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Original research

Local application of gentamicin-containing collagen implant in the prophylaxis and treatment of surgical site infection following vascular surgery

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ABSTRACT

Background: The development of surgical site infection (SSI) following vascular surgery is an important issue for healthcare providers as it has serious implications for both patient morbidity and mortality.
Methods: Five publications were identified using the PubMed online database and search terms 'gentamicin-containing collagen implant' plus 'surgical site infection', 'wound infection' and 'vascular surgery'.
Results: The reviewed publications demonstrated that prophylactic use of GCCI in conjunction with standard treatment reduces the SSI rate in patients operated on for femeropopliteal bypass grafting. The prophylactic use of GCCI may also have a role to play in patients at high-risk of infection (e.g. in those with co-morbidities such as obesity) and in high-risk procedures (e.g. surgical revision to correct anastomotic aneurysm or dehiscence). GCCI in conjunction with systemic antibiotics may also be effective in the treatment of wound infections of the groin following vascular reconstruction.
Conclusion: This review demonstrates that GCCI have a role to play in preventing and treating SSI following vascular reconstruction when used in conjunction with standard treatment approaches. Additional randomised, controlled studies are required to further establish the efficacy and cost-effectiveness of GCCI in vascular surgery.

1. Introduction

The development of surgical site infection (SSI) following vascular surgery is an important issue for healthcare providers as it has serious implications for both patient morbidity and mortality.[1] Furthermore patients stay in hospital longer increasing length of stay and incurring significant costs for healthcare providers. The risk of SSI following vascular surgery reported in retrospective studies has ranged between 4% and 43%.[2–10] In prospective studies the incidence of SSI has ranged between 4% and 25%, being highest when related to the distal incisions used for femoropopliteal and femerodistal bypasses.[11–13] In a recent analysis of 184 consecutive patients from several centres in Finland who underwent a range of vascular surgical procedures the overall rate of SSI was reported as 27%.[1]

Independent predictors of SSI following vascular surgery have been established in a number of studies.[1,5,8,10,11,14] McAlister and colleagues identified post-operative hyperglycaemia as a risk factor for post-operative infection in patients who underwent coronary artery bypass grafting.[14] In 2010 Turtiainen and colleagues identified a significantly higher rate of infection in those patients who underwent infrainguinal surgery (OR 7.2, 95% CI 2.92–17.65, $p < 0.001$) and in those where the angiography puncture site was within the operative area (OR 2.5, 95% CI 1.13–5.48, $p = 0.02$).[1] This group also identified obesity (BMI > 25) as an independent predictor of SSI (OR 6.1, 95% 2.44–15.16, $p < 0.001$). This is an important finding given the increasing incidence of obesity in the developed world and therefore in patients undergoing vascular surgery.

The development of SSI following vascular surgery may result in exposure of the underlying graft and may also require subsequent removal of the vascular prosthesis if the infection persists.[1] SSI is therefore associated with a higher risk of subsequent amputation and also mortality.[8,9,15] In an analysis of 1404 patients who underwent lower limb vein bypass the rate of SSI was 20%.[9] The patients with SSI were at increased risk of limb loss (HR, 1.511; 95% CI 1.096 to 2.079; $p = 0.0116$) and had a higher mortality risk (HR, 1.449; 95% CI 1.098 to 1.912; $p = 0.0089$).[9] The cost attributable to developing an SSI following vascular surgery has been estimated at €3320 in a study published in 2010.[1]

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The mainstay of SSI prevention in addition to strict aseptic surgical technique is the use of antibiotic prophylaxis.[16] However, long-term administration of systemic antibiotics may lead to a risk of antibiotic resistance and toxicity.

The emergence of technologies such as resorbable gentamicin-containing collagen implants (GCCI), which deliver high local concentrations of gentamicin with corresponding low serum levels offer both a means of lowering the risk of antibiotic resistance by reducing the need for long-term administration of systemic antibiotics and also avoiding the toxicity of these regimens.[17–19] The use of GCCI also avoids the need for reoperation, as the implant is fully resorbable unlike polymer polymethylmethacrylate (PMMA) beads, which require subsequent removal.[20] The use of collagen as a carrier also has a positive effect on wound healing and haemostasis.[18,20]

The objective of this article is to review the published clinical data for prophylactic and therapeutic application of resorbable GCCI in vascular surgery in order to provide an overview of the efficacy and safety of GCCI in this indication.

2. Methods

Candidate publications were identified using the National Institutes of Health PubMed database for articles published between January 1985 and July 2011. Articles were identified using the search terms 'gentamicin-containing collagen implant' plus 'surgical site infection', 'wound infection' and 'vascular surgery'. Reference lists of recent review articles were also scanned for additional citations. The literature search was further supplemented by abstracts from international vascular surgery congresses, which took place between January 2009 and July 2011. Review publications were excluded from the analysis. The search identified five potential publications focusing specifically on the prophylaxis and treatment of SSI in vascular surgery. These studies concerned the use of one GCCI i.e. Collatamp® (EUSA Pharma [Europe], Oxford, United Kingdom). Collatamp contains gentamicin sulphate at a rate of 2 mg/cm.[2] The collagen in Collatamp is present at 2.8 mg/cm^2 and is type I collagen from a renatured bovine or equine source.

The outcome measures of primary interest were the SSI and wound healing rates. The level of evidence for each study was graded according to the criteria developed by Carruthers et al.[21]

3. Clinical experience

3.1. Prophylaxis

To date there have been five clinical studies which have focused on the local application of GCCI in the prophylaxis and treatment of SSI following vascular surgery (Table 1). One of the studies was of randomised, controlled design; one was a prospective study with contemporaneous controls and three studies included a consecutive patient series without contemporaneous controls. One of the studies was graded as level 1.[21] In total these studies represent experience in $n = 109$ patients with GCCI in vascular surgery.

One randomised, single centre study (level 1) and a second prospective study with contemporaneous controls (level 3) have focused specifically on the prophylactic use of GCCI following various vascular procedures.[22,23] A recently published randomised study was carried out in non-diabetic patients with lower limb ischaemia with indication for femoropopliteal bypass graft.[23] Polytetrafluoroethylene (PTFE) supported grafts were used and all patients were operated on by the same team to ensure consistency. The use of GCCI (applied in the groin incision) together with systemic antibiotics was compared to use of systemic antibiotics alone. At the 30-day follow-up none of the patients in the GCCI group had developed any signs of SSI compared to five out of 20 in the standard treatment group. None of the patients in whom GCCI were used suffered any local or systemic allergic reactions.

The second of these studies compared use of GCCI to no adjunctive treatment in a group of patients with renal insufficiency undergoing vascular access for haemodialysis.[22] None of the patients in the GCCI group developed an SSI compared to two out of 20 in the control group. One patient in each group suffered from a peri-graft-reaction, which disappeared without specific therapy. Patients did not experience any systemic side effects following use of GCCI despite having poor renal function.

Three patient case series (level 5) have been published on the therapeutic use of GCCI in patients with existing wound infection following vascular surgery.[24–26] Two of these publications also contained data on the prophylactic use of GCCI.[24,25]

3.2. Prophylaxis and treatment

Belz and colleagues analysed the results of 30 patients of mixed aetiology in which GCCI were used either on a prophylactic or therapeutic basis (+peri-operative systemic antibiotics) (Table 1).[24] The patients ranged in age between 20 and 81 and the male:female sex ratio was 4:1. The majority of the patients where GCCI were used therapeutically had exposed synthetic prostheses. GCCI prophylaxis was used in patients at high-risk of infection including those undergoing bypass revision, aseptic bypassing and in those with stage IV arterial occlusion. At least one and a maximum of five GCCI were implanted (10 cm × 10 cm) at time of operation. Out of the 26 evaluable patients 22 recovered and four had persistent infection.

Holdsworth and colleagues subsequently studied the prophylactic and therapeutic use of GCCI in a similar group of patients to Belz, however, they reported the results for each group separately (Table 1).[25] GCCI prophylaxis was used in patients at high-risk of infection including those undergoing removal of an infected prosthesis and those with persistent lymphatic leak, anastomotic aneurysm and anastomotic dehiscence. The majority of the patients where GCCI were used therapeutically had a graft infection in the groin area. Between one and three GCCI were inserted on wound closure.

Wounds were sutured over closed suction drains, which were removed once the daily fluid collection had reduced to an acceptably small amount (3–5 days). GCCI were inserted on a second occasion if symptoms did not resolve.

Eleven of the 12 patients in whom GCCI were used prophylactically did not grow microorganisms post-surgery and none developed infective complications on follow-up. One patient died in hospital. Seven out of the 11 *in situ* infections and all of the superficial infections treated with GCCI were cleared. Grafts were removed in all three of the treatment failures and two of these patients subsequently lost a leg. One patient who failed treatment died before the outcome was known. None of the patients treated successfully had a recurrence of their infection on follow-up (4–42 months).

3.3. Treatment

Jørgensen and colleagues analysed the clinical effect of GCCI (+systemic antibiotics) in a group of 14 patients with deep but localised groin infection after vascular reconstruction (Table 1).[26] The average age of the patients was 67 years (range 47–86 years). Twelve of the 14 patients had a Szilagyi type III[1] infection. Signs of infection included abscess ($n = 10$), discharge ($n = 3$) and fistula ($n = 1$). One GCCI (10 cm × 10 cm) containing 130 mg gentamicin was inserted prior to wound closure. Systemic antibiotic treatment was started immediately post-surgery with 1.5 g of IV cefuroxime given three times daily. The systemic treatment was later changed in five patients upon culture results. Systemic treatment was continued for three days in four patients; for 10 days in five patients and for three months in the remaining five patients.

Table 1
Overview of GCCI clinical publications in vascular surgery.

Author & evidence grading	Product	Study design and population	Number of subjects and treatment groups	Results
Prophylaxis				
Horch (1989)[22] Level 3	Collatamp®[a]	Prospective, open, single centre study with contemporaneous controls Patients with renal insufficiency undergoing grafts for vascular access for haemodialysis	$n = 40$ total patients, Group I: $n = 20$ gentamicin-collagen implant, Group II: $n = 20$ control	**Wound infection:** Group I: 0/20 vs Group II: 2/20
Costa Almeida (2010)[23] Level 1	Collatamp® One implant placed adjacent to prosthesis	Randomised, prospective, single centre study Non-diabetic patients with lower limb ischaemia with indication for femoropopliteal bypass graft PTFE supported grafts were used	$n = 40$ total patients, Group I: $n = 20$ gentamicin-collagen implant + systemic antibiotics (piperacilin + tazobactam), Group II: $n = 20$ systemic antibiotics (piperacilin + tazobactam)	**Wound infection:** Group I: 0/20 vs Group II: 5/20 at 30 day follow-up
Prophylaxis & treatment				
Belz (1989)[24] Level 5	Collatamp®	Patient case series Patients undergoing vascular surgery for a variety of indications	$n = 30$ patients treated with gentamicin collagen implant of which $n = 26$ were evaluable, $n = 10$ GCCI prophylaxis + systemic antibiotics, $n = 16$ GCCI treatment	**Wound healing:** 22/26 evaluable patients recovered and 4/30 had persistent infection.
Holdsworth (1999)[25] Level 5	Collatamp®	Case series report Patients with infective and potentially infective complications of vascular bypass grafting	$n = 25$ total patients Prophylaxis ($n = 12$): $n = 4$ at removal of infected prosthesis, $n = 4$ for persistent lymphatic leak, $n = 3$ anastomotic aneurysm, $n = 1$ anastomotic dehiscence. Treatment ($n = 13$): $n = 11$ *in situ* for proven graft infection, $n = 2$ superficial wound infection over underlying graft. In 3 patients GCCI were used with rifampicin-soaked collagen impregnated Dacron®	Prophylaxis: **Wound infection:** 11/12 patients did not grow microorganisms post-surgery and none developed infective complications on follow-up. One patient died in hospital. Treatment: **Wound infection:** 7/11 *in situ* infections and 2/2 superficial infections were cleared. Grafts were removed in all 3 of the treatment failures and 2 of these patients subsequently lost a leg. One patient died before the outcome was known. None of the patients treated successfully had a recurrence of their infection on follow-up (4–42 months).
Treatment				
Jørgensen (1991)[26] Level 5	Collatamp® One implant was wrapped around the graft and the wound closed with suction drainage placed in contact with the implant and graft	Patient case series Patients with localised groin wound graft infection after vascular reconstruction. All patients were treated by surgical revision	$n = 14$ patients treated with gentamicin collagen implant plus systemic antibiotics (cefuroxomine 1.5 g tid initially with 5 patients requiring change of antibiotic on culture result)	**Wound infection:** Of the 14 patients treated 13 were cured of infection with patent grafts. Of the 12 patients with Szilagyi type III prosthetic infection[b], 11 were cured

[a] Also known as Collatamp® EG, Collatamp® G Cronocol®, Duracoll® Implant, Garacol®, Garacoll®, Garacoll® Implant, Garamacin® Pads, Garamycin®, Garamycin® Schwamm, Gentacoll®, Gentacoll® Implant, Gentalyn®, Gentimplant®, Sulmycin®, Sulmycin® Implant E Schwamm, Sulmycin® Implant Schwamm

[b] deep groin infection requiring operative debridement with graft involvement (Szilagyi III).

This group also studied the pharmacokinetic profile of GCCI in the early post-operative phase in 11 out of the 14 patients.

Of the 14 patients treated with GCCI and systemic antibiotics, 13 were cleared of infection and had patent grafts following surgical revision. Of the 12 patients with Szilagyi type III prosthetic infection, 11 were cleared of infection. The wounds in the cleared patients had healed by the seventh post-operative day without signs of infection. One of the 13 cleared patients died two months following surgical revision. Patients were followed up for an average of 10 months (range 6–15 months) and remained free of clinical signs of infection and with normal white cell counts. No adverse events were observed. In particular toxic effects of gentamicin were not seen even in patients with mild pre-operative uraemia (serum creatinine $>$ 0.17 mmol/L).

The pharmacokinetic analysis showed a high initial gentamicin concentration in wound fluid, which exceeded the minimum inhibitory concentration (MIC) values for the majority of bacteria causing graft infection. These MIC values were sustained for 2–3 days.

4. Discussion

This review has demonstrated that prophylactic use of GCCI in conjunction with standard treatment can reduce the SSI rate in patients operated on for femeropopliteal bypass grafting. The prophylactic use of GCCI may also have a role to play in patients at high-risk of infection (e.g. in those with co-morbidities such as obesity) and in high-risk procedures such as surgical revision to correct anastomotic aneurysm or dehiscence. These are important findings given the high risk of amputation and also mortality associated with graft failure.

This review has also demonstrated that GCCI in conjunction with systemic antibiotics may be effective in the treatment of wound infections of the groin following vascular reconstruction. The cure rate even in patients with Szilagyi III infection was high and sustained. Few adverse side effects were associated with the prophylactic or therapeutic use of GCCI even when used in patients with mild renal impairment.

The results of the reviewed studies were consistently positive across a range of patient types and procedures. However, additional randomised controlled studies are required to evaluate the efficacy, safety and cost-effectiveness of GCCI in the prevention and treatment of SSI following vascular reconstruction. A multicentre, prospective, randomised, controlled trial focusing on the prophylactic use of GCCI in vascular groin access procedures has recently been registered with the EU Clinical Trials Register.[27] Primary outcome measures will include SSI rate, prosthetic graft infection (classified according to Szilagyi) at 30 days post-surgery. Secondary endpoints include isolation of causative bacteria, length of hospital stay, readmission and reoperation. Safety parameters will include measurement of creatinine clearance.

5. Conclusion

This review demonstrates that GCCI does have a role to play in preventing and treating SSI following vascular reconstruction when used in conjunction with standard treatment approaches. Additional randomised, controlled studies are required to further establish the efficacy and cost-effectiveness of GCCI in vascular surgery.

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Ethical approval

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Author contribution

Syed Tahir Hussain critically reviewed the manuscript for important intellectual content and approved the final version of the manuscript to be submitted.

Conflicts of interest

Syed Tahir Hussain has received an honorarium and consultancy fee from EUSA Pharma.

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