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Authors' reply to the comment by Shan etc. al.

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Dear Editor

We would like to thank Dr. Jjang et al. for raising these questions regarding our recently published work and would like to provide clarification.(Beilstein et al., 2022)(Comment Ref)

First question (primary endpoint): Assuming that baseline QoR-15 values in all groups are comparable (which in fact was the case, see table 2), it is from minor relevance if one compares absolute values or differences to baseline.(Beilstein et al., 2022) In fact, the latter has the advantage of eliminating variation in baseline values. The drop in QoR-15 scores after surgery (respectively the increase during recovery) are relevant to the patient and the treating team – and not only the absolutes values, which might be flawed by the patients' individual perception of his quality of life.

The minimal clinically important difference in QoR-15 is nowadays believed to be as small as 6.(Myles, 2021) This is already stated in the manuscript. At the time of study design (2017/2018), this was much less clear, and therefore we had decided to choose an even more conservative approach.

Regarding the sample size calculation: As mentioned in the discussion section, size and distribution of QoR-scores were unknown during study planning, so sample size calculation had to be based on previously published studies. We expected both regional techniques to have a clear effect compared to the systemic analgesia (SA), but only limited differences between the two regional techniques. We had set the a priori objective that all pairwise comparisons are of interest. As the difference between transversus abdominis plane block (TAP) and spinal single shot (SSS) would be the most difficult to prove, this difference was initially used for sample size calculation. This approach to the sample size has both advantages and disadvantages: An advantage is that no additional assumptions regarding the magnitude and distribution of the QoR-15 scores in the SA control group had to be made, which would have been uncertain since no prior QoR-15 scores were available at our institution. A disadvantage is that we performed group comparisons (i.e. SSS vs. SA) for which the study was not explicitly powered, and we acknowledge that this is a clear limitation of the study and a simulation study could have been performed for the sample size calculation.

Second question: According to the study protocol, indication for rescue analgesia during surgery was a blood pressure and/or heart rate increase of >20%, after surgery any reported break through pain. This was defined as a value of >3 on a numeric rating scale from 0-10.

The use of rescue analgesia in more than 50% of patients in the first 24 hours is correct, but the use of fentanyl was not different in the three groups (p-value for POD 1 is 0.587 as reported in table 3).

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The use of oxycodone after discharge from intermediate care was not different between groups on POD 1 (SSS, 7.5%, TAP, 13.6%, SA, 8.3%) respectively POD 2 (SSS 10.0%, TAP 15.9%, SA 17.0%)(p-value=0.46 based on a generalised linear mixed-effect model with a binary outcome).

We thank the authors to highlight the importance of using morphine equivalents. We have therefore calculated them according to the conversion factors published by Doleman et al.(Doleman et al., 2018)

	Surgery (only fentanyl)	**6 h** (only fentanyl)	**POD 1**	**POD 2**
ME iv (in mg):				
SSS	50.0 [40.0;56.2]	5.00 [0.00;10.0]	0.00 [0.00;2.88]	0.00 [0.00;0.00]
TAP	50.0 [50.0;60.0]	5.00 [2.50;7.50]	2.50 [0.00;6.25]	0.00 [0.00;0.00]
SA	50.0 [50.0;60.5]	2.50 [0.00;7.50]	0.00 [0.00;1.00]	0.00 [0.00;0.00]
p-value (timepoint-wise)	0.200	0.236	0.013	0.287

Total fentanyl and oxycodone dosage in morphine equivalents. Median and interquartile ranges are shown as summary measures. Group-comparison for each time point are based on the Kruskall-Wallis test. ME, morphine equivalents; POD, postoperative Day; SSS, spinal anaesthesia; TAP, transversus abdominis plane block; SA, systemic analgesia

On POD 1, there is a statistically significant difference, but due to the very low numbers, the data has to interpreted with caution because of zero inflation (many patients did not receive any rescue opioids). As a consequence, the clinical relevance of this statistically significant result is questionable.

This study was not powered to assess a potential reduction in opioid consumption. Therefore, these results can only be seen as hypothesis generating. It remains for example unclear, if and why the use of rescue analgesics seems to be higher in POD 1 in the TAP group (p=0.008), despite the global test being insignificant. In addition, our study does not contain any data about opioid consumption after hospital discharge, so the issue raised by Rajput et al. cannot be addressed based on our data.(Rajput et al., 2022)

Third question: the authors correctly state that QoR-scores on POD 1 are to be classified as medium as defined by Kleif et. al.(Kleif, 2018) Nevertheless, these values are above the values for major surgery as reported by the validation studies for the QoR-15 (92 ± 23 respectively 96 ± 24).(Kleif et al., 2015; Stark et al., 2013). According to the clinical anchors defined by Kleif et. al.(Kleif & Gögenur, 2018), we had chosen and reported QoR-15 at hospital discharge as clinically relevant. But in view of the higher complication rate at 30 days associated with poor QoR-15 scores on POD1, we concede that the optimal analgesic regimen for patients undergoing open or robotic-assisted radical prostatectomy is still to be sought and further research is required.(Kleif & Gögenur, 2018)

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