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Response to Hubers and Wuetrhichs Letter to the Editor: Importance of accounting for repeated measure designs when evaluating treatment effects at multiple postoperative days

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Editor,

We thank Huber M. and Wuetrhich P. (1) for their interest in our study (2) and we are happy to respond to their concerns.

Patients in our study reported pain at rest and movement after ambulatory arthroscopic shoulder surgery in the group treated with metamizole, ibuprofen, and paracetamol (MIP) or in the group treated with ibuprofen and paracetamol, which was indeed evaluated at multiple time points i.e. the PACU and on postoperative days (POD) 1-4, 7, 14, 28 and 3 months after the surgery.

We acknowledge the fact that the original analyses did not take into account the repeated measures and the longitudinal nature of the data.

To address this issue, we have reanalyzed the data using a marginal mixed model for repeated measures (MMRM). This model incorporates treatment group, timepoint, and a treatment-by-timepoint interaction as fixed effects, with timepoint treated as a categorical variable. This approach allows us to model unstructured group-specific trends over time. We employed an unstructured variance-covariance matrix to account for the correlation between repeated measurements on the same patient. The assumptions of the model were assessed through residual and QQ plots, confirming that the model fits were satisfactory.

Regarding statistical significance and methods of inference, we utilized the MMRM to estimate the least square mean differences between the Metamizole and Control group at each time point, accompanied by 95% confidence intervals and two-sided p-values for evaluating the null hypothesis of no treatment effect (Table 1).

The primary outcome of this trial was the difference in pain scores at movement measured by an 11-point NRS (where 0=no pain and 10= worst imaginable pain) on POD1 between both groups. In the article, the following result was reported: mean difference (95%CI): -0.08 (-1.00, 0.84). In Table 1, we obtain similar results for POD1 with the MMRM approach. Moreover, we can conclude that there is not enough evidence to rejct the null hypothesis of no difference in pain score at movement between the Metamizole and Controle group.

Furthermore, the least square means (LSmeans) obtained for the MMRM are calculated per time and group and are displayed in figure 1a, which is similar to the figure reported in the original article. However, in figure 1b, the response profiles per patient are added as requested by the rebuttal. We agree that including the patient trajectories over time in the corresponding figures are important to

assess the evaluation of pain at movement over time between and within patients. However, Figure 1b shows a high variability within and between individual patients, rendering it difficult to distinguish one patient's trajectory from another's.

The evaluation of the pain score at movement over time was checked in the MMRM. It is observed that the treatment-by-timepoint interaction was not significant at a 5% significance level (p= 0.62).Therefore, as a sensitivity analysis, we also estimated the treatment difference using a MMRM that included only the treatment group and timepoint as fixed effects. This model assumes a treatment effect that is constant throughout the study. This treatment effect was also not statistically significant at a 5% significance level (p=0.29).

The same MMRM, as described above, was used to analyse pain scores at rest in the Metamizole and Control group at PACU and on postoperative days (POD) 1-4, 7, 14, 28 and 3 months after the surgery. Similar results were obtained as reported in the original manuscript, i.e no statistically significant differences in the LSmeans were found between both groups.

To conclude, in a randomized controlled superiority trial with a repeated measures design, the correct model for analyses of the data should be used as suggested by Huber M. and Wuetrhich P. Here, a re-analysis of our data using a marginal mixed model for repeated measures (MMRM) was applied, which resulted in similar uncertainty estimates of the treatment effect, concluding no fundamental differences to the original manuscript.

References

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