Author's response to reviews

Title: Does using a femoral nerve block for total knee replacement decrease postoperative delirium?

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Author's response to reviews: see over
Authors thanks referees for the constructive comments. In this revision, we added 14 more patients thereby increasing the sample size to a total of 85 patients. With this increase in sample size, we found that the rate of postoperative delirium was significantly lower in the femoral nerve block group when compared with the PCA group.

Referee 1.
First, the assignment to the groups was not randomized. This led to an imbalance with three times more patients in the “PCA only” group. This imbalance accentuates the problem of insufficient statistical power. 
The original paper included the patients enrolled from 2001 to 2006. In this revision, we included an additional 14 patients who were studied from 2007 to 2011 for analysis. The PCA only group now has 54 subjects and femoral nerve block group has 31 patients, total of 85 patients.

Minor essential revision 1: Even though this was not a randomized trial, I think it would be important to know how many patients were screened for inclusion, how many completed the trial and what were the reasons for not completing the study.
This is a prospective nested cohort study. The total number of patients who underwent noncardiac surgery was 674. 85 patients met our inclusion criteria for this study. Overall, 14 patients had incomplete preoperative TICS score or postoperative delirium assessment due to patients’ refusal or medical condition. We included this additional information in the revised results section.

Were there any catheter complications such as dislocations? Was there any scheduled sensory testing to ensure proper functioning of the catheter, was the analysis based on the intention to treat?
No catheter related complications were noted. The anesthesia team performed sensory and motor testing of femoral nerve block right before surgery. We included this information in the methods and results section.

Second, there was no effect of the femoral catheter on opioid consumption. The differences in pain scores between the two groups were small and statistically not significant. Hence, pain management was not more efficient with the femoral catheter in this group of patients which makes interpretation of the data and testing the authors’ hypothesis very difficult. The authors address this issue with a multivariate logistic regression. However, missing data (only 63 of 71 patients were included; why only 63, according to Table 1 TICS scores are available for 64 patients?), and the small number of risk factors included in the model (again in part due to the small study size) limit the conclusions that can be drawn from this analysis.
Results of this study should be considered as pilot because of the overall small sample size. In the new analysis, there was a trend for improved pain levels on postoperative day one in the femoral nerve block group compared to the PCA group (Change in pain levels 0.9 ± 3.2 vs. 1.9 ± 3.7, P= 0.20). In addition, there was also a
trend for lower hydromorphone use on postoperative day one in the femoral nerve group when compared with the PCA group (4.3 ± 4.6 mg vs. 5.9±6.1 mg, P=0.24). Therefore, the present results should be considered hypothesis generating rather than hypothesis testing, and should be confirmed by future randomized clinical trial.

Major compulsory revision 1: Please check the number of patients included in the multivariate analysis.
14 patients had incomplete delirium assessment or TICS score.
It includes 71 subjects (85-14) in the multivariate analysis.

Minor essential revision 2: I suggest expanding the discussion regarding the lack of effect of the femoral catheter.
In addition to the previous discussion, we also found that patients used less opioids in femoral nerve block group compared to PCA group during surgery. This is likely due to opioid sparing effects of of local anesthetic administered via the femoral nerve catheter. This is direct evidence that the femoral nerve catheter was effective in providing analgesia. However, the duration of bolused local anesthetic can be variable, it may last up to 12-24 hrs. Capdevila et al. (1) reported that the course and location of femoral catheter is often unpredictable, this variability may have affected the result of the block. We included this information in discussion.

Discretionary revision 1: please consider reporting also absolute pain scores (table or preferably figure) in addition to the differences between pre- and postoperatively which you provide.
In addition to the differences between pre-and postoperative pain level, preoperative pain level, and pain level on POD 1 are added to Table 1 and Table 2 respectively.

Third, the two groups differ significantly regarding baseline CNS disease including delirium and dementia. Preexisting cognitive impairment is a key risk factor for the development of delirium which in my view makes this imbalance relevant. The authors acknowledge the insufficient power of their study and suggest that a study of 2x 62 patients would be sufficient to demonstrate or exclude an effect of a femoral catheter on the incidence of delirium. I have some reservations regarding this statement. This calculation is based on the assumption that the observed proportions would again be 58 and 33% in the two groups. In view of the higher rate of CNS disease in the “PCA only” group this difference is in my opinion likely to be lower, hence the suggested sample size is too low. Personally, after looking at these data I would be reluctant to embark on the larger study you propose and perhaps rather investigate an intervention that is more “multimodal”. However, it is up to the readers to make up their mind on this issue.
Discretionary revision 2: Please consider adding this line of thought (multimodal intervention rather than femoral catheter only) to the discussion.
In this revised version, there is no difference between 2 groups regarding baseline CNS diseases.

Referee 2:

The authors examine a subset of data from a prior study to determine if those who received continuous postoperative analgesia via a femoral nerve block AND pca experienced less delirium than those who received PCA only. The working hypothesis is that the opioid-sparing effect of the nerve block would then have a beneficial effect regarding postoperative delirium incidence. Indeed, there is a trend toward a decrease, and group assignment was significant in a logistic regression related to delirium formation. Since postoperative pain is also hypothesized to be contributory to delirium development, it would be preferred if pain levels in the different groups were more easily accessed by the reader. More speculation as to why the groups differed as to delirium incidence should be included since the primary hypothesis of reduced opioid consumption was not observed. Also, the literature contains some estimates as to the amounts of opioid that has been associated with increased rates of delirium. How do the amounts of opioid administered to these patients compare with these earlier studies? Do the amounts used here even come close?

Specific Comments:

Abstract (Results) - It would be useful to see data regarding the hypothesized opioid sparing effect. Did the femoral NB group actually use less opiod? We have included intraoperative opioid usage in the new analysis. Intraoperative opioid usage was less in femoral nerve block group.

In Table 3 it is not possible to know, just from looking at table, whether the odds ratio was in direction of the femoral NB group or the PCA-only group (thought apparent from the text).
Please see the revised Table 3.

In Table 2 it is not possible to readily determine the amount of pain actually experienced by the patients. Only differences with respect to preop are give, and one cannot find preop data in Tables 1 or 2. It would be desirable to see that the levels of preop pain did not differ between groups. Only information on the number taking opioids is given in Table 1. Then, it would be desirable to see the level of postop pain experienced by each group compared. Ideally, it would be done as a very short (two observations) longitudinal analysis, which could be conditioned on the preop pain level.Was it specifically determined whether postop pain and level of level of opioid analgesic therapy influenced delirium? This is
implied in the use of variable with p<0.2, but since pain and opioid consumption are linked to delirium, it would be nice to see it mentioned explicitly here. 

Preoperative and postoperative pain levels are added to the tables.

In the Discussion in the section describing evidence-based preventive therapy, the authors neglect to site recent work by Sieber et al Mayo Clinic Proc 85:18-25, 2010.

We thank for the suggestion. We have added this article in the discussion.

Figure 1 could just as easily been one line in Table 2.

We have eliminated Figure 1 and the result has added in Table 2.