Letter in Response to the Article: A comparative analysis of the effect of norepinephrine and dobutamine on hepatic blood flow

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To the Editor,

We read with great interest the article by Van Damme et al., "Effects of norepinephrine and dobutamine on portal vein and hepatic arterial flow in patients with pancreatoduodenectomy"[1]. Intraoperative transit-time flowmetry for direct measurement of portal vein and hepatic artery flows has been an important technical advantage of this study. However, we think that interpretation of the obtained findings about DOBU effects versus NOR effects should be done cautiously because of several drawbacks in this methodology[1].

Firstly, the comparison of NOR to DOBU is made using two separate prospectively observed groups, one treated with NOR and the other with DOBU, rather than using a randomized control experiment in which patients would be randomly assigned to one treatment or the other[1]. It makes the research design highly prone to bias and weakens its internal validity. Even though the inclusion criteria and exclusion criteria for both groups was similar, they were still recruited in a consecutive manner, meaning that any difference in perioperative, surgical or anesthetics practices may have been responsible for the differences seen between the two cohorts. Consequently, it means that the results seen in relation to these groups cannot be due to the vasoactive drugs used in the study alone. According to the researchers themselves, the design does not allow causative interpretation of the results[1].

Secondly, baseline disparities and possible confounding factors were not taken into account adequately. The preoperative mean arterial pressure and heart rate were much higher in DOBU group participants, while the total remifentanil dose was noticeably larger in the NOR group participants; the above factors may have considerable impacts on the hemodynamic characteristics of the body and liver[1]. Also, the DOBU study used another exclusion factor, that is, sinus tachycardia, leading to a possible deviation from the physiological population of patients from the NOR group participants. Moreover, somatostatin, a pharmaceutical drug capable of reducing portal flow and changing the hemodynamic response of the liver, was given to patients in both groups, though not considered a confounding factor[1,2]. Under such conditions, mixed effects models including only drug type and dose as fixed factors might be insufficient in controlling for important preoperative and intraoperative differences[1].

Thirdly, there are issues related to multiplicity and validity of the conclusions based on statistical analysis. The systemic parameters, cardiac index, mean arterial pressure, and heart rate as well as liver parameters PVFi, HAFi, and HBFi have been analyzed in relation to three different time intervals of two different medications with significance being defined at $p<0.05$ 1. The adoption of this analysis technique makes it more susceptible to Type I errors, especially considering that the experiment is an exploratory one with a sample size that is not very large[3]. Although linear mixed-effects models with random intercepts were adopted and the assumption of normality confirmed using histograms and Q-Q plots, there were limited discussions on other important issues, such as diagnostic checks for residuals. In addition, there was no a priori calculation of the sample size; rather, post hoc power analysis for hepatic blood flow at T3 was conducted, although it should be noted that post hoc power analysis cannot replace sample size calculation[1].

Fourthly, the way in which the results have been expressed could lead to an unintentional exaggeration of the impact of DOBU. Several portions of the paper highlight the importance of the fact that "the degree of changes induced by DOBU was greater compared to that of NOR for portal venous, hepatic arterial, and total hepatic blood flow," despite the absence of randomization in this study[1]. On the other hand, there is no information provided about liver functions after surgery, complications and other patient outcomes, which makes it difficult to understand whether these physiological changes will have any clinical value or not[1]. It is especially relevant considering the previous research demonstrating that physiological improvement in the splanchnic perfusion variables is not associated with improved

survival or function of the organs of patients with critical illnesses and surgical procedures[4]. We propose that these results be considered descriptive but not evidence-based for one agent compared to the other.

Furthermore, there are several aspects related to the presentation of results that should be explained. Firstly, as per the results described, there were 44 subjects overall, 16 participants involved in the DOBU study, and 28 in the NOR study; however, from Table I, it can be seen that DOBU n=14 and NOR n=28, with even a distribution of male and female patients among DOBU n=16[1]. Secondly, information about measurement procedure used by the authors is missing; specifically, it would be interesting to learn about how many times repeated measures have been done and the level of variation between individual results[1]. Lastly, following certain reporting guidelines for observational comparative studies, such as STROBE statement, will improve this study greatly[5].

In Conclusion, Van Damme et al.'s work should be acknowledged for conducting technically difficult intraoperative measurements to improve knowledge regarding the impact of norepinephrine and dobutamine on the hemodynamics of hepatic blood flow in pancreatoduodenectomy surgery[1]. However, any observed differences between groups must be interpreted with caution considering the design of the nonrandomized pooled cohort study, imbalances at baseline, minimal adjustment for possible confounding variables, numerous unadjusted tests of hypothesis, and no follow-up data on clinical outcome after surgery[1]. We believe that additional evidence obtained from a randomized controlled trial would be necessary prior to recommending one particular inotropic/vasopressor regimen.

References

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doi.org/10.56126/77.3.28