

■ TRAUMA

The use of high-dose dual-impregnated antibiotic-laden cement with hemiarthroplasty for the treatment of a fracture of the hip

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THE FRACTURED HIP INFECTION TRIAL

Aims

A fracture of the hip is the most common serious orthopaedic injury, and surgical site infection (SSI) is one of the most significant complications, resulting in increased mortality, prolonged hospital stay and often the need for further surgery. Our aim was to determine whether high dose dual antibiotic impregnated bone cement decreases the rate of infection.

Patients and Methods

A quasi-randomised study of 848 patients with an intracapsular fracture of the hip was conducted in one large teaching hospital on two sites. All were treated with a hemiarthroplasty. A total of 448 patients received low dose single-antibiotic impregnated cement (control group) and 400 patients received high dose dual-antibiotic impregnated cement (intervention group). The primary outcome measure was deep SSI at one year after surgery.

Results

The rate of deep SSI was 3.5% in the control group and 1.1% in the intervention group ($p = 0.041$; logistic regression adjusting for age and gender). The overall rate of non-infective surgical complications did not differ between the two groups (unadjusted chi-squared test; $p > 0.999$).

Conclusion

The use of high dose dual-antibiotic impregnated cement in these patients significantly reduces the rate of SSI compared with standard low dose single antibiotic loaded bone cement.

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A fracture of the hip is the most common serious orthopaedic injury¹ and as the incidence of osteoporotic fractures increases, the burden on healthcare systems continues to grow.² According to The National Hip Fracture Database, in 2015, in England and Wales, more than 22 000 people had a cemented hemiarthroplasty following a fracture of the hip.³ The current annual cost of all fractured hips to the National Health Service and social care services is £1.7 billion, estimated to increase to £2.2 billion by 2025.⁴

Surgical site infection (SSI) remains an important complication of the treatment of these fractures. It results in increased mortality (30% at 90 days), prolonged stay in hospital, further revision operations, the increased use of antibiotics and extended follow-up and rehabilitation.⁵ SSI is the third most commonly occurring healthcare-associated infection, accounting for

16% of reported infections.⁶ Rates of infection of between 1.3%⁷ and 9%⁸ for hemiarthroplasty have been reported around the world. In England, this rate has been reported to be 4.06% by Wilson et al.⁹ Parenteral antibiotics in total hip arthroplasty (THA) have been shown to reduce SSI from 3.3% to 0.9%¹⁰ and antibiotic loaded cement, combined with systemic antibiotics is considered to be the most effective prophylaxis against deep infection.¹¹

Hemiarthroplasty of the hip can be cementless¹² or cemented. However, both the British Orthopaedic Association (BOA) and British Geriatric Society (BGS) have endorsed¹³ the use of cemented implants as described in two recent studies.^{12,14,15}

Rates of SSI are higher in frail patients with a fracture of the hip than in those undergoing THA, even though the operating times and antibiotic prophylaxis are similar. It has been

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Table I. Health Protection Agency definition of superficial and deep surgical site infection (SSI)

Superficial incisional infection	Deep incisional infection
SSI that occurs within 30 days of surgery, involves only the skin or subcutaneous tissue of the incision and meets at least one of the following criteria: Purulent drainage from superficial incision Culture of organisms and pus cells present: Fluid/tissue from superficial incision wound swab from superficial incision At least two symptoms of inflammation: Pain, tenderness, localised swelling, redness, heat and either: Incision deliberately opened to manage infection or: Clinicians diagnosis of superficial SSI	SSI involving the deep tissues (i.e. fascial and muscle layers), within 30 days of surgery (or one year if an implant is in place) and the infection appears to be related to the surgical procedure and meets at least one of the following criteria: Purulent drainage from deep incision (not organ space) Organisms from culture and pus cells present in: Fluid/tissue from deep incision or wound swab from deep incision Deep incision dehisces or deliberately opened and patient has at least one symptom of: Fever or localised pain/tenderness Abscess or other evidence of infection in deep incision: Re-operation/histopathology/radiology Clinicians diagnosis of deep incisional SSI
Note: Stitch abscesses (minimal inflammation/discharge at suture point) do not classify as SSI	Note: An infection involving both superficial and deep incisional inflammation/discharge at suture point do not classify as SSI

suggested that this increase is related to the grade of surgeon,¹⁶ the comorbidities of the patients¹⁷ and the lack of preparation of patients who sustain a fracture as they present as an emergency.¹⁸ However, in a study of 540 000 patients with a fracture of the hip, it was concluded that the risk of mortality in these patients was linked to the fracture itself and the post-operative complications rather than to pre-existing comorbidity.¹⁹

We have conducted a quasi-randomised controlled trial to compare the clinical effectiveness of low dose single-antibiotic *versus* high dose dual-antibiotic impregnated cement in patients with an intracapsular fracture of the hip. The null hypothesis was that the rate of SSI at one year after hemiarthroplasty does not differ between patients undergoing surgery using standard low dose antibiotic impregnated cement and those in whom high dose dual-antibiotic impregnated cement is used.

Patients and Methods

This study was a two hospital, two arm, patient and assessor blinded, quasi-randomised controlled trial with group treatment allocation. Full details of the trial have been described previously,²⁰ to ensure consistency, methodology and outcome measure reporting, but no outcomes have been published. The trial is registered as ISRCTN25633145. The patients were eligible if they were aged > 18 years, medically fit for an operation and suitable for a cemented hemiarthroplasty, could provide informed consent and fulfilled the criteria for the study (as previously described).²⁰

Patients were recruited between May 2008 and November 2012 from all acute admissions at Wansbeck General Hospital and North Tyneside General Hospital, part of Northumbria Healthcare NHS Foundation Trust. Potential participants were screened and, if eligible, recruited under Good Clinical Practice (GCP) protocols.²¹ Specific ethical approval was gained for patients with impaired mental capacity, for whom consent was obtained from their next of kin or, if they were unavailable, by a senior member of nursing staff who was not involved in the study. The deci-

sion regarding capacity was made by a senior member of the medical staff and confirmed by the treating orthopaedic consultant.

More than 95% of patients in each unit underwent surgery within 48 hours (NHFD report 2012).¹⁴ Allocation to the treatment group was based on the date that surgery was performed providing one treatment for the whole calendar month at each centre. The following month this process was reversed to ensure comparable groups. It was not practical to attempt individual randomisation due to the lack of specific local support. Participating surgeons were not blinded to the allocation of treatment; however, the patients and all other staff involved in assessment of outcomes were blinded.

The forms of treatments were hemiarthroplasty with low dose single-antibiotic (current standard of care) or high dose dual-antibiotic impregnated cement. Pre-operatively, all patients followed the same pathway from the Accident and Emergency department to the ward and had the same preparation. Patients were allocated to surgery according to the preferred surgical approach of the operating surgeon. All procedures were performed with a standard hemiarthroplasty stem, cement mixing system and volume of cement. Post-operatively all patients underwent the same exercises, supervised by physiotherapists, and unless the surgeon specifically advised otherwise, all patients were fully weight-bearing immediately. Administration of analgesia and the type of anaesthesia were not stipulated.

The control group received high viscosity cement with low dose single-antibiotic (Palacos R + G, 0.5 g of Gentamicin; Heraeus Medical, Heraeus Medical Division, Newbury, United Kingdom), which was inserted using a retrograde technique with a cement gun and a cement restrictor.

The intervention group received cement impregnated with high dose dual-antibiotics, consisting of 1g Clindamycin and 1g of Gentamicin (Copal G+C, Heraeus Medical Division),²² using the same technique.

Please tick any of the following additional symptoms that applied to your wound:

- Pain or soreness in addition to the discomfort experienced following the operation.
- Redness or inflammation spreading from the edges of the wound.
- The area around the wound felt warmer/hotter than the surrounding skin.
- The area around the wound became swollen
- The edges of any part of the wound separated or gaped open.

Did any health care worker take a sample from your wound to send to the laboratory?
 Yes No

If you saw a health care worker because of these symptoms, please indicate who you saw from the list below-

- GP
- District nurse
- Midwife
- Doctor or nurse at the hospital
- Other – please specify _____
- Did not see one about my wound

Please tell us the date you noticed these symptoms.
 If you cannot remember the exact date, please give an approximate date ____/____/____

Have you been prescribed antibiotics for an infection in the wound?
 Yes No

If yes, who prescribed them? _____

Have you been re-admitted to hospital with an infection of the surgical wound?
 To the hospital at which the operation was carried out? Yes No
 To another hospital? Yes No

If yes, which one? _____

Other comments _____

For Office Use Only: (To be completed by surveillance co-ordinator only)

Patient reported SSI meets definition Yes No

If yes enter criteria for SSI-

- Criterion 1 Discharge plus + antibiotics prescribed
- Criterion 2 Clinical signs* + dehiscence
- Criterion 3 Clinical signs* + antibiotics prescribed

*Clinical signs- at least 2 of pain, heat, redness or swelling.

Enter criteria selected into weblink record for this patient.

Note: Do not report split abscess (discharge confined to points of suture penetration, minimal inflammation)

Form designed by Surgical Site Infection Surveillance Service, Health Protection Agency, July 2009

Fig. 1

30 day questionnaire designed by the English Health Protection Agency (now Public Health England).²⁴

During the study there was a change in prophylactic parenteral antibiotics to reduce the risk of acute renal failure. At the start of trial the regimen was single dose Gentamicin (4.5 mg/kg) and this was changed to single doses of Gentamicin (3 mg/kg) and Teicoplanin (400 mg) on 1 February 2009.²³

The primary outcome measure was deep SSI based on the definitions as part of the Surgical Site Infection Surveillance Scheme (SSISS) published by the Health Protection Agency (HPA)²⁴ (Table I).⁹

Data were collected for this outcome at 30 days and patients were monitored for re-admission for up to a year. In order to ensure complete data on SSI post-discharge, patients were asked to report problems with wound healing 30 days after the operation using the HPA designed questionnaire and research nurses telephoned the patients on or soon after their 30th post-operative day (Fig. 1).²⁴ Readmission, patient reporting and clinical team reporting was used for monitoring between 30 days and 12 months. The rate of infection up to 12 months post-operatively was the primary endpoint for the trial.

Data for secondary outcome measures were collected pre-operatively where appropriate and at defined time points including superficial SSI, 30- and 90-day mortality

(in and out of hospital), length of stay in hospital (days), *Clostridium difficile* infections and surgical and medical complications.

Statistical analysis. In order to detect a reduction in the rate of deep SSI from 4% to 1% for a two-sided 5% level of significance and 80% power, for the selected binary outcome we needed a total of 848 participants, assuming a chi-squared test as the definitive analysis.

Baseline demographical and comorbidity data were summarised to check comparability between treatment arms. Additional comorbidities that have been shown to increase the rate of SSI were also recorded, such as diabetes²⁵ and rheumatoid arthritis.²⁶ Due to concerns about the (sub-optimal) method of randomisation that was used, we undertook formal statistical testing of differences in baseline characteristics between treatment arms to assess whether there was any evidence of systematic imbalance introduced by the randomisation procedure. Independent samples *t*-tests and Fisher's exact test or chi-squared tests were used, with significance set at the 5% level.

The main analysis assessed differences in the primary outcome, deep SSI, on an intention-to-treat basis between treatment groups using logistic regression analysis of complete data, adjusting for the age and gender of the patients. Regression coefficients were considered to be significant at $p < 0.05$ (5% significance level). A per-protocol analysis was also undertaken as an analysis of sensitivity to assess the effects of deviations from the protocol. Also the overall number of infections, either deep or superficial were analysed in a similar manner to assess the total number of SSIs in the patients. Differences between the groups for other secondary outcomes including mortality and critical care stay and post-operative complications were assessed using chi-squared and Fisher's exact tests as appropriate. Length of stay was compared between groups using a Mann-Whitney U test. All analyses were undertaken using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).²⁷

Results

A total of 1210 patients were eligible for inclusion; 362 were excluded. In all, 848 patients consented to take part in the trial and 448 were randomised to low dose dual-antibiotic cement (133 at site 1 and 315 at site 2) (control group) and 400 to high dose antibiotic cement (82 at site 1 and 318 at site 2) (intervention group). A total of 24 consultant surgeons and many junior surgeons performed the operations. An orthopaedic consultant was the lead surgeon in 154 (18.2%) of them, trust doctors in 55 (6.5%), and trainees 639 (75.3%). The proportion of consultant to trainee surgeons was similar in the two groups (chi-squared test; $p = 0.366$).

No patient withdrew consent after randomisation. At the primary endpoint of 12 months, loss to follow-up was less than 6% in both groups (Fig. 2). Table II summarises the demographical characteristics of the patients pre-

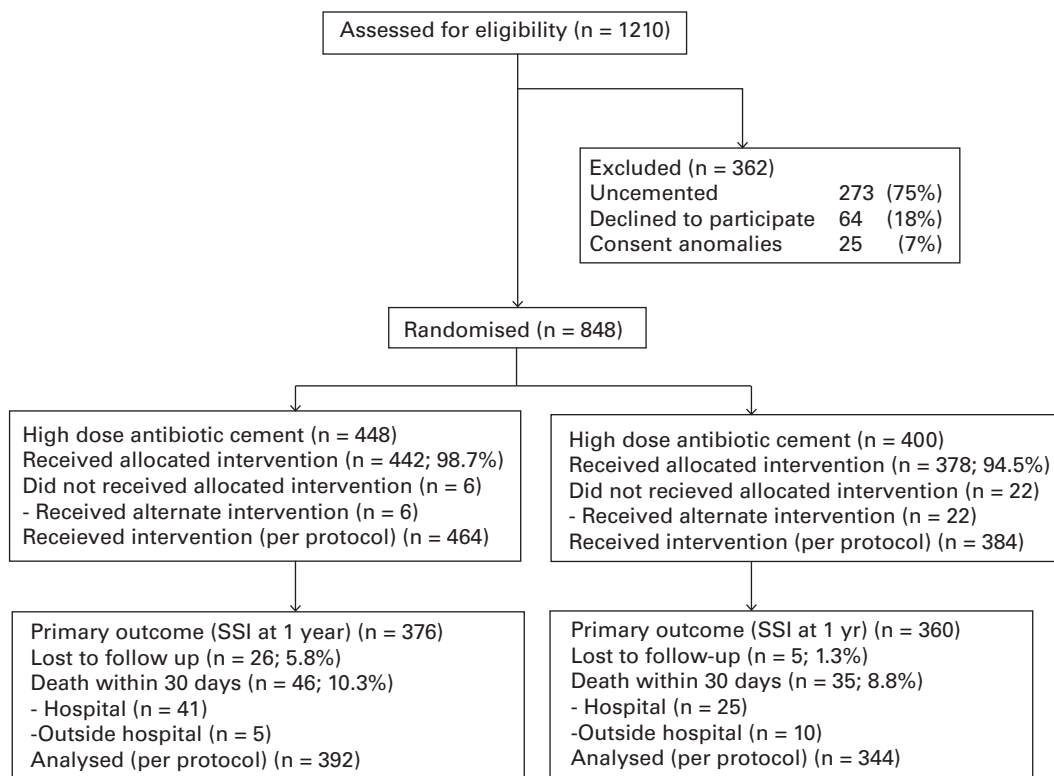


Fig. 2

Overall flow of patients in the Fractured Hip Infection Trial.

operatively. The characteristics of the two groups were similar and were representative of the wider population of patients undergoing hemiarthroplasty of the hip in England during this time.²⁸ There was no difference in the distribution of gender (chi-squared test; $p = 0.951$), age (t -test; $p = 0.239$), American Society of Anesthesiologists (ASA) grade²⁹ (chi-squared test; $p = 0.962$) or any other comorbidities between the groups (Table II).

Primary outcome. The incidence of deep SSI (Table III) was lower in the intervention group (1.1% *versus* 3.5%; odds ratio (OR) 0.31, 95% confidence interval (CI) 0.09 to 0.88; t -test; $p = 0.041$) based on an intention-to-treat age and gender-adjusted analysis. The unadjusted OR was 0.31 (95% CI 0.07 to 1.03) with some weak evidence that this difference was significant (Fisher's exact test; $p = 0.047$). As the rate of deep SSI in the control group was 3.5%, the relative risk reduction in favour of the intervention was 0.31 (95% CI 0.09 to 0.88) and the number needed to treat to prevent one infection was approximately 42.

Secondary outcomes. When data were combined such that deep or superficial SSIs were counted, the rates were 5.3% (95% CI 3.4% to 8.2%) in the control group and 1.7% (95% CI 0.7% to 3.8%) in the intervention group (Table III). An analogous analysis to that undertaken for deep SSI alone gave estimates of the unadjusted odds ratio from Fisher's exact test of 0.30 (95% CI 0.10 to 0.79) and adjusted OR from logistic regression of 0.30 (95% CI 0.11 to 0.71); p -val-

ues from these two analyses were 0.009 and 0.010, respectively, providing reasonably strong evidence that the total number of infections both deep and superficial differed significantly between groups.

Repeating the analyses on a per protocol (as treated) basis as a sensitivity analysis, gave similar estimates of ORs and inferences for both deep SSI and combined superficial and deep SSI data; the adjusted OR for the former outcome measure was 0.33 (95% CI 0.09 to 0.95 and $p = 0.056$) and for the latter was 0.32 (95% CI 0.12 to 0.77 and $p = 0.016$). The reported rates of SSI were calculated after excluding patients who died within 30 days of operation. If the most extreme position is taken and assuming that these all had an SSI then the estimated rates would increase to 15.6% (66/422) and 10.4% (41/395) in the control and intervention groups, respectively. However, even in this extremely unlikely setting, due to similar death rates, there would still be reasonable evidence of a difference in rates between groups (unadjusted OR 0.63, 95% CI 0.40 to 0.97; $p = 0.029$). Including variables in addition to age and gender in the logistic regression models such as hospital site, diabetes and ASA grade did not significantly improve the model fits (p -values from chi-squared tests were > 0.05). Therefore, the effects of the variables reported in Table II on outcomes, other than age and gender, are negligible (i.e. their ORs were approximately one).

Table II. Breakdown of demographics and co-morbidities between the intervention (high dose dual-antibiotic cement) and control (low dose antibiotic cement) groups; entries are frequencies unless stated otherwise

	Control (n = 448)	Intervention (n = 400)	p-value
Age (mean and SD)	82.34 (7.69)	82.96 (7.48)	0.239*
Gender (F:M) (%)	333:115 (74.3)	299:101 (74.8)	0.951
Surgeon Grade			0.245
Consultant (%)	59 (16.0)	67 (20.7)	
Trust doctor (%)	23 (6.3)	22 (6.8)	
SpR (%)	286 (77.7)	234 (72.5)	
ASA			0.962
1 (%)	14 (4.1)	11 (3.7)	
2 (%)	83 (24.2)	76 (25.6)	
3 (%)	220 (64.1)	186 (62.6)	
4 (%)	26 (7.6)	24 (8.1)	
Previous medical history (Y : N):			
Hypertension (%)	198 : 211 (48.41)	191 : 194 (49.61)	0.790
Atrial Fibrillation (%)	99 : 310 (24.21)	70 : 315 (18.18)	0.047
Ischaemic heart disease (%)	61 : 348 (14.91)	70 : 315 (18.18)	0.253
Hypothyroid (%)	51 : 358 (12.47)	37 : 348 (9.61)	0.242
IDDM (%)	4 : 405 (0.98)	2 : 383 (0.52)	0.687†
NIDDM (%)	68 : 341 (16.63)	54 : 331 (14.03)	0.359
PVD (%)	59 : 350 (14.43)	55 : 330 (14.29)	> 0.999
COPD (%)	44 : 365 (10.76)	46 : 339 (11.95)	0.677
Dementia (%)	69 : 340 (16.87)	58 : 327 (15.06)	0.551
Alzheimers (%)	39 : 370 (9.54)	35 : 350 (9.09)	0.926
Pressure sores (%)	24 : 385 (5.87)	16 : 369 (4.16)	0.347
Psoriatic arthritis (%)	1 : 408 (0.24)	0 : 385 (0)	> 0.999†
Rheumatoid arthritis (%)	6 : 403 (1.47)	10 : 375 (2.6)	0.316†
Hypercholesterolaemia (%)	63 : 346 (15.4)	61 : 324 (15.84)	0.942

p-values are from chi-squared tests unless stated otherwise

* independent samples t-test

† Fisher's exact test

SD, standard deviation; SpR, specialist registrar; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease

There was no evidence of a difference between the groups for length of stay in hospital. The medians for the control and intervention groups were 23 days (interquartile range (IQR) 11 to 41) and 21 days (IQR 10 to 41) (Mann-Whitney U test, $p = 0.265$) or post-operative mortality (chi-squared test; $p = 0.858$). Stay in a critical care unit (CCS) differed between the two groups, with 19 (4.7%) of the control group requiring this treatment, compared with two (0.5%) of the intervention group (Fisher's exact test; $p < 0.001$) (Table III). There was weak evidence for an association between length of CCS and SSI, both superficial and deep, with 3% (21/699) of those patients without a CCS having a SSI, compared with 13% (2/15) of those with a CCS and an SSI (Fisher's exact test $p = 0.08$). A total of three patients with SSIs did not have data on whether they had a CCS and were not included in the analysis. The difference in length of CCS was in part due to the different rate and represents a marker of increased risk of SSI.

There was no evidence that the rate of development of any of the complications differed between the groups (Table IV).

Discussion

Methods for reducing infection following joint arthroplasty have included the use of laminar flow^{30,31} and aseptic techniques such as the use of antiseptics and double glove-

ing.^{32,33} Systemic antibiotics have also been used³⁴ but, prophylactic antibiotics are not without complications such as intestinal bacterial overgrowth.³⁵ In order to minimise these complications, the local release of antibiotics from bone cement has been used.^{36,37}

In elective arthroplasty surgery, trials have compared different antibiotic regimens in primary THA and total knee arthroplasty,³⁸ differences between locally delivered and systemic antibiotics³⁹ and with high *versus* low viscosity cement.⁴⁰ The use of antibiotic cement for primary THA is now accepted as an effective means of prophylaxis against SSIs.^{11,41-43}

However, in hemiarthroplasty of the hip, there have been no randomised control trials, which was a pivotal stimulus for our trial. *In vitro* studies have shown that high dose impregnated cement (1 g Gentamicin and 1 g of Clindamycin) inhibits bacterial growth on agar plates for up to 672 hours, whereas with standard antibiotic loaded cement (0.5 g Gentamicin) activity stops after 48 hours.²² This suggests that a broader bacterial spectrum can be achieved for a longer period of time.⁴⁴

As well as the primary endpoint of deep SSI, our randomised clinical trial found a statistically significant reduction in combined SSI between patients having low *versus* high dual dose antibiotic cement when treated surgically for an intracapsular fracture of the hip. This could have an effect

Table III. Primary and secondary outcome measures at one year post-operative; counts with frequencies of events in parentheses, for control and intervention groups and total (combined) population (n) (%)

Status	Control		Intervention		Total	
	events	n	events	n	events	n
Primary Outcome						
Deep SSI (%)	13 (3.5)	376	4 (1.1)	360	17 (2.3)	736
Secondary Outcomes						
Critical care stay (%)	19 (4.7)	404	2 (0.5)	384	21 (2.7)	788
Death (%)	60 (15.4)	390	56 (16.1)	347	116 (15.7)	737
Deep or superficial SSI (%)	20 (5.3)	376	6 (1.7)	360	26 (3.5)	736

Analysis of SSI data excluded all patients who died within 30 days of operation and some loss to follow-up; for critical care stay and mortality there was also a small amount of missing data (< 10%) SSI, surgical site infection

Table IV. Reported complications, summarised by group (Y : N); p-values are from Fisher's exact test unless indicated otherwise

	Control (n = 376)	Intervention (n = 360)	p-value
Deep vein thrombosis (60 days) (%)	4 : 360 (1.10)	0 : 350 (0.00)	0.124
Pulmonary embolism (60 days) (%)	4 : 360 (1.10)	3 : 347 (0.86)	> 0.999
Stroke (30 days) (%)	2 : 362 (0.55)	5 : 345 (1.43)	0.278
Transient ischaemia (30 days) (%)	1 : 363 (0.27)	2 : 348 (0.57)	0.617
Gastrointestinal bleed (30 days) (%)	3 : 361 (0.82)	3 : 347 (0.86)	> 0.999
Renal failure (30 days) (%)	14 : 350 (3.85)	15 : 335 (4.29)	0.914*
Urinary tract infection (30 days) (%)	53 : 311 (14.56)	47 : 303 (13.43)	0.743*
Myocardial infarction (30 days) (%)	5 : 359 (1.37)	8 : 342 (2.29)	0.412
Pneumonia (30 days) (%)	15 : 349 (4.12)	13 : 337 (3.71)	0.848
<i>Clostridium. difficile</i> infection (%)	5 : 359 (1.37)	9 : 341 (2.57)	0.289
Re-admission (%)	17 : 347 (4.67)	13 : 337 (3.71)	0.579
Aspiration pneumonia (%)	4 : 359 (1.10)	4 : 346 (1.14)	> 0.999
Hyponatraemia (%)	21 : 342 (5.79)	20 : 330 (5.71)	> 0.999*
One or more event(s) (%)	128 : 235 (35.26)	132 : 218 (37.71)	0.547*

* chi-squared test

on the rate of superficial SSI because of a higher elution of antibiotics into the wound exudate in the treatment group. The groups were equally matched and the overall the rates of complications were similar, but there was evidence of slightly increased CCSs in the low dose antibiotic group.

Less than 5% of patients in both groups did not receive their allocated intervention. We had expected this rate to be lower with this method of randomisation. Contamination generally occurred in the crossover phase of the trial, being at the start of a month when the alternate intervention was being introduced.

Opponents of the use of local antibiotics have argued that using antibiotic impregnated cement can lead to the development of bacterial resistance.⁴⁵ This theory is based on having sub-inhibitory concentrations and the development of resistance among infecting organisms.⁴⁶ While there is *in vitro* data to suggest that prolonged exposure of organisms to sub-inhibitory levels of antibiotics encourages mutational adaptations that confer resistance,⁴⁷ there remains little clinical evidence to support this theory. On the other hand, higher dose, dual action antibiotic cement *in vivo*, results in a more potent and more prolonged inhibition of bacterial growth.⁴⁶

In our study, we did not find any significant change in the profile of the infecting pathogens between groups.

The main strength of this trial is that it was entirely pragmatic. Although we recruited patients from only two centres, the large number of surgeons of various grades involved in the study realistically reflects surgical practice.²⁸ Other strengths included the use of a nationally recognised definition of SSI, which was assessed by HPA trained nurses, and the high levels of complete follow-up data at the primary endpoint (95%).

The key limitation was the use of quasi-randomisation, which is widely recognised as being less rigorous than conventional randomisation. Differences in the target population, local environment and procedures at each of the sites of the study had the potential to confound the effects of the intervention. Therefore group randomisation was used and interventions were alternated on a monthly basis at each site in an attempt to balance the characteristics of the patients and unknown systematic effects of the treatments. There is also potential bias near the time of change over, though the presence of a best practice tariff ameliorates this fact as 90% of patients are operated on within 36 hours and 24 consultant surgeons were involved in recruit-

ment. Secondly, these patients were all discussed in a multidisciplinary meeting. Thirdly, the parenteral antibiotic regimen was modified during the course of the trial. However, this change did not have any statistically significant impact on the comparative analysis of the rates of deep SSI between the groups. A similar analysis for combined deep and superficial infections also showed that inferences were unchanged after adjusting for the change in antibiotic regimen (likelihood ratio test; $p = 0.187$).

With rigorous statistical interrogation, the two groups were found to be comparable in terms of the demographics and important expected comorbidities. The rates of SSI were calculated after excluding those patients who died within 30 days of operation. It is possible that some or all of these patients could have had a SSI, therefore the reported rates might be underestimates of the true rates of SSI in these patients. However, given that the rates of death were similar in both groups, it is unlikely that this would explain the difference in the rate of SSI between the groups.

Finally, there was some deviation from the original statistical plan. A random effect was to be included in the logistic regression model to account for heterogeneity due to the operating surgeon. However, the relevant data were not consistently reported, so the simpler fixed effects model only was fitted to the data. This would not have modified the outcome in any significant way.

In conclusion, this trial has provided evidence that high dose dual-antibiotic impregnated cement leads to a reduction in the rate of SSI in the treatment of patients with an intracapsular fracture of the neck of the femur, with no associated increase in complications. Orthopaedic surgeons will be able to use this information when deciding on which type of bone cement to use in the treatment of these patients.



Take home message:

The use of high dose dual-antibiotic impregnated cement in these patients significantly reduces the rate of SSI compared with standard low dose single antibiotic loaded bone cement.

Author contributions:

A. P. Sprowson[†]: Conception, Protocol, Ethics, Writing the paper.
 C. Jensen: Data collection, Patient recruitment, Data analysis, Performed surgeries, Writing the paper.
 S. Chambers: Patient recruitment, Data collection, Performed surgeries.
 N. Parsons: Data analysis, Writing the paper.
 N. M. Aradhyula: Writing the paper, Performed surgeries.
 I. Carluke: Trial design, Engagement of surgical colleagues, Writing the paper.
 D. Inman: Performed surgeries, Editing the paper.
 M. R. Reed: Chief investigator, Protocol, Writing the paper.

[†]Deceased

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Heraeus Medical (the manufacturer of both the intervention and control cements) provided the high dose dual-antibiotic cement at the same cost as their standard cement. No additional funding was received.

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