Author’s response to reviews

Title: The MOVE-trial: Monocryl® vs. Vicryl Rapide™ for skin repair in mediolateral Episiotomies: a randomized controlled trial.

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Author’s response to reviews:

Concerning the re-submission of the manuscript PRCH-D-16-00466

“The MOVE-trial: Monocryl® vs. Vicryl Rapide™ for skin repair in mediolateral Episiotomies: a randomized controlled trial.”

Dear Madam/Sir,

We would like to re-submit the manuscript and we would like to thank the editors and reviewers for the assessment of the manuscript and for the suggestions made to improve the manuscript. You will find our response to each comment of the reviewers below, itemised one by one.

All line numbers indicated in this cover letter correspond with the line numbers in the revised version of the manuscript. This means the line numbers in the comments also have been changed to match the revised manuscript.
Reviewer 1.

Odijk et al. present a well designed and properly performed randomized controlled trial comparing two types of material commonly used for episiotomy repair. The topic is original, the article is well written and data well presented. However I have some concerns regarding citations and interpretation of the results.

Major comments:

Comment 1: The type (RCT) and setting (when and where performed) of the study is not provided in the Abstract.

Response: The required information has been added to the abstract. (“In a randomized ……2013”, Line 30-31)

Comment 2: it should be disclosed in the abstract that all other layers of episiotomy repair were sutured by the same material.

Response: The suture material for the non-skin layers has been described in the abstract. (“All other layers ….groups”, line 33)

Comment 2: line 57: the referenced study does not deal with childbirth perineal trauma and its repair. It is an RCT comparing episiotomy suturing techniques. The numbers provided are based on the West Berkshire perineal management trial (Sleep 1984) and an RCT concerning care of the perineum in the 2nd stage of labor (McCandlish 1998)

Response: It is indeed true that a reference to the article was made aiming at a percentage of perineal trauma mentioned in the introduction of the article, which did not originate in this article itself. We looked into it and the percentages presented were found by several researchers. The old reference has been removed and the original references have been added, among which the two mentioned references.

Comment 3: line 63: The scope of the present study is three months. Data regarding persisting perineal pain 3 months after vaginal delivery with mediolateral episiotomy should be presented preferably (65/306, 21.2%) (Necesalova 2016).
Response: The mentioned reference, which had just been published at the time of our submission, has been added and is a useful addition to the manuscript because of the similarity of the follow up to ours. The mentioning of the longer-term complaints, although out of the scope of our RCT, merely was done to point to the significance of finding an optimal protocol for repair after perineal trauma post partum.

Comment 4: lines 124-129: Since all layers apart from the skin were sutured the same way using the same material, why did the authors expect any difference in the pain scores after the childbirth. Furthermore, Morano et al (2006) suggested a continuous knotless technique for episiotomy repair using a single thread. Why did you not compare the two materials in the repair of the whole episiotomy (single thread).

Response: The idea for the RCT came from continuing discussion in our department whether Monocryl® or Vicryl Rapide™ would cause more complaints when used for the skin. One of these complaints was pain. In order to find out if there was a difference this RCT was performed.

Discussion did indeed take place on the second point raised. At the time the interrupted technique was used in our hospital. In order not to influence the results by adding a parallel learning curve for the continuous technique it was decided to use the interrupted technique for the duration of the trial. After cessation of the trial a switch has been made to the continuous technique. In hindsight this decision is indeed regrettable for it might have provided us with more useful information now that the continuous technique has become the standard.

Comment 5: line 127: Why was Vicryl Rapid 3-0 used for the repair instead of Vicryl 2-0? Vicryl 2-0 is frequently described for episiotomy repair including the skin closure (Kettle 2002, Morano 2006, Kindberg 2008, Karbanova 2014,...). Your results could have been affected by the caliber of the thread. Karbanova et al. (2014) used Vicryl 2-0 for the repair and reported a self-reported dehiscence rate in the mediolateral episiotomy group 13/262 (5%) after 10 days compared to 22% in this study. This should appear in the discussion section.

Response: Before the trial in our hospital Monocryl® 3-0 and Vicryl Rapide™ 2-0 were used for the suturing of the skin. In order to prevent criticism that 2 different sizes were used and compared it was decided that we would use Monocryl® 3-0 and Vicril Rapide™ 3-0.

It is indeed a possibility that the higher prevalence of dehiscence is caused by the calibre of the thread. It could also have been affected by the low response rate, which has the potential of bias towards a higher response rate of women who had complications. A mention of these considerations has been made in the discussion. (The percentage of …response”, lines 279-283)
Comment 6: lines 181-183: The response rate is quite low. Both age and race/background affect the quality of healing a perception of pain. Is that not a possible limitation of the study? The pain scores, healing complications and dyspareunia rates are worse than described previously (Karbanova 2014, Necesalova 2016). The young women with no problems were possibly less likely to complete and send the questionnaires.

Response: As stated in the discussion the low response rate is indeed a limitation of the study.

It could indeed be hypothesized that the pain scores and healing complications are overestimated in our trial due to the low response rate and possible bias with more women with complications returning the questionnaires then women without complications. However there seems to be no reason to assume this effect would be greater for any of the used materials since both materials had the same loss to follow up. The final conclusions about the differences between the materials therefore are likely not influenced by a potential bias.

Comment 7: Table 4: Consider shortening the table and moving some of the information in the text (e.g. intercourse 10 days etc.)

Response: As suggested we re-evaluated the secondary outcomes and moved the less relevant outcomes to the text and removed them from table 4. (“Only one woman….analgesia “, lines 210-213 )

Comment 8: lines 301-308: The results of the study should be compared to another study concerning mediolateral episiotomy with a similar follow-up (Necesalova 2016)

Response: The trial of Necesalova has been included in the discussion. Similar numbers were found regarding resumption of intercourse. Unfortunately the specific questioning on dyspareunia in their trial differs from ours in that we asked if women had had painfree intercourse yet at any given moment, whereas in the trial of Necesalova women were asked how many times women experienced dyspareunia. This makes comparison difficult.

Comment 9: Self-reported dehiscence can be anything from a patient’s perception of a change in shape of their external genitalia to a complete dehiscence of the suture. The latter being undoubtedly more clinically significant. Do you have any data on the secondary suture rate of the two episiotomies?

Response: None of the patients reporting dehiscence mentioned that a secondary suturing was performed in their questionnaires. This question however was not specifically adressed in the
questionnaires. In our hospital dehiscence is almost always treated expectatively and secondary closure is rare so it is to assume no secondary closures were performed.

A Cochrane review from 2013 concluded that there was not sufficient evidence to make an adequate clinical decision (Dudley et al. 2013)

Only recently data are starting to emerge suggesting that secondary repair might be beneficial. (Dudley et al, 2017, reference 26)

Comment 10: reference 29 (Mader et al, ) is a pilot study on healthy volunteers from 2003. Its potential of questioning a traditional, widely used and effective tool for pain assessment is very limited. Consider removing the reference.

Response: The statement in the manuscript indeed seems to overestimate the weight of the small pilot study. It was meant to emphasize that pain scores, due to their subjective nature can be difficult to interpret and can require large trials due to large variances in VAS scores. This could make other outcomes more useful. The reference has been removed and the sentence has been rephrased. (“Due to the….participants”, lines 356-358)

Minor comments:

Comment 1: line 96 Consider adding ...skin after a vaginal delivery with mediolateral episiotomy in ....

Response: The suggestion has been accepted and was inserted

Comment 2: line 101 Consider providing the total number of deliveries/vaginal deliveries in the study period

Response: The total amount of deliveries during the trial period has been provided in the results section, as was the total amount of primiparous women who delivered vaginally. (“Between November 2010….vaginally”, lines 185-186)

Comment 3: line 105 The women were technically nulliparous at this stage of the trial

Response: “Primiparous” was replaced by “nulliparous”
Comment 4: line 114 please provide the mode of delivery in the inclusion criteria (any vaginal delivery, excluding forceps)

Response: Mode of delivery was added to the inclusion criteria

(“Both women with…..included”, line 114)

Comment 5: line 231-233 the sentence is rather difficult to understand, consider rewording

Response: The sentence has been rephrased

(“After six weeks…..dehiscence”, lines 231-233)

Comment 6: consider shortening the discussion

Response: We had a critical look at the discussion and removed two sections of less importance. Unfortunately however, due to the adaptations made in response to some of the other comments, the shortening of the discussion is marginal.

Reviewer 2

Jerry Lowder (Reviewer 2): The authors conducted a randomized controlled trial of suture types (Monocryl® vs Vicryl Rapide™) for repair of uncomplicated episiotomy after vaginal delivery. They met their goal sample size of 250 patients based on a 90% power to detect a difference in pain in the sitting position 10 days after vaginal delivery. They found no difference in Visual Analogue Scale (VAS) scores at 10 days or the other time points evaluated when they controlled for the difference in ventouse deliveries, which was found to be significantly higher in the Vicryl Rapide™ group after randomization. The secondary outcome of self-reported wound dehiscence was significantly higher in the Vicryl Rapide™ group at all time points, but the remainder of the secondary outcomes evaluated were not significantly different between groups. The authors used questionnaire data for collection of their primary and secondary outcomes. Overall, this appears to have been a well-conducted study, which addresses a critical question in obstetric laceration and episiotomy repair. As the authors mention, there is limited high-quality data to favor monofilament or multifilament suture for this indication, thus an RCT on this topic is highly relevant. The choice of primary outcome and methods to measure primary and secondary outcomes leaves some unanswered questions at the conclusion of this study. Additionally, questionnaire data is prone to loss-to-follow-up, which was significant in this study. The
subgroup analysis for patients who had ventouse delivery and those lost-to-follow-up compared to those with questionnaire data was a valuable addition to the study and strengthens the findings reported here.

Specific Comments:

Comment 1. Since all of the outcome measures are based on patient self-report, it would be helpful to include the questionnaires used to elicit the answers in the supplemental material.

Response: The questionnaire has been translated and is included as supplemental material.

Comment 2. Please explain the rationale behind use of self-reported outcomes, particularly for the secondary outcomes of infection, dehiscence, and need for suture removal, which should be available in medical record data.

Response: In the Netherlands, after delivery, patients who return home have their post partum check-ups mostly performed by community midwives. These are organized in private practices that do not work under supervision of the gynecologist and do not share their medical files with the hospital. Only in case of medical complications patients are referred to the gynecologist. With patients coming from a dozen different community midwifery practices maintaining uniformity in records was impossible to achieve. Apart from this the primary outcomes and many secondary outcomes are by definition self-reported and lead us to believe that an additional check-up in the hospital for the purpose of the trial would not be appropriate.

Comment 3. The repair technique is well-described, and the use of a standardized repair protocol is a strength of this study, however, the protocol involves use of Vicryl Rapide™ for a significant portion of the episiotomy repair in both groups. Was this a consideration in the development of this repair protocol? If suture hydrolysis contributes to pain, the inclusion of this suture type in both study arms may have obscured the findings.

Response: In fact Vicryl 2-0 and Vicryl 0 were used for the repair of the vaginal wall and perineal muscles respectively in both groups, no Vicryl Rapide™. Prior to the trial these were used as standard materials in our hospital. There was discussion on the material for closure of the skin lead to the decision to perform the RCT. It could be argued that in the Monocryl® group all sutures should have been made with Monocryl®. This would however lead to other problems in the interpretation of the results. Differences in pain could in that case be attributed to skin or deeper layers. We wanted to look specifically at the skin sutures.
As already stated in response to a comment made by reviewer 1 in retrospect it is indeed regrettable we did not use only Monocryl® in one group and Vicryl Rapide™ in the other. There is however some hesitance towards using Vicryl Rapide™ for the deeper layers.

Abstract:

Comment 1. The conclusions reported in the abstract merely restate the results section. Please modify to report the conclusions drawn from these results.

Response: A just critique. The conclusion has been modified. ("Use of Monocryl ...... episiotomies”, lines 42-46)

Background:

Comment 1: Lines 89-92: this paragraph, which describes the properties of Vicryl Rapide™, should include a citation.

Response: A report by Katz et al. dealing with the microscopic events around suture material in vivo was cited.

Comment 2: Line 84-85: this sentence, beginning with 'Both materials are frequently…' appears out of place. It would be more appropriate to precede line 86 where the authors begin their discussion of the individual properties of the 2 sutures.

Response: The suggested change in order has been made.

Comment 3. Lines 80-82: Would recommend rewording. "Until now, few studies..." This wording suggests that more studies are about to released when in fact 1 study is be added to the literature. Maybe, "To date, few... [15]. I would combine the 2 sentences. "To date, few RCTs comparing Monocryl® and Vicryl R have been performed and no trials have looked specifically at use of both of these materials for skin closure in episiotomies [15]."

Response: The suggested changes were performed
Methods:

Comment 1: Lines 101-103: These 2 sentences sound more like results than methods. Consider phrasing like, "On average, this centre provides care for almost 2000 medium and high-risk deliveries per year." AND "The population attending this hospital is known to have/typically of a wide socioeconomical and ethnical range."

Response: The proposed changes have been made

Comment 2. Lines 107-108: This is a result and should be presented there not in the Methods.

Response: This sentence has been moved to the results section. (“over the research….47%”, line 159-160)

Comment 3. Line 109: This is a Result and should be listed in the Results section, not in the Methods.

Response: The number of women has been moved to the Results section. (two-hundred-and-fifty women were randomized”, line 161)

Comment 4. Lines 113-121: Great that Inclusion and Exclusion criteria are listed however format is odd. I would use prose and say "Inclusion criteria were defined as…” or "Our study inclusion criteria were defined as…” instead of. "Inclusion criteria:….". Otherwise, place them in a table if you want to list them.

Response: The wording used is indeed somewhat oddly chosen. This section has been re-written where appropriate (“Inclusion criteria were…..exclusion criterion”, lines 113-121)

Comment 5. Please explain why a 1-point difference on the VAS was chosen as the significant difference. Has a 1-point difference in perineal pain been shown to be clinically significant? Is there a minimally important difference (MID) for this measure for perineal pain?

Response: The decision to aim for a 1 cm difference is indeed a somewhat arbitrary one. (for clarity we changed “1 point” into “1 cm” in the methods section)
We based our estimation on the difference in VAS used in the existing previous literature. Kokanali et al aimed at finding a difference of 5mm, Morano et al did their power analysis based on a 15 mm difference. Others did not use VAS as their primary outcome and aimed at finding a difference in % of women reporting pain. (Kettle et al 2002, Leroux 2006 and Mahomed 1989). Dencker et al measured their outcomes only at 8-12 weeks

To our knowledge no Minimal clinically important difference has been proposed specifically for perineal pain in the literature.

Previous trials suggested an MID for pain scores in 350 patients on the emergency room at 1.4 on a 11 point NRS scale (Kendrick et al, Am J Emerg Med. 2005 Nov;23(7):828-32. The minimum clinically significant difference in patient-assigned numeric scores for pain.)

And in 224 postoperative patients a MID for the VAS was given at 9,9 mm (P. S. Myles et al. Br J Anaesth 2017. Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state)

Results:

Comment 1. Table 2: No need to include the 'Non-Caucasian' line as this represents all participants not included in the line above. It does not add information to the table beyond what is already presented. If kept in table, please add p-value.

Response: The Non-Caucasian section was removed in both tables 1. and 2.

Comment 2. Line 199-201: results presented in the abstract (line 42), discussion, and Table 4 show less skin dehiscence with Monocryl® compared to Vicryl Rapide™, however this line says the opposite. Please correct.

Response: A very just critique. It has been corrected

Comment 3. Please clarify 'analgesic use'. Is this patients using any analgesia or a certain threshold amount?

Response: In order to facilitate statistical analysis a decision was made to ask this question in a binary fashion. In the questionnaires a question was asked: “did you use any analgesia in the past 24 hours?” Therefore there was no threshold value.
Comment 4. Lines 214-216: the first two sentences in this paragraph essentially say the same thing. The first sentence could be removed without losing any meaning.

Response: The difference found in dehiscence and the difference found in number of ventouse deliveries could easily lead the reader to think that there the one could be caused by the other. In order to make clear that this line of thought is incorrect we think it is good to stress that this is not the case and give an explanation as to how we came to this conclusion. The sentence has been re-written. (“Women who delivered….delivery”, lines 214-216)

Comment 5. Line 199-201 and 214-216: You describe dehiscence as a result but this was not described/defined in the Methods section as variable to be collected nor how it was going to be collected.

Response: All outcomes were self-reported through the use of the questionnaires. This adjustment has been made in the Methods section. (“All the secondary…questionnaires”, line 137-138)

Discussion:

Comment 1: Line 354: the report that pain scores did not correlate with analgesic use is an interesting finding, but it was not presented in the results section. This should be presented in the results section with the appropriate correlation coefficient prior to discussion within the limitations.

Response: A correlation coefficient was calculated for the correlation between pain while sitting after 24 hours and analgesia use. The correlation coefficient was 0.1041 which technically is a positive correlation but very weak.

The same was done for pain in sitting position after 10 days and analgesia use. Although the correlation was a little stronger, at 0.2237 it was still weak. (“Analgesia use and…… analgesia”, lines 239-244)

Comment 2: Line 369-372: while the finding of increased self-reported dehiscence in the Vicryl Rapide™ group is an interesting one, it should be presented in the context of the limitations of the measurement. This sentence seems to overstate the finding in the study, which is subject to significant recall bias given the self-reported nature of the outcome.
Response: It is indeed true that the clinical significance of the self-reported dehiscence remains to be determined. This statement has been added to the conclusion. (“It has to be determined”, lines 370-372)

Because of a lack of differences favouring Vicryl Rapide™ however a suggestion was made that Monocryl® might be slightly favourable over Vicryl Rapide™ when a decision has to be made about the suture material.

In addition to the responses to the comments of the reviewers we found that not all references had the label “Validated” attached to it in the editorial manager program. It was unclear to us whether any action had to be taken by us. Please let us know if this is the case.

We hope we addressed all comments of the reviewers appropriately and think we have improved the quality of our manuscript. We would like to thank the reviewers who made such a great effort of carefully reading the manuscript and provided such useful feedback.

We hope that it is suitable for publication in your journal in its current form.

We look forward to your response.

Yours Sincerely,

On behalf of the research group,

Roeland Odijk