Author’s response to reviews

Title: Variation in postoperative non-steroidal anti-inflammatory use after colorectal surgery: a database analysis

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Author's response to reviews: see over
Regarding the revised version of the manuscript: “Variation in postoperative analgesic use after colorectal surgery: a prospective database study”

Dear Editor

We wish to thank the reviewers for their thorough revisions and comments and appreciate the opportunity to submit a revised version of the above-mentioned article. In the following sections, each comment made by the referees are followed by our response in italic. In the submitted revised article, changes are highlighted in yellow.

We wish to point out that referee 1 (Girish Joshi) has conflicts of interests reviewing this paper. Dr. Joshi is the first author of reference no. 10 in the paper, which we criticize for the recommendation of COX-2 specific NSAIDs for postoperative analgesia after colorectal surgery as this may lead to an increased risk of anastomotic leakage.

**Referee 1:**

Remark 1:

TITLE: Please modify the title to “Variation in postoperative non-steroidal anti-inflammatory use after colorectal surgery: a database analysis”. Please note that this is not a prospective study and including the word prospective in the title is misleading. Also, instead of using analgesic, it is better to use specific term – that is NSAIDs.

*This is a good point raised by the referee. We have changed the title as proposed.*

Remark 2:

ABSTRACT: In the results section, please provide the number of patients included in the analysis as well as the values for the variables.

*Again a good point made by the referee. The requested numbers have been provided.*
Remark 3:
ABSTRACT: In the conclusions section, please briefly include other potential reasons for the variation that are mentioned in the discussion section of the paper – lack of compliance to guidelines, concerns of potential side effects etc.
A good point again. This has been added to the conclusion of the abstract.

Remark 4:
INTRODUCTION SECTION: What was the hypothesis of this study?
The hypothesis of the study has been described in the last sentence of the first paragraph, which states the following: “whether NSAIDs are prescribed and actually taken by the patients as part of a multimodal post-operative analgesic regimen has not been evaluated for colorectal surgery and it remains unclear whether consensus exists between departments regarding this treatment”. We believe this describes the hypothesis. If this is not satisfactory, we are of course willing to change the wording.

Remark 5:
METHODS SECTION: Please provide us with the guidelines from the 6 departments. It is necessary for us to know if there was any similarity in guidelines from these places. The amount of space used up in the discussion section on lack of compliance with guidelines requires this information.
An excellent point raised by the reviewer. We have contacted the departments to obtain information on the guidelines, but unfortunately without success. Most departments have not responded to our request. The rest have changed the guidelines after the investigated period and do not have the information on the previous guidelines. So unfortunately, we are unable to provide this information.

Remark 6:
The doses of ibuprofen and diclofenac appear to be inappropriate.
Recommended ibuprofen dose is 800 mg three times a day NOT 800 mg/day and diclofenac should be 50 mg twice a day not 50 mg/day.
We agree with the reviewer that the doses appear inappropriate, but they were not based on the recommended daily doses. The chosen doses were arbitrary and based on our assumptions of which doses would pose a risk for anastomotic leakage in the patients. Moreover, the data were entered into the database as dichotomous values when we visited
the individual departments, based on whether the dose was exceeded or not. Therefore, unfortunately it is not possible for us to change the cut-off values for these doses, because this would necessitate full collection of raw data from all six departments again.

Remark 7:
Please change p.n. to p.r.n. throughout the document. This has been changed throughout the document.

Remark 8:
RESULTS SECTION:
Tables 2 and 3 should include the number of patients from each department. We must know the spread of patients for completion. Figures 3 and 4 should be deleted and the information should be included in the tables 2 and 3. There is no point separating this information.
We see the referees point and have included the information in the tables. However, the information from former figure 4 cannot be included in the tables, as it is not divided into NSAID type. Therefore, figure 4 has been left unchanged and is now named figure 3.

Remark 9:
DISCUSSION SECTION: This section needs to be focused and address the findings from this study rather than discuss irrelevant issues. As you will see from the statements below, the discussion section is confusing and contradictory at times. Some major inappropriate statements are made in this section such as stating that diclofenac is a COX-2 selective drug. Obviously, the discussion that follows this statement is completely flawed, as diclofenac is a non-specific traditional NSAID not a COX-2 selective drug.
There is debate whether diclofenac can be categorized as a COX-2 selective drug. One study found that diclofenac has a COX-1/COX-2 ratio comparable to that of celecoxib (Patrono C et al.. Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. J Clin Invest 2001;108:7–13.). However, another study claims that diclofenac is a non-selective NSAID (Gorrissen et al. Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. Br J Surg. 2012 May;99(5):721-7.). To avoid any confusion, we have avoided referring to diclofenac as having a specific COX affinity and have instead just used the name of the drug in the text.
Remark 10:
Also, the authors are confusing the data on efficacy of NSAIDs with concerns of potential side effects. There is no question that NSAIDs have excellent analgesic efficacy and reduce opioid requirements. However, some people choose not to use these drugs due to their concerns of potential side effects such as cardiovascular and renal effects or the effects on anastomotic leaks. Obviously, the procedure specific guidelines recommend the use of these drugs due to their efficacy and clearly state that potential adverse effects should be considered. Thus, several statements made by the authors are misleading. Unfortunately, the authors are using this study with limited clinical relevance to criticize the published guidelines.

*We did not wish to indicate that the published guidelines do not recognize the potential adverse effects of NSAIDs. This has been moderated in the text.*

Remark 11:
Obviously, the only finding from this study is that there is significant variation in the use of NSAIDs between different departments in Eastern Denmark. It is good to discuss the possible reasons for these variations, which could include inadequate guidelines, lack of compliance with guidelines (then provide possible reasons for lack of compliance such as concerns of potential side effects).

However, the authors have speculated too much and over interpreted the minimal information we have from this study.

*We respect the view of the referee and we have revised and moderated the text accordingly.*

Remark 12:
The fact that the authors have spent significant amount of space on conflicting guidelines, it is necessary that they provide us with the information on these guidelines from the various departments.

We need to know if all the departments propose use of NSAIDs? What were doses of NSAIDs and their duration of use recommended in these guidelines?
This is critical given that the authors have criticized recently published guidelines.

*Please see the answer to remark 5.*
Remark 13:
I am concerned that the authors have used specific references to make their point regarding the adverse effects of NSAIDs, although several Cochrane reviews and other reviews have been unable to find significant side effects with NSAIDs when used for a few days in the postoperative period. The authors have confused concerns with long-term use of these drugs with short-term use. Unfortunately, a biased discussion, and I do not understand how this extensive discussion is relevant to this study.

We respect the referee’s opinion, but unfortunately, we do not agree on this point. We believe, as sited in the paper, that there is good evidence for adverse effects (increased risk of anastomotic leakage) even with a few days of diclofenac use (Klein M, Gogenur I, Rosenberg J: Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. BMJ 2012, 345:e6166.).

Remark 14:
The authors have made some contradictory statements, which cast some doubts on their discussion. For example, “Even though each department in the study had local guidelines…” is contradictory to the statement “In Denmark, pre-specified analgesic regimens may be available…” Thus, my question is are they available or are they “may be” available.

We do not believe that these statements are contradictory. The first sentence refers to the 6 departments included in the study, whereas the second sentence refers to guidelines in general in Denmark.

Referee 2:
Remark 1:
Unfortunately, we are not told if the overall prescription rate was in agreement with the rate of pre-existing contra-indications and if the case mix cannot explain the difference (this is an unlikely explanation but which should be formally eliminated). The authors also do not report on patients who were users of NSAIDs preoperatively and if this rate was similar in all Departments.

This is a good point raised by the referee. Unfortunately, we do not have information on neither pre-existing contraindication or preoperative NSAID users. However, the recorded
data was on the postoperative analgesia prescribed by the departments and the regular NSAID use in the patients is not considered to interfere with these results, as this treatment normally is paused in relation to surgery.

Remark 2:
On one hand, anesthesiologists are generally willing to prescribe this class of drugs to improve multimodal analgesia and obtain a morphine sparing effect. This efficacy has been confirmed in small randomized trials in colorectal surgery (see for example Chen JY et al, 2009) which cannot evaluate the rate of side effects, especially those with a low incidence. On the other hand, surgeons generally emphasize the risk of anastomotic leakage and are prone to avoid using NSAIDs. This discrepancy and the general picture are not well described in the Introduction section in which the reader cannot really understand why such an audit would be useful.

This is a very good point raised by the referee. A statement about this has been added to the introduction section of the paper.

Remark 3:
The avoidance of Cox-2 inhibitors, well described in the Discussion section, would be a nice solution which should allow to find a reasonable medium position if confirmed because it is still possible that non-selective NSAIDs may also be associated with anastomotic leakage (Gorissen KJ et al, Br J Surg 2012). This should be mentioned in the text.

Excellent suggestions. A statement about that includes the reference, has been added to the discussion section.

Remark 4:
Another significant problem is the statement that doses are insufficient or not. There is not a single reference to support the statement that ibuprofen daily dosage should be 800 mg or more. As well, there is no mention of what should be the minimal daily dose for diclofenac. This is not an easy task as the reviewer is not aware of well performed dose-response studies in postoperative patients with these two drugs. A plateau effect should be seen with NSAIDS after acute administration as shown for with ketorolac for example. Unfortunately, very few
drugs have been studied similarly. This also suggests that the question that should be asked is not necessarily if the drug has been used in “sufficient” dosage” but rather if the drug has been used at the minimum dose. Storm et al for example have shown that if ketorolac is used at low doses (i.e. corresponding at the plateau effect), gastrointestinal hemorrhage or renal failure does not occur. The authors should modify their manuscript by showing what are the doses that produce the plateau with either ibuprofen or diclofenac and using these doses as threshold for good or poor practice. For example, with the new formulation of intravenous diclofenac (Dyloject®), the clinical efficacy was similar with 37.5 and 75 mg and possibly also similar with 18.75 mg. With intravenous ibuprofen, 800 mg every 6 hours produces a significant morphine effect which is not observed with 400 mg every 6 hours (Southworth S et al et al, 2009).

This is a good point raised by the reviewer. However, as described in the answer to remark 6/referee 1, we do not have the possibility to alter these definitions now as they where used for the data collection. Thus, the raw data for the doses is not available in the database. We have changed the term “sufficient” to “a pre-defined dosage as a minimum” throughout the paper to avoid confusion.

Remark 5:
The authors do not describe the duration of NSAIDs use. This is unfortunate as the duration ay be important for both the occurrence of gastrointestinal and renal side effects (Strom L et al, 1996 & 1997) and the risk of anastomotic leakage (Gorissen KJ et al, Br J Surg 2012).

We agree that the duration is important. However, as stated in the former answer, we did not record the specific details on this. We only recorded whether or not the patients received the pre-defined dosage for two days or more. In a simple way, this represents the duration of the use.

Remark 6:
The authors state that their review will permit to evaluate the doses prescribed and those received. In fact, if the reviewer is right, only prescribed doses can be analyzed here. The manuscript should be modified accordingly.

We think this is misunderstood. The strength of this study (and electronic prescription system) is that we have only recorded the NSAIDs actually received by the patients.
Therefore, the drugs prescribed but not received by the patients, which are less relevant, can be left out.

Remark 7:
An additional problem is the fact that they studied only 6 departments whereas their database could have led to a national audit. Why limiting the study to a portion of Danish practice?

*Good point. However, it was a practical issue that limited the study. To collect the data, we had to be in the specific hospital physically, as the computer systems of the different hospitals cannot exchange data. It would be practically impossible for us to collect data on every hospital in Denmark, so we narrowed it down to the six important centers in Eastern Denmark.*

Remark 8:
Finally, because of apparent technical problems, the list of references is largely incomplete. As well, Figures cannot be read as legends are lacking. It is thus impossible for the reviewer to address any question associated with these Figures.

*We are sorry about that. This must be due to a technical issue as both items should be complete in the submitted manuscript.*

**Referee 3:**

Remark 1:
The abbreviation for medication as required is usually PRN (from 'pro re nata') not p.n. - please correct!

*This has been corrected throughout the document.*

Remark 2:
It is difficult to understand why it is claimed that in Dept 1 the dose of NSAID was insufficient, when the median dose described in Table 2 for ibuprofen is identical to most other departments with 1200 mg and for diclofenac in Table 3 is actually the highest reported with 150 mg?

*Good point raised by the reviewer. This is because the “insufficient” dose was defined both by daily dose and duration (two days or more) and the dose alone reflects the daily dose. As*
described under the answer to remark 4/referee 2, the term insufficient is misleading and has been changed in the text to clarify the meaning.

Remark 3:
Was the calculation on sufficient dosage for Fig 2 based only on the regular or on the sum of regular and PRN doses?

It was based on the total mg drug taken by the patient regardless the drug was prescribed as p.r.n. or regular doses. Thus, we measured the sum of p.r.n. and regular doses taken by the patient and not the prescribed doses.

Remark 4:
In the discussion, there is a some confusion on the use of the term COX-2 selective NSAID, which is used specifically for diclofenac. This is in line with a number of other publications in the surgical arena, which are specifically describing diclofenac, but are not naming the drug, but describe it as a COX-selective NSAID. While there is a certain COX-selectivity in diclofenac in vitro, most pharmacologists would only regard celecoxib, parecoxib and etoricoxib as clinically relevant COX-2 inhibitors. Therefore it might be more appropriate and less confusing to state that for diclofenac there has been a possibly increased risk of anastomotic leakage described; and even this is under debate, when you look at the letters to the editor of the BMJ in response to reference 8.

We agree with the referee that there is some disagreement in the literature regards diclofenac. As suggested, we have avoided stating the COX specificity of diclofenac and instead referred directly to the name of the drug when describing the studies. See also remark 9/referee 1.

Remark 5:
This confusion becomes even more obvious, in the sentence on stroke, vascular events and death, where again high COX-2 affinity has been linked by the authors to increased risk. the data currently suggest that this is true for diclofenac, but not for celecoxib and parecoxib.

We agree with the reviewer that this may be confusing and have therefore deleted it in the text.
Remark 6:
Therefore this part needs to be more focussed on diclofenac specifically and in particular the conclusion should not suggest that 'COX-2 selective NSAIDs should not be used', but that diclofenac should not be used!
*We agree with the referee. The specific section of the discussion has been rephrased.*

Remark 7:
The design of the figures is unusual - why not use in Figures 1,2 and 4 only one bar and the height shows the use instead of the confusing YES and NO colours. Similarly in Fig 3 it would be much more intuitive to use 2 bars per centre - one for diclofenac, one for ibuprofen use!
*Again we agree with the referee. The suggested alteration have been made. However, according to remark 8/referee 1, figure 3 has been removed. If the editor prefers, we can make the changes as referee 3 suggests instead.*

Once again, thank you for giving us the opportunity to submit a revised manuscript. We hope these clarifications and alterations are satisfactory and that the revised manuscript can be considered for publication in BMC Anesthesiology.

Sincerely yours,
Hans-Christian Pommergaard