**Author's response to reviews**

**Title:** The effect of high dose antibiotic impregnated cement on rate of Surgical Site Infection after hip hemiarthroplasty for fractured neck of femur: A protocol for a double-blind quasi randomised controlled trial.

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**Author's response to reviews:** see over
Author's response to reviews

The effect of high dose antibiotic impregnated cement on rate of Surgical Site Infection after hip hemiarthroplasty for fractured neck of femur: A protocol for a double-blind quasi randomised controlled trial.

Reviewing Author:
Andrew Sprowson
Mike Reed

Version: 2 Date: 23 October 2013
Author's response to reviews: see over
Response 1

Reviewer's report

Title: The effect of high dose antibiotic impregnated cement on rate of Surgical Site Infection after hip hemiarthroplasty for fractured neck of femur: A protocol for a double-blind quasi randomised controlled trial.

Version: 2 Date: 26 May 2013

Reviewer: Olof Sköldenberg

Reviewer's report:

The authors should be commended on performing a trial on this patient-group. True intervention studies on such large materials are few and far between and is really hard work as I am well aware of. I believe the protocol for the study is worthy of publication but I have a few remarks.

Major Compulsory Revisions:

EFFECT SIZE
On what basis do the authors think that the effect will be as large as removing 75% of all SSIs? A reduction from 4% to1% is a very large effect size and since this is the basis for the sample size it should be elaborated upon. Are there any pre-clinical or clinical data that supports this large effect size?

The aim of this trial was to assess a simple intervention to reduce the rate of SSI to that of total hip replacement at 1%. At the initiation of the study the national rate of SSI was 4.68% for hip hemiarthroplasty, based upon Health Protection Agency data. There is no definitive information in the literature to guide this effect size, as a large trial such as the one we are performing is needed to guide this decision.

The only reference they have regarding this very foundation of the study is the Norwegian register study on revision surgery for total hip arthroplasty patients (not FNF-patients in this study [!]). The Norwegians had a 0.4% risk for revision due to infection in patients treated with both systemic and local antibiotics (in the cement) and 0.7% for patients only treated with systemic antibiotics. This 0.3% difference represents a 42% reduction in the occurrence of infection. Based on what will this new cementmix (in the current study) be much more effective?

The infection rate in the UK at the time was much higher within this patient group at 4.68%. The research team also analyzed the organisms causing infection within this setting, and the border spectrum of antibiotics covered 90% of these organisms. In addition for such a strong effect is the use of such cement in infected single stage
revisions where it is able to eradicate infections in about 80% of cases.

The authors also state that a local application of gentamycin can only be applied by cement; there are of course other, perhaps even more efficient methods of doing this, for instance by using Gentaflecce or some other version of this (collagen pads with gentamycin).

We have modified this sentence to reflect this point.

Sample size calculation

The sample size calculation is mathematically correct but, in my opinion, still faulty since the effect size is overestimated.

This sample size is ambitious, but clinicians felt such a strong effect would be a strong driver to change practice and based upon the effect of infected revision was plausible.

CHANGE OF SYSTEMIC ANTIBIOTICS

The number of days or doses that prophylactic antibiotics is administered is not stated. In addition; Teicoplanin; a broad spectrum antibiotics with effect on multi-resistant strains of bacteria was added after the first 1/3 of the study. This could have a profound effect on the primary outcome and the authors must elaborate on how they have controlled for this.

1. We accept this limitation and both groups will be similarly affected. This will be analysed on completion of the study.

2. On the initiation of the study the latest systematic review stated: There was insufficient evidence to suggest that there was a significant difference in the efficacy of cephalosporins compared with that of teicoplanin or penicillin-derivatives, or that a particular generation of cephalosporins was more effective than another.

PRIMARY OUTCOME

The definition of a SSI is not in line with the current literature on periprosthetic joint infections (PJI). One could argue that a SSI is a different definition on an infection than a PJI. The implant itself and its biofilm-inducing properties are not considered in the 1992 definition of a deep SSI. In my opinion they should have used the current PJI definition as the primary outcome variable. IF the authors still would like to have their (arguably older) definition of SSI instead of PJI the should argue for this in the discussion and why the general definition of SSI also is valid for prosthetic joints.

Defining PJI

A definite diagnosis of PJI can be made when the following conditions are met:

1. A sinus tract communicating with the prosthesis; or
2. A pathogen is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint; or
3. Four of the following six criteria exist:
   a. Elevated serum erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) concentration
   b. Elevated synovial white blood cell (WBC) count
   c. Elevated synovial neutrophil percentage (PMN%)
   d. Presence of purulence in the affected joint
   e. Isolation of a microorganism in one culture of periprosthetic tissue or fluid
   f. Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 times magnification

The definition used is that defined by the UK Health Protection Agency at the time of the study and is still the nationally agreed definition. This criteria is based on the well-established and validated CDC criteria. We appreciate the advantages of the new definition of PJI, but this trial was started in 2008. Our definition is routinely collected by surveillance and a further definition would have increased the costs of the study.

Minor essential revision

PARTICIPANT ALLOCATION

Having 2 different; premade; versions of bone cement as the primary intervention could, arguably, be a perfect tool for a true randomized controlled trial. The authors have not done this however and I think the main reason for this is lack of resources. Having a central randomization procedure is arguably easier than a local.

“… concerns about the impact on the credibility and fidelity of the study interventions were identified as problematic issues if individual participant randomisation.”

I am not sure what this means? Surgeons would protest if they were given cement with a new antibiotic mix if there was an individual randomization? but not, as now, if they were forced to use it every other month? Please elaborate on this.

The surgeons could easily have been blinded since the antibiotics (as I understand it from the paper) is already pre-prepared in the mixing system of the cement. The argument for NOT blinding this for the surgeons is very weak “….handling characteristics could potentially be different and the surgeon would need to be aware”.

This could, and should, of course have been investigated prior to the study. If the handling characteristics of the cement truly is different the surgeons have now for
the last years learned that every other month the cement cures differently then the month before.

We admit the limitations of the randomisation system, but as pointed out these are partly due to logistical reasons. Although the cement characteristics are very similar an experienced surgeon may be able to tell the difference. Additionally the boxes were not blinded and therefore the surgeon could see the type of cement used.

PARTICIPANT RECRUITMENT

Please describe the inclusion/exclusion criteria first and then how informed consent was acquired,

Informed consent was only performed using Good Clinical Practice (GCP) principles.

Inclusion criteria

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests

Major Compulsory Revisions:

Response 2

Reviewer's report

Title: The effect of high dose antibiotic impregnated cement on rate of Surgical Site Infection after hip hemiarthroplasty for fractured neck of femur: A protocol for a double-blind quasi randomised controlled trial.

Version: 2 Date: 19 September 2013

Reviewer: Peter Pilot

Reviewer's report:
The authors describe a nice study that is highly relevant.
No major compulsory revisions.

When assessing the work, please consider the following issues:

1. Will the study design adequately test the hypothesis? Yes

2. Are sufficient details provided to allow replication of the work or comparison
with related analyses: if not, what is missing? Would like to see the power calculation explained in more dept. How are drop outs and LTFO taken into account

Once the patients have been randomised, they will all be analysed. The patient follow up is based upon readmission rates at both hospitals, which both have a robust mechanism to ensure all patients are captured. This is also linked to HES (Hospital Episode Data) data, as a further capture method.

3. Does the manuscript adhere to the relevant standards for reporting and data deposition: if not, in what ways?

Excellent

4. Is the writing acceptable? Yes
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests
My competing interest: Have working relation with Biomet