Author's response to reviews

Title: Bleeding and first-year mortality following hip fracture surgery and preoperative use of low-dose acetylsalicylic acid: an observational cohort study

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To the Editor of BMC Musculoskeletal Disorders

MS: 1971338937556477  Bleeding and first-year mortality following hip fracture surgery and preoperative use of low-dose acetylsalicylic acid: an observational cohort study

Response to Reviewers:

We thank Drs Lee and Miller for their thorough reviews and helpful comments. Added or changed text is highlighted in the revised manuscript. All concerns raised by the reviewers have been addressed as clarified below and the manuscript revised accordingly.

Reviewer John Lee

Even with the original trial explained in detail elsewhere, please indicate which patients received compression bandages in the methods section of the report.

Q. Did all patients analyzed have compression bandages?
A: We have added data about the proportion of compression versus non-compression patients in each group (Table 1). As requested we have clarified that the patients in the trial were randomly assigned to the compression group or the non-compression group (P 5, first paragraph).

Q. Was this study’s analysis done on both arms of the original trial?
A. Patients in both arms of the original trial were combined for this study; we have clarified this (P5, first paragraph).

Q. Briefly mention in the methods and also note in the discussion whether it was believed that the bandages had or did not have any bearing on the results of this report.
A. We have mentioned this in the Methods section (P 5, first paragraph). We have also stated that adding whether the patients had compression or not as a covariate in the models did not change the results (P8, last paragraph). As requested the issue is also commented on under Discussion (P 15, second paragraph).

Reviewer Anna Miller:

Major Compulsory Revisions:

1) Authors should explain what happened to the 222 patients not included in the study cohort (p. 8, Results, Paragraph 1).

A. The orthopaedic surgeon on duty at the Emergency Department was responsible for assessing eligibility and recruiting patients for the trial. These 222 patients were not assessed for eligibility for participation in the trial for one of several possible reasons: a few surgeons were probably not aware of the trial, patients were in fact assessed to be ineligible but the surgeon failed to document this, the patient was transported to the Orthopaedic Department without seeing the surgeon at admission due to other commitments (e.g. major trauma call), or the surgeon was unwilling to recruit patients because of the extra work involved. We do not know the exact reason in each case, but we have added a brief comparison of the characteristics of these patients with those assessed for eligibility (P 9, first paragraph) and commented on this issue (P15, second paragraph).
The patients not assessed for eligibility were treated and followed up according to routine clinical care at the department (http://www.skane.se/Public/Hassleholm/nya%20hässleholm/broschyrer/Vårdprogram%20för%20patienter%20med%20höftfraktur.pdf). We agree that it would have been ideal if all eligible patients had been enrolled and accepted participation in the trial but unfortunately this is rare in clinical trials. However, since we have described the exact inclusion criteria for the trial we believe the patients in this study are representative of patients fulfilling these criteria.

2) With the increased blood loss in an intertrochanteric (extracapsular) vs. subcapital (intracapsular) hip fracture, authors should further delineate differences in these two subgroups and whether they influenced the findings of this study as they have in others (see their own Reference #10)

A. As stated in the manuscript non-displaced subcapital (intracapsular) fractures planned for pinning were not included in the trial because they seldom require blood transfusion (P 5, first paragraph) and they are thus not part of the present study. However, displaced subcapital fractures treated with hemiarthroplasty were included as they usually require blood transfusion because of bleeding in association with the surgery (P 5, first paragraph). Additionally, we have adjusted for type of surgery and type of fracture in all analyses with no influence on the results (P 15, third paragraph).

3) Examination of M vs. F patients, since their own discussion states that women often have higher acetylsalicylic acid blood concentrations than men.

A. This is an interesting question and we thank Dr. Miller for raising the issue of potential gender differences with regard to the effect of LdAA. In all our previous analyses gender was adjusted for as a covariate (Tables 2 and 3). As shown in Table 3, gender was not a significant factor for 1-year mortality in the Cox regression (adjusted for LdAA use). In the revised manuscript, we have also added crude mortality data for women and men grouped according to LdAA use (P 10, second paragraph) as well as repeating the Cox regression analysis adding an interaction term between gender and preoperative LdAA use (P 10, first and second paragraph). The results of this analysis have been added (P 10, first and second paragraph) and commented on (P 12, first paragraph). In summary, the sex-specific hazard ratio of preoperative LdAA use on 1-year mortality was higher in men than in women but it was not statistically significant which means that the effect of LdAA on mortality did not differ significantly between men and women. We have commented that the question may need to be addressed in a larger study.

4) Do they have any explanation for why the preoperative ASA patients had more thromboembolic events? If they had the same postoperative regimen, the same types of fractures, and a statistically significantly higher aPTT and INR preoperatively, this doesn’t seem to make sense. In addition, any explanation for why these patients had a “significantly” higher aPTT and INR (although from the Table, it appears that the numeric differences are actually quite small), since ASA is metabolized through the kidneys and doesn’t affect aPTT or INR?
A. We agree with Dr Miller that this finding seems surprising. We do not have an apparent explanation as to why the ASA patients had higher thromboembolic events and we have added this comment to the Discussion (P 14, second paragraph). We agree that although the higher INR and aPTT values preoperatively were statistically significant the numerical differences were relatively small and the clinical relevance is uncertain and, as noted, theses values are usually not affected by ASA; we have commented on this in the Discussion (P 14, second paragraph). With regard to metabolism, ASA ingested per os is absorbed and metabolized in the liver mainly with glycine conjugation and hydroxylation, the so-called first-pass effect, and the metabolic products are thereafter excreted by the kidneys.

5) Is it possible for them to do any further characterization of the ASA dosages? Clearly 75-320 mg is a large span, and, in their discussion, they mention that “most side effects of acetylsalicylic acid are dose-related,” so perhaps they should further break down the cohort and assess whether more of these complications were in the higher “low dose” population.

A. There is no strict consensus in the literature defining ASA dosages, but up to around 300 mg daily is usually considered as low-dose. However, we agree with Dr Miller that this might be of importance and have therefore added 1-year mortality data for the patients who had ≤75 mg (n=69) and those who had ≥150 mg (n=49) (P 10, first paragraph) and included a comment in Discussion (P11, third paragraph).

6) Authors should include reference to and discussion of the following relevant article and how their article adds differently to the literature, as their conclusions are in stark contrast: “Manning BJ, et al. The effect of aspirin on blood loss and transfusion requirements in patients with femoral neck fractures. Injury. 2004 Feb; 35(2): 121-4.”

A. This reference has been added to the revised manuscript and commented on (P 14, third paragraph). In fact, the study by Manning et al. found that patients on aspirin were significantly more likely to have postoperative blood transfusion (p<0.05) which is similar to our finding, although they did not find a significant difference in perioperative blood loss (we did not find a significant difference in intraoperative blood loss either). That study was relatively small with the analysis including only 24 patients in the aspirin group as compared to 118 in our study.

7) The authors should discuss why they believe that the increased post-operative mortality is due to pre-operative ASA use, as opposed to the significantly increased numbers of patients with HTN, cerebrovascular, and cardiovascular disease in the pre-operative ASA group.

A. These comorbidities were adjusted for in the Cox regression analysis which showed a significant independent effect of preoperative use of ASA on 1-year mortality. We have discussed the possible explanations although the exact reason is not known (P 15, third paragraph).

2011-10-15 Annika Kragh