S. aureus' MIC. Within six months, there were two complications: an early non-union and a wound infection. Two allograft infections, three late fractures, and three confirmed non-unions were late-onset problems [55]. There hasn't been a direct comparison to unimpregnated grafts.
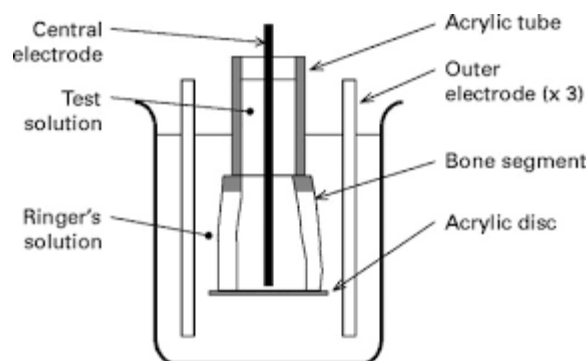
Figure 6: iontophoresed cortical allografts

Clinical proof of use in therapy

Among the 45 papers, eight talked about therapeutic use. In a two-stage procedure to cure an infected hip arthroplasty, vancomycin-supplemented bone allografts were evaluated [55]. Parenteral antibiotic therapy and implant removal were used to treat thirty hips. In a subsequent step, bone grafts that had been impregnated with vancomycin powder were used for repair.

One further infection, one periprosthetic fracture, two single dislocations, and four displacements of the greater trochanter were complications. The most recent follow-up revealed radiographic consolidation in 29 hips [55]. A two stage method was used to repair 18 tibial nonunions in a study of a similar nature [54]. Debridement, gentamicin PMMA bead chains filling, and external fixation stabilisation made up the first stage. The second stage involved removing the antibiotic beads and reconstructing the area using cancellous autografts that had been soaked with vancomycin powder. In all cases, infection control was attained. Five patients experienced nonunion, necessitating a second operation, but eventually all patients displayed satisfactory consolidation of the grafted bone [37].

The idea of a one-stage revision of infected implants was looked into as a next step in the clinical evaluation of vancomycin-impregnated bone grafts [33,34]. A one-stage debridement, lavage, and filling with lyophilized antibiotic-impregnated cancellous allografts was used to complete 48 revision procedures. Cement wasn't applied. Revision of an infected complete hip replacement, a total knee replacement, or intramedullary nailing were among the procedures. Depending on the microorganism, vancomycin or tobramycin were the antibiotics employed for impregnation. Vancomycin drain levels ranged from 8 to 2243 g/l, while post-operative serum levels were between 0 and 4.2 g/ml. Renal function exhibited no variations. Infection recurrence was noted in 2 instances. Implants did not become loose or dislocate [33].

In 96 patients with an infected tibial nonunion, a direct comparison of autografts with antibiotic powder and those without was carried out [39]. All patients received a first surgery that involved debridement and filling with PMMA bead chains infused with antibiotics. A second surgery removed antibiotic bead chains, and the defect was then repaired. Either ordinary cancellous autografts or autografts with antibiotics were applied. The pathogen for which the antibiotic was selected was only susceptible to vancomycin and piperacillin. Following up for 4 to 6 years revealed that all patients who received pregnant autografts experienced successful bone union. In this group, just two infections occurred, leading to an infection arrest rate of 95.6%. The infection arrest rate was 82% in the group getting plain autografts, which was noticeably poorer [39].

There were no additional infections as a result of the use of iontophoresed grafts in septic circumstances in a study of 12 two-stage revisions in which the second stage involved flucloxacillin and gentamicin-iontophoresed bone grafts [54; figure 7]. In one clinical investigation, bone grafts with antibiotics added are used for maxillofacial surgery. Treatment for peri-implantitis consisted of debridement immediately followed by filling with allografts that were tobramycin- and vancomycin-impregnated. After a year, the bone defect was greatly decreased, there was no evidence of ongoing bone loss, and no implants required replacement [44].
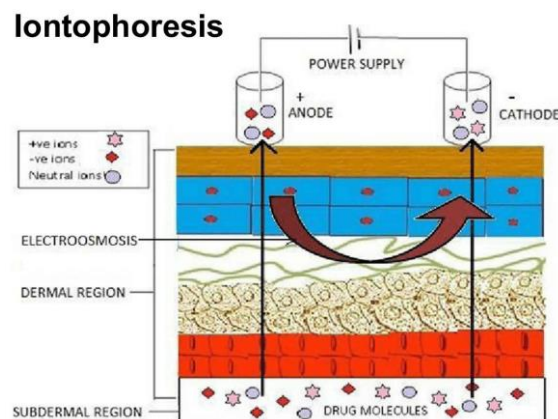

Figure 7: Iontophoresed grafts in septic conditions grafts in septic conditions

DISCUSSION:

It is challenging to compare results in a systematic manner because of the wide variance in approach. In tiny bone defects, cancellous bone is the preferable bone graft type [46], and it also appears to be superior for antibiotic impregnation. Antibiotic elution concentrations were lower in cortical bone because it is less accessible to antibiotics than cancellous bone [28]. Although allografts are the most often used, both human and bovine bone function similarly in terms of antibiotic binding and elution [28]. So, only broad concepts can point you in the direction of the optimal decision. Processing xenografts is necessary to prevent disease transmission and improve biocompatibility. The more typical allografts can also undergo processing. Although autograft bone poses no immunogenicity risk, its usage is constrained by its scarcity and donor site morbidity [51].

One graft procedure modifies the characteristics: the removal of blood and fat after lyophilization creates more free space. A lyophilized bone transplant is less immunogenic and can be stored at room temperature for a long time [47]. There was no discernible difference between impregnated morselized bone and freeze-dried bone powder in the gentamycin and vancomycin elution profiles [31]. This runs counter to the assertion that freezing and removing bone marrow significantly improves an antibiotic's ability to be absorbed [28]. The antibiotic elution profile may be altered using special impregnation techniques. Grafts can be more fully impregnated by iontophoresis, resulting in greater elution concentrations [24] An antibiotic-enriched bone wax or polysaccharide coating can be employed to delay release [32].

In situations when there is a high risk of infection, antibiotic-tethered bone grafts may be beneficial. For instance, the bonded antibiotic may ensure that the avascular grafts are protected for an extended period of time [39]. The least osteotoxic antibiotic was shown to be vancomycin [43,44]. Due to its large molecular weight, it exhibits a favourable elution profile both in vitro and invitro [18]. The rate of bone incorporation is unaffected by vancomycin

[41, 53]. Clinically, both aseptic and septic procedures had a low rate of postoperative infection [55]. Local vancomycin levels were high, while systemic levels remained low [33,34].

Vancomycin is used to treat infections brought on by microorganisms that are resistant to cephalosporins or penicillins, but it should not be used excessively as this could raise resistance rates [39]. Vancomycin also has a narrow gram-positive spectrum [20]. An additional antibiotic with gram-negative effectiveness, such as gentamicin or tobramycin, should be added to achieve a broad-spectrum coverage for general use. Gentamicin considerably reduced infections in patients and had a suitable elution profile [42]. In contrast, tobramycin looked to be less osteotoxic than gentamicin, [43] did not impact bone incorporation, and [51, 52] is clinically effective when combined with vancomycin [33].

Although initially large antibiotic concentrations can be established locally, potential toxicity should be taken into consideration. Initial antibiotic concentrations can reach levels harmful to osteoblasts, according to a comparison between initial elution concentrations and the findings of in vitro osteotoxicity investigations [21,28]. However, clinical investigations did not show an increase in nonunion [34] and the rate of bone incorporation was never impacted in vivo [51,53]. Systemically, low serum levels were found [34], and harmful side effects as ototoxicity, hepatotoxicity, and nephrotoxicity were not noticed.

Only two related impregnated bone products are presently marketed [31]. They are allogenic cancellous bone grafts that have been cleansed with supercritical CO_2, processed, and either impregnated with vancomycin or tobramycin. The purpose of lyophilization is to maximise storage life [32]. Initial local concentrations after rehydration are quite high, reaching up to 20000 g/ml for vancomycin and up to 13000 g/ml for tobramycin. These high antibiotic concentrations are suitable for removing biofilm, allowing for one-stage treatment of bone infection [33].

It is noteworthy that this high local concentrations are not reached by previous research. [20–22]. According to the statement, the grafts' highly pure nature mostly accounts for these high concentrations [27]. It's important to keep in mind that many research still evaluate antibacterial inhibition against the MIC. This is probably true in situations where there has never been an infection, but greater doses are required to eradicate biofilm [44]. Compared to microorganisms in a planktonic form, biofilms exhibit particular biological characteristics. Extracellular matrix produced by biofilm communities hinders the efficiency of the host's defence mechanisms as well as the penetration of antibiotics [26].

Numerous writers claim that using bone that has been treated with antibiotics can reduce the growth of biofilms [21,26,38].Furthermore, one-stage correction using bone that has been impregnated with antibiotics appears possible [33,34]. If biofilm-related infections need to be treated, comparing the elution kinetics to the MBEC would be more pertinent.

Bone grafts may be appropriate for preventative usage, as proposed by Frommelt et al. [45]. High levels during the initial days of the elution profile prevent contamination. Eventually levels decrease but remain many weeks over the MIC. As a result, the environment around the surviving delicate organisms becomes poisonous and bactericidal [20–22]. The initial clinical investigations show a clear reduction in infection rates [46].

CONCLUSION:

We draw the conclusion that bone grafts have been demonstrated to be acceptable for local antibiotic administration despite the significant methodological variation. High initial antibiotic concentrations, necessary for prophylaxis and even biofilm eradication, were produced by a number of methods. No proof was established that antibiotic impregnation of bone would cause osteoblast toxicity and impact bone incorporation in vivo, despite the fact that high antibiotic concentrations cause osteoblast toxicity in vitro. In complex situations, when used as a preventative measure, antibiotic-impregnated bone grafts were linked to reduced infection rates. When used therapeutically, a one stage process for the treatment of bone infection appears to have some value, although further research is required. Despite these first encouraging results, research comparing various methods are still insufficient, and independent validation of results in larger cohorts would be justified.

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