The Effectiveness of Local Antibiotics in Treating Chronic Osteomyelitis in a Cohort of 50 Patients with an Average of 4 Years Follow-Up

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Abstract: The treatment of chronic osteomyelitis requires both appropriate surgical and antibiotic management. Prolonged intravenous antibiotic therapy followed by oral therapy is widely utilised. Despite this, the long-term recurrence rate can be up to 30%.

A cohort of 50 patients from a 7-year period, 2003 to 2010, with chronic osteomyelitis was identified. This cohort was treated by surgical marginal resection in combination with local application of antibiotics (Collatamp G - gentamicin in a collagen fleece), a short course of systemic antibiotics post-operatively and conversion to oral antibiotics on discharge. Information was retrieved from case notes and computerized records. Outcomes from this cohort were compared with a historical cohort treated with marginal resection followed by 6 weeks of systemic antibiotics and 6 weeks of oral antibiotics.

The mean follow-up duration was 3.2 years (SD 1.8). The average length of admission was 9.8 days (SD 11.4). 6 patients (12%) suffered recurrence of infection requiring further treatment. We used the Cierny and Mader classification to stratify the patients. 'A' hosts had a shorter duration of admission (7.1 days) than 'B' hosts (12.3 days). There was no significant difference between recurrence rates of 'A' and 'B' hosts. Where available, we found pre-operative C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels had no correlation with disease recurrence. Disease-free probability for this cohort compared favourably with the historical cohort.

We believe local administration of gentamicin in a collagen fleece is a useful component in the management of chronic osteomyelitis.

Keywords: Chronic osteomyelitis, gentamicin, local antibiotics.

INTRODUCTION

Chronic osteomyelitis frequently occurs as a result of direct contamination from open fracture, open surgery or as a result of spread (haematogenous or direct) from other sources of infection. Chronic osteomyelitis is classified according to its transverse extent and the 'host status', which is dependent on the immune status of the patient. Systemic and local factors affecting immune competence, metabolism and local vascularity are taken into account with the Cierney and Mader classification (Table **1**).

The treatment of chronic osteomyelitis consists of excision of devitalised material, skeletal stabilisation, obliteration of dead space, obtaining good soft tissue cover and reconstruction of the bone, all in conjunction with antibiotics. The antibiotics are frequently given for 6 weeks intravenously, followed by a further 6 weeks orally. There has been increasing interest in systems to deliver antibiotics locally. Collatamp G, a gentamicin-impregnated collagen matrix, can be inserted intra-operatively following surgical debridement. After insertion, gentamicin quickly reaches local concentrations exceeding the minimum inhibitory concentrations (MIC) of most causative organisms; it also assists in reducing dead space. Importantly serum concentrations of gentamicin never exceed dangerous levels [1].

The purposes of this cohort study were to examine the effectiveness of surgical marginal resection in combination with local application of antibiotics (Collatamp G - gentamicin in a collagen fleece). With the information gathered, we aimed to compare our cohort with a historical cohort, in order to determine whether local application of antibiotics leads to a lower rate of disease recurrence.

MATERIALS AND METHODS

This is a single surgeon, single centre, cohort study at the Royal Infirmary of Edinburgh, Scotland, United Kingdom. Patients treated for clinically confirmed osteomyelitis with Collatamp G, between January 2003 and January 2010, were identified from the hospital database and cross-checked with theatre records. All patients in this cohort were treated with marginal resection, followed by insertion of Collatamp G into area of resection. Post-operatively patients received intravenous antibiotics whilst they were in-patients and were converted to oral therapy when they were ready for discharge.

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Table 1. Factors affecting immune surveillance, metabolism and local vascularity.

Systemic factors (Bs): Malnutrition, renal or hepatic failure, diabetes mellitus, chronic hypoxia, malignancy, extremes of age, immune deficiency, steroid therapy, alcohol abuse, tobacco abuse
Local factors (Bl): chronic lymphedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis

Cierny G, Mader JT, Pennick JJ. A clinical staging system for adult osteomyelitis. *Contemp Orthop* 1985; 10:17-37.

Medical documentation from in-patient records and out-patient consultations were reviewed to determine host status, post-operative outcomes, complications and recurrence. Laboratory databases were accessed for peri-operative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and haemoglobin levels. Microbiology reports were studied to determine the causative organism.

The historical cohort selected for comparison is from the paper by Simpson and colleagues [2]. This cohort had marginal resection of infected tissue, followed by 6 weeks of intravenous administration of antibiotics and 6 weeks of oral antibiotics.

Statistical analysis including basic descriptive analysis, Kruskall-Wallis tests for post-operative CRP and ESR values, Kaplan-Meier plots for survival probability were performed with SPSS v18 *(SPSS Inc, Chicago, USA*).

RESULTS

50 patients were identified. Of these patients, 24 'A' hosts and 26 'B' hosts were identified. Demographics are summarised in Table **2** and are recorded in Tables **3** and **4** according to host status. 70% (n=35) of patients were male and the age range of the group was 15 to 77 years (mean 40.9, SD 15.9). The most commonly affected bones were the femur (38%) and tibia (36%). Length of admission ranged from 1 to 77 days (mean 9.8, SD 11.4). 'B' hosts spent an average of 12.3 days in hospital whereas 'A' hosts spent 7.1 days. The most commonly isolated organisms were Staphylococcus aureus (32%, n=16), Coagulase-negative staphylococci (22%, n=11) and Pseudomonas aeruginosa (8%, n=4). In 16% (n=8) patients, no organism was cultured. Details of post-operative complications are recorded in Table **5**.

Those with a recurrence of infection required further conservative or surgical treatment. Further treatment was considered indicated if there was a recurrence of symptoms and signs, or if there was a rise in CRP or ESR accompanied by localised warmth or pain. In total, 6 patients (12%) suffered a recurrence of infection. 5 underwent further surgery for the infected focus and 1 was managed conservatively on an out-patient basis. Half of the patients were 'A' hosts and the other half were 'B' hosts. No patient required amputation and there was no mortality as a result of recurrence.

All but 2 patients had less than 2 weeks of intravenous antibiotics post-operatively. One patient continued on daily intravenous Ertapenum for a total of 5 weeks, including after discharge from hospital, as this was the only antibiotic the causative organism was sensitive to, and he was the only patient to have out-patient systemic antibiotic treatment. The other patient who had more than 2 weeks intravenous therapy had a two-stage operation during the same admission and had prolonged administration of systemic antibiotics in order to cover both operations. 4 patients (8%) received oral antibiotics only. All patients, except those with active fracture healing, had a total of 6 weeks of antibiotic therapy.

Table **6** shows the proportion of patients with abnormal pre-operative CRP and ESR levels. 45% (n=17) of these patients demonstrated elevated CRP and ESR levels. However, 34% (n=13) patients had normal CRP and ESR levels. For 12 patients, pre-operative inflammatory markers were not available, while for 10 patients the post-operative inflammatory markers were not available. Results sampled during the post-operative period were examined. No relationship was found between the mean CRP or ESR values and disease recurrence, either within 2 weeks post-operatively or after 2 weeks post-operatively.

As in the tumour field, there is a variable length of follow up and disease-free interval. Therefore, survival analysis, a technique developed in the tumour field has been utilised to analyse the current cohort of patients. For comparison, we have constructed a similar disease-free plot with data from our study and the historical cohort from Simpson and colleagues' study [2] and this is shown in Fig. (**1**). This shows a lower probability of recurrence in the current cohort, compared to the historical cohort.

DISCUSSION

Chronic deep bone infection is difficult to treat, with a poor response rate to systemic antibiotics alone. Disadvantages include potential toxicity, difficulty in achieving high concentrations at the site of infection, and compliance problems [3]. Despite advances in therapy, long-term recurrence rates have been reported to be 20-30% [4].

A Cochrane review of antibiotics for treating chronic osteomyelitis reported that the remission rates at 12 months were not found to be different between oral and parenteral antibiotics [4]. The disadvantages and poor success rate of systemic antibiotics has prompted development of systems to deliver antibiotics directly to the infected focus. The need for a local antibiotic delivery system has been recognised for many years.

Polymethyl methcrylate (PMMA) bone cement beads loaded with gentamicin have been widely used in clinical practice for over 30 years [5]. Combining antibiotics such as gentamicin with acrylic cement allows gradual release of the drug, typically over weeks to months [6, 7]. This provides sustained postoperative antibacterial cover. Pharmacokinetic studies show that on average, 5.78% of the gentamicin implanted is eluted from the cement [6]. Serum

Table 2. Cohort demographics.

Total Number of Patients		50	
Age (years)		15 to 77	Mean 40.9, SD 15.9
Sex		Male: 35 (70%)	Female: 15 (30%)
Host Status		Type A: 24 (48%)	Type B: 26 (52%)
Length of admission (days)		1 to 77	Mean 9.8, SD 11.4
	Type 'A' hosts		Mean 7.1, SD 6.8
	Type 'B' hosts		Mean 12.3, SD 14.1
Length of follow-up (years)		0.4 to 6.7	Mean 3.2, SD 1.8
	Type 'A' hosts	0.7 to 6.7	Mean 3.0, SD 1.7
	Type 'B' hosts	0.4 to 6.6	Mean 3.5, SD 1.9
Recurrence after surgery	Type 'A' hosts	3/24 (12.5%)	
	Type 'B' hosts	3/26 (11.5%)	
Bone infected	Femur	19 (38%)	
	Tibia	18 (36%)	
	Ulna	3 (6%)	
	Radius	2 (4%)	
	Humerus	2 (4%)	
	Fibula	2 (4%)	
	Clavicle	2 (4%)	
	Ischium	1 (2%)	
	Sacrum	1 (2%)	
Organisms Cultured	S. aureus	16 (32%)	
	CNS	11 (22%)	
	P. aeruginosa	4 (8%)	
	E. coli	2 (4%)	
	MRSA	2 (4%)	
	E. cloacae	2 (4%)	
	S. milleri	1 (2%)	
	S. pyogenes A	1 (2%)	
	C. striatum	1 (2%)	
	Salmonella	1 (2%)	
	P mirabilis	1 (2%)	
	No growth	8 (16%)	

concentrations remain low, but local to the implant, concentrations of gentamicin exceed the minimum inhibitory concentrations (MIC) of the most likely pathogens. However there are several drawbacks with cement as various factors restrict antibiotic choice. The drug must be water soluble to allow diffusion out of the cement. It also has to be heat-stable at temperatures of 100°C which occur during the exothermic curing process of the cement. The antibiotic also has to be bactericidal at low doses, as when higher doses of antibiotic are mixed with cement, the mechanical strength of

Table 3. Demographic and clinical details of group 'A' hosts.

Patient Number	Age (at Admission)	Sex	Bone Affected	Length of Admission	Causative Organism	IV Antibiotic Prescribed	Recurrence
1	35	M	Tibia	3	Staph aureus	Tazocin IV	No
2	57	M	Tibia	1	Coagulase Negative Staph	Vancomycin IV	No
3	53	F	Fibula	26	MRSA	Vancomycin IV	No
4	28	M	Clavicle	2	Coagulase Negative Staph	Tazocin IV	No
5	35	M	Femur	25	Staph aureus	Gentamicin IV	No
6	55	M	Tibia	8	No Growth	Vancomycin IV	No
7	68	M	Fibula	4	P. aeruginosa	Pipercillin IV	No
8	30	M	Femur	3	P. aeruginosa	Tazocin IV	No
9	18	F	Femur	1	E. coli	Tazocin IV	No
10	30	M	Tibia	5	Salmonella	Data not available	No
11	25	M	Humerus	6	Staph aureus	Vancomycin IV	No
12	20	M	Femur	1	Staph aureus	Oral antibiotics only	No
13	27	F	Femur	8	Staph aureus	Data not available	No
14	48	F	Femur	3	No Growth	Flucloxacillin IV	No
15	36	M	Radius	2	Coagulase Negative Staph	Data not available	No
16	38	F	Femur	14	P. aeruginosa	Gentamicin IV	No
17	15	F	Tibia	12	Coagulase Negative Staph	Vancomycin IV	No
18	65	M	Tibia	7	Corynebacterium striatum	Vancomycin IV	Yes
19	40	M	Tibia	3	E. coli	Vancomycin IV	Yes
20	40	F	Ulna	9	Staph aureus	Vancomycin IV	No
21	25	M	Tibia	14	Streptococcus pyogenes Group A	Ertapenum IV	Yes
22	56	M	Tibia	4	Staph aureus	Metronidazole IV	No
23	26	M	Radius	3	Staph aureus	Vancomycin IV	No
24	38	M	Femur	7	Coagulase Negative Staph	Vancomycin IV	No
	Mean = 37.8	Male = 71%		Mean = 7.1			Total recurrences = 3
	SD = 14.8	Female = 29%		SD = 6.8			

the mixture is compromised [8, 9]. Also, PMMA is not biodegradable and so a second surgical procedure is required in order to remove the implants after the infection has been treated. The removal surgery is often more difficult due to local tissue scarring and adhesions may lead to further infection. In addition, a second operation adds further expense and poses the risk of further pain and anaesthetic complications.

Another local delivery system is the Lautenbach method. This involves the insertion of a double-lumen, suction-irrigation system after reaming and debridement of the intramedullary canal. This establishes both a local antibiotic delivery system and allows the volume of the cavity to be measured and the drainage fluid to be cultured. The patient is declared as free of infection when the irrigate produces three consecutive clear cultures with improved inflammatory markers and obliteration of the cavity volume [10]. A recurrence rate of 12% has been reported which is no lower than rates of patients treated with debridement and systemic antibiotics. Due to the duration the drainage tube has to remain in situ, there have been concerns of infection being introduced and further organisms have been grown from the drainage fluid that were not present in the operative samples. Hashmi and colleagues report a mean hospital stay of 27 days (range = 14-48 days) when using this technique [11]. This is a considerably longer hospital stay than our cohort of patients (mean = 9.8 days).

Collagen sponge matrices as carriers for gentamicin were developed in the early 1980s and have several advantages over other systems. Collagen is considered to be fully biodegradable and locally re-modellable. However in one case 'fibro-gelatinous' looking material was removed from

Table 4. Demographic and clinical details of group 'B' hosts.

Patient Number	Age at Admission	Sex	Bone Affected	Length of Admission	Causative Organism	IV Antibiotic Prescribed	Recurrence
25	54	M	Tibia	7	Enterobacter cloacae	Teicoplanin IV	No
26	28	M	Femur	16	Staph aureus	Meropenem IV	No
27	55	M	Femur	73	Proteus mirabilis	Vancomycin IV	No
28	37	F	Femur	16	No Growth	Vancomycin IV	No
29	20	F	Tibia	2	Staph aureus	Benzyl Penicillin IV	No
30	55	F	Tibia	7	P. aeruginosa	Vancomycin IV	Yes
31	36	M	Tibia	14	Streptococcus milleri	Oral antibiotics only	No
32	60	F	Femur	11	Coagulase Negative Staph	Oral antibiotics only	No
33	44	M	Ulna	7	Coagulase Negative Staph	Vancomycin IV	No
34	31	M	Ulna	7	No Growth	Vancomycin IV	Yes
35	16	F	Femur	2	MRSA	Vancomycin IV	No
36	77	M	Femur	20	No Growth	Tazocin IV	No
37	62	M	Tibia	5	Coagulase Negative Staph	Vancomycin IV	No
38	42	M	Tibia	5	Staph aureus	Vancomycin IV	No
39	45	F	Clavicle	3	Staph aureus	Oral antibiotics only	No
40	46	M	Femur	12	Coagulase Negative Staph	Vancomycin IV	Yes
41	59	M	Ischium	10	Staph aureus	Flucloxacillin IV	No
42	76	F	Tibia	12	Enterobacter cloacae	Vancomycin IV	No
43	17	M	Femur	6	No Growth	Data not available	No
44	41	F	Sacrum	15	No Growth	Tazocin IV	No
45	42	M	Femur	3	Coagulase Negative Staph	Data not available	No
46	25	M	Tibia	9	No Growth	Vancomycin IV	No
47	36	M	Femur	31	Staph aureus	Vancomycin IV	No
48	32	M	Femur	2	Staph aureus	Vancomycin IV	No
49	37	M	Tibia	8	Coagulase Negative Staph	Vancomycin IV	No
50	65	M	Humerus	17	Staph aureus	Flucloxacillin IV	No
	Mean = 43.7	Male = 69%		Mean = 12.3			Total recurrences = 3
	SD = 16.7	Female = 31%		SD = 14.1			

Table 5. Post-operative outcomes in patients with recurrence of infection.

Patient Number	Host Status	Discharging Sinus	Local Warmth, Redness or Pain	Fever	CRP/ESR Rise	Days to Recurrence	Days to Re-Admission for Surgery
18	A	**Yes**	No	No	No	90	No surgery
19	A	**Yes**	No	No	No	**1400**	**1400**
21	A	**Yes**	**Yes**	No	No	**965**	**1100**
30	B	**Yes**	**Yes**	No	No	**330**	**450**
34	B	**Yes**	**Yes**	**Yes**	No	**113**	**290**
40	B	**Yes**	**Yes**	**Yes**	No	**116**	**705**

Table 6. Pre-operative inflammatory markers.

	Normal CRP		Elevated CRP	
	Number of Patients	**Percentage (%)**	**Number of Patients**	**Percentage (%)**
Normal ESR	13	34%	5	13%
Elevated ESR	3	8%	17	45%
Results not available	12			

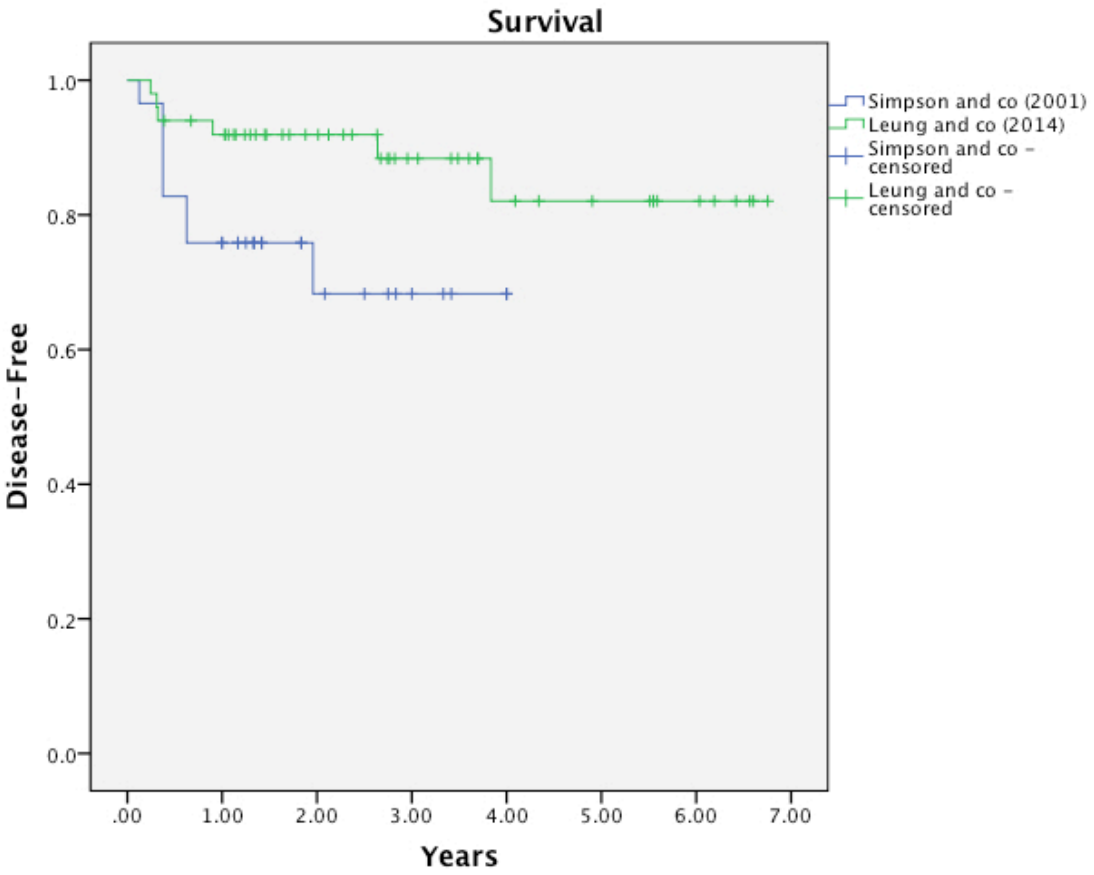

Fig. (1). Disease-free plot of current cohort and cohort (Group 2) from Simpson and colleagues (2001).

the medullary canal of a tibial case that had suffered a recurrence and histology of this material was consistent with it being derived from the implanted collagen. Currently, therefore we use gentamicin collagen in areas where it will be in contact with tissue macrophages, such as the cortical window. This system achieves high local gentamicin levels with low serum concentrations. In rats with osteomyelitis, treatment with gentamicin-collagen has been proven to reduce bacterial colony count and to give significant therapeutic effect [12]. The effect was less marked with gentamicin-PMMA beads.

In humans, gentamicin-impregnated collagen has been shown to minimise wound infection following cardiac surgery. When compared to intravenous antibiotics only, insertion of collagen-gentamicin sponges between the two sternal halves reduced the incidence of wound infection [13]. Similarly, perineal wound healing is improved by the insertion of gentamicin-collagen fleeces after excision of rectal cancer [14].

Cierny and Mader attempted to predict which patients had a greater risk of recurrence. The 'host status' is determined by the presence or absence of systemic and local factors which compromise the immune system's ability to elicit an effective response to infection [15]. This classification system allows treatment to be scaled to biological grade of disease as in the surgical management of malignancies. 'A' hosts have healthy immune systems and responded very well to marginal resection (resection margin < 5mm) in a previously reported series. 'B' hosts however, have compromised defences and have poorer success rates with similar clearance margins.

We examined the perioperative serological markers. Nearly half of patients (45%, n=17) with available blood results had raised CRP and ESR levels, whereas a third of

patients with chronic osteomyelitis had normal CRP and ESR (34%, n=13) levels. Inflammatory markers such as CRP and ESR have been used to quantify the degree of tissue damage and invasiveness of a procedure. They have also been used to detect post-operative complications such as infection or loosening of an implant. Peak CRP levels are reached two days post-operatively [16, 17] and usually normalise within 3 weeks [18]. Peak ESR levels are detectable five days following surgery, after which they decrease in a slow and irregular manner. ESR can remain abnormally high for up to 42 days after uncomplicated, elective, orthopaedic surgery and so CRP is considered to be a more reliable aid in detecting post-operative complications than ESR [19]. We also attempted to distinguish the relationship between CRP and ESR levels with disease recurrence. However, no significant correlation was found.

With regards to the survival analysis, in the cohort reported in this paper, all of the patients had marginal resection and had received much shorter total antibiotic treatment and particularly shorter systemic administration. It is therefore interesting to note that the disease-free probability is higher in the cohort from this study.

CONCLUSION

We have reviewed the results of a cohort of patients with chronic osteomyelitis treated with a local delivery system of gentamicin. The disease-free probability in our cohort, treated with marginal resection and a shorter post-operative course of antibiotics, compared favourably with a similar cohort treated with prolonged systemic and oral antibiotics. This local delivery system of gentamicin is a valuable tool for treating patients with chronic osteomyelitis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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