Author’s response to reviews

Title: A randomized controlled double blind trial comparing the effects of the prophylactic antibiotic, Cefazolin, administered at Caesarean delivery at two different timings (before skin incision and after cord clamping) on both the mother and newborn

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Author’s response to reviews:

Reviewer 2

Response to Reviewer Comments (Version 2):

Reference No:PRCH-D-16-00087R2

Title: A randomized controlled double blind trial comparing the effects of the prophylactic antibiotic, Cefazolin, administered at Caesarean delivery at two different timings (before skin incision and after cord clamping) on both the mother and newborn

Authors: Chinta Annie Jyothirmayi, MD; Ajay Halder, MD; Bijesh Yadav, M.Sc.; Santosh Thomas Samuel, MD, DGO; Anil Kuruvilla, MD; Ruby Jose

BMC Pregnancy and Childbirth

Reviewer reports:

Elizabeth Moore (Reviewer 2): The authors have addressed many of the concerns raised by the reviewer. However, there is still concern about how some of the statistics are reported. In
additions there are some areas that need to be clarified and some minor errors that need to be addressed.

Comment 1:

Page 8, Statistical methods section, 4th sentence: What are quantitative variables? Do you mean interval/ratio or continuous? Was an independent t test used? Also, how was risk ratio calculated for the continuous variables that were compared used a t-test? You should describe how it was calculated. Did you test for normality of the data for the continuous variables? It is rare that length of stay would be normally distributed. If it was tested, what test was used?

Reply 1:

Thank you for the comment. Quantitative variables meant interval/ratio or continuous. However, in this paper we categorized continuous variables into clinically meaningful and interpretable categories as described below and produced the risk ratios or relative risks taking the “normal” group as reference category.

Gestational age:

Only term babies were included in the study (i.e. - Mothers who have 37 completed weeks of gestation). The inclusion and exclusion criteria specifies this. It was decided to exclude preterm babies since the problems related to them and their duration of hospital stay would change the results.

Baby weight (Kg):

1-2
2-3
3-4
>4

Even the minimal weight was included since there would be term small for gestational age babies.

Duration of hospital stay:

1-3 days
4-7 days
>7 days
Normally in our institution mothers undergoing cesarean section are discharged by 72 hours (if the mother and baby are well. Even if the mother or baby had minor complications, they would be mostly discharged in a week's time.

In newborn: sepsis/ jaundice / not gaining weight

In mother: urinary tract infection / surgical site infection / endometriosis.

Comment 2:

Page 8, Statistical methods section: Did you conduct post hoc tests? If yes, did you use the Bonferroni correction? From the results displayed in Table 2, it appears you did use post hoc tests.

Reply 2:

We removed the comparisons of continuous variables across the groups using independent t-test. We did not use any continuous variables for comparison across the groups. All continuous variables were categorized into groups. Hence there was no need of any Bonferroni correction and this was removed from the statistical method section too.

Comment 3:

You need to describe how you compared post op complications. for example, did you compare febrile illness yes/no between the pre and post groups? If yes, then why do you not have a p value for comparing "none" between the two groups?

Reply 3:

“Not having any Post op complications categorized as “None” in the data was considered as the reference category. For example, having post op complication such as “febrile illness” was compared with “none” as the reference. Similarly, “UTI” was compared with “none”. In statistical terms we created dummy variables with “none” as the reference. Therefore, we will not produce any p values for “none”.

Comment 4:

How did you compare Hospital days as a categorical variable? If you compare all three categories between the pre and post groups, you get a significant difference, $p = 0.005$. To find out where the difference is, you have to do post hoc test between the groups. When you do that,
you need to use the Bonferroni correction. From the comparisons, the only one that is statistically significantly different between the groups is 4-7 days vs. >7 days (p =0.005). The p values you have reported do not match those that I calculated, so please check your numbers. Also, when you interpret the post hoc test results, you have to say that it means the post group compared to the pre group had significant more mothers with a length of stay >7 compared to having a length of stay of 4-7 days. It does not mean the post group had great length of stay. You should report the more rigorous test of the mean which shows there was not a statistically significant difference in length of stay (p = 0.87).

Reply 4:

As mentioned earlier (please refer response 2), we did not use any Bonferroni correction to compare which categories made the difference.

Now, interpretation of length of stay has been modified as you suggested.

Comment 5:

Page 10, second paragraph says the mean gestational age of the mothers was 38 weeks, then it says the mean was 38.5. Which was it? Also, it should say mean gestational age at delivery was 38.5 +/- 1.8.

Reply 5:

Thank you for pointing this out. Now, the gestational age has been corrected to 38.5 weeks and the necessary correction in the sentence has been made as you suggested.

Comment 6:

Page 12, Results of the secondary outcomes in the mother and newborn: The first sentence should say, There were no maternal death OR readmission, not and readmission. The next sentence should say, and the percentage of infants who had weight gain at 6 weeks was similar.

Reply 6:

Thank you. The recommended changes have been made to the sentence on page 12 as per you suggestion.

Comment 7:
In the limitations you state that the study was not powered to address the neonatal outcomes. I suspect is also wasn't powered to find differences in some of the maternal outcomes. This should also be stated.

Reply 7:

Thank you. The limitations have been expanded as suggested, as the study was powered only for the main maternal outcomes.

Comment 8:

There are numerous spacing errors throughout the manuscript. This may be due to the conversion to a pdf; however, they need to be fixed. It is very distracting.

Reply 8:

Sorry about the spacing errors. They had all been painstakingly corrected at the last revision, but seem to have crept up again in the pdf version. They have been corrected again.

Reviewer 3

Response to Reviewer Comments (Version 2):

Reference No:PRCH-D-16-00087R2

Title:A randomized controlled double blind trial comparing the effects of the prophylactic antibiotic, Cefazolin, administered at Caesarean delivery at two different timings (before skin incision and after cord clamping) on both the mother and newborn

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Reviewer reports:

Scott A Sullivan (Reviewer 3): BMC

Manuscript title: A RCT double blind comparing the effects of Cefazolin administered at cesarean delivery at two different timings (at cord clamp and prior to incision) on both mother and newborn
Comment 1:

Abstract: Why was death from sepsis chosen as an outcome? That is vanishingly rare. It is not clear to me what 2-3 % means in terms of cord blood?

Reply 1:

Thank you for the clarifications requested. This study was done in India and India being a developing country, maternal deaths due to sepsis constituted 13.7% (3.3 to 35.9) in the 2014 census and was the second leading cause of maternal death in the country. As for neonatal deaths, sepsis constituted 36% to 45% of the neonatal deaths in the urban and rural areas respectively. Hence these variables were included in the analysis of the outcomes.

As for the percentage of antibiotic Cefazolin present in the cord blood, a total of 139 samples of cord blood were analyzed for the levels. Nineteen of them had cord blood levels less than 1mg/dl, 43 of them had 1-10mg/dl, 60 of them had between 10 and 20mg/dl and 17 babies had levels between 20 and 30 mg/dl. The average of these values ranged from 2 to 3% of the total dose of Cefazolin used per patient.

Comment 2 & 3:

Background: there are some spacing issues in the last paragraph

Patients and Methods: There are some spacing and punctuation problem in this section as well.

Reply 2 & 3:

Sorry about the numerous spacing and punctuation errors. The spacing errors and punctuations were meticulously corrected at the last revision. However, they seem to have occurred at conversion to pdf probably. They have been corrected once again.

Comment 4:

Results: There are some spacing and punctuation problem in this section as well. I am not sure if these are only in my copy. They are numerous

Reply 4:
Comment 5:
How was consent obtained if most patients had emergency c-sections? When did they consent? On admission?

Reply 5:
Informed consent for the study for emergency Cesarian were obtained after the decision for Cesarian was made.

Did all the patients have blood cultures?

Thank you for clarification request.

Blood cultures for mothers were taken only in those who had clinical features of endometritis, surgical site sepsis, urinary tract infection or persistent high grade fever post operatively. As for the neonate, any neonate with clinical features of early or late onset sepsis and included those whose mothers had fever, chorioamnionitis or prelabour rupture of membranes.

Comment 6:
Discussion: No comments

Comment 7:
References - No comments