Author’s response to reviews

Title: Efficacy of single dose Gentamicin in combination with Metronidazole versus multiple doses for prevention of post caesarean infection

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Responses for Reviewer's report

**Title:** Efficacy of single dose Gentamicin in combination with Metronidazole versus multiple doses for prevention of post caesarean infection

**Major points for revision**

**Reviewer**

1. The hypothesis being studied is that there is a difference in post-caesarean infections between a single dose of gentamicin in combination with metronidazole and multiple doses of gentamicin and metronidazole. In the background the authors reference two studies (24, 25) that demonstrate that a single dose of antibiotics is as effective as multiple doses. They do not describe in enough detail why, despite these studies and other evidence supporting just a single dose of antibiotics for prophylaxis, their study is still needed.

**Author**

In the two studies, administration of antibiotic prophylaxis has been done intraoperatively, while ours will be administered 30-60 minutes before operation. Gentamicin has not been used in the mentioned studies above. We have chosen Gentamicin as one of the prophylactic antibiotics simply because at our setting, it has been found to be effective in preventing gram negative bacterial infection, and also effective against methicillin sensitive Staphylococcus aureus.

**Reviewer**

2. Although their hypothesis is that there is a difference between a single and multiple doses of antibiotics, in the section on data analysis they say “there (this) will be an equivalent(ce) trial to test the hypothesis that there is no
significant difference in ... infection”. The sample size is calculated to show a
difference of 20% between the two groups, not calculated as an equivalence
study and a 20% difference is too large for an equivalence trial.

4. There is no justification for the estimated infection rate of 40% used to
calculate the sample size. This seems like a very high rate of infection and not
consistent with the reports in the literature, even when antibiotics are not
used for prophylaxis.

**Author**

Estimation of the sample size has been revised. The incidence of surgical site
infection ranges between 2.5% and 20%. However it can be higher than 20%
in centers where there are many emergency caesarean sections compared to
elective caesarean sections[31].

When it comes to the incidence of wound infection, many studies have shown
non-significant results with difference of less than 5% [13, 29, 32, and 33].

Since we want to do equivalence trial, we assume that the difference of more
than 10% to be of clinical importance.

For the purpose of this study which involves candidates who undergo
emergency or non elective caesarean section, we set $P_0$, which is the
proportion of participants in single dose antibiotic prophylaxis group expected
to develop surgical site infection post caesarian section at 5% and $P_1$ which is
proportion of participants in the multiple doses antibiotic prophylaxis
expected to develop surgical site infection is set at 15%.

Therefore using the formula:

$$f(\alpha, \beta) \times 2P(1-P)$$
\[(P_0 - P_1)^2\]

Where \( P = P_0 + P_1 / 2 = 10, \)

\( f(\alpha, \beta) \) is the function of \( \alpha \) and \( \beta \) which is 7.845. \( \alpha = \) level of significance (probability of making type 1 error) is 5%, \( \beta = \) probability of making type 2 error is 20%, therefore \((1-\beta) = \) power of study, which is 80%.

Then sample size per group will be 142.

Allowing 10% attrition rate the minimum sample size for this study will be 310, i.e. 155 per group.

Change of sample size will affect the date for end of trial, this it will be 30\textsuperscript{th} of April 2012.

**Reviewer**

3. There is no rationale for the antibiotic regimen chosen, and although it probably is reasonable, there should be a discussion about the likely organisms covered rather than the statement in the background “the effectiveness of the current regimen is unknown”. There are some studies that have used this combination for prophylaxis (for a complete list, the authors could review the Cochrane Reviews on C-section prophylaxis and comparison of regimens). There should be a discussion about what are the commonest organisms associated with surgical site infections in their centre and the pattern of Resistance. Is Staphylococcus aureus common (which wouldn’t be expected to be covered by the combination)? The doses are not justified – gentamicin is usually dosed as mg/kg.
Authors:
Post-caesarean infections are polymicrobial. The main source of postpartum infection after caesarean section is the lower genital tract, particularly if the membranes are ruptured, but this still occurs with intact membranes following preterm birth. The most common isolated pathogens are anaerobes and gram negative aerobes. Gram negative aerobes include *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp, and *Proteus* spp. The anaerobes includes *Bacteroides* spp, *Clostridium* spp, and *Fusobacterium* spp. Mawalla et al., in a prospective cross-sectional study reported that most common isolates in surgical site infection at bugando medical centre are gram negative bacteria. *Staphylococcus aureus* were found in only 28.6% of study patients; and only 3% were MRSA (Methicillin resistant *staphylococcus aureus*) [12]. A combination of Gentamicin and metronidazole has been recommended as drugs of choice in the prevention of postcaesarean infection, since they cover most of the pathogenic bacteria commonly involved in post caesarean infection.
However in the end we are testing methods of admistration, single versus multiple, later we might need to study on microbial pattern and sensitivity on surgical site infection, specifically related to caesarean section.

Reviewer

5. Although there may be operational and practical issues why the study is not double-blinded (with placebo doses given post-partum), there should be a discussion of this in the protocol. Similarly there should be a discussion as to how to reduce bias – the choice of envelopes to allocate patients can be subjecttobias and other ways (e.g. a call to the pharmacy) should be considered. There should be an attempt to blind the patient and observer to study allocation, or at least have a discussion that the person making an
assessment about the outcomes should not be aware of the study group allocation.

**Author**

Simple randomization will be used to allocate study participants. About 310 opaque envelopes of the same size and color will be prepared for this study. 155 envelopes will contain papers marked “study arm A” and the remaining envelopes will contain papers marked “study arm B”. Then all envelopes will be mixed thoroughly in a box before selection of an envelope is done.

Each study participant will select one sealed envelope and give it to the research assistant to open. Then will get antibiotic prophylaxis according to her study allocation group. Study participants will not know the type of antibiotics given.

**Blinding**

The study is aimed at testing methods or mode of administration of drugs, and not new a drug. Blinded studies are known to be superior and especially where bias can be a confounding problem. We are constrained by low budget for this study. So this will remain as open label and unblinded.

**Minor revisions**

We could not include Urinary Tract Infection in outcome measure due to limited funds.

Necessary changes on grammar has been made, including adherence to Journal’s format.