when patients are receiving multimodal treatment; which drug caused the side effect?

The battery of cognitive tests was carefully chosen to assess several different aspects of cognitive function. The Cambridge Neuropsychological Test Automated Battery tests are widely used by the pharmaceutical industry and clinicians to test effects of drugs on cognitive function. So-called "parallel tests" make sure retests are not identical (to avoid learning effects), yet comparable and reliable. We did not find it appropriate to readdress this carefully documented test system. The correlation between the tests was not a topic of interest since they test different aspects of cognitive function, and this was an exploratory analysis. The test battery used was quite extensive; most patients used 40 to 50 min each time, and thus repeated testing was not an option.

Drs. Allen and McEvoy find it questionable that 20% of the patients in the control group not were tested at 24 h due to pain or postoperative nausea and vomiting. We agree that this is a real weakness of our trial, and we have discussed this thoroughly in our article.

Drs. Allen and McEvoy also ask what a fraction of an error on day 3 to 5 really means clinically. Our attention has been on the effects on day 1 when patients took the drug. The tests 3 to 5 days after were done only to document whether day 1 changes had disappeared.

Yes, we speculate that the documented changes induced by pregabalin may affect motor control and may increase the risk of falls. There is extensive literature to document that the influences of motor and sensory impairments on falls are moderated by executive functioning. A number of studies suggest this.[6,7] We must admit we were not prepared on this issue, and did not register falls systematically. However, three patients, all three receiving pregabalin, had registered falls in their electronic patient journals. We did not mention this in our article since it was not a part of our preplanned systematic documentation of side effects.

The value and beauty of our study, and the need for exploratory analyses such as ours, are to aid future researchers to better document the effects of the intervention; first do no harm.[8]

Competing Interests

The authors declare no competing interests.

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References

1. Myhre M, Jacobsen HB, Andersson S, Stubhaug A: Cognitive effects of perioperative pregabalin: Secondary exploratory analysis of a randomized placebo-controlled study. Anesthesiology 2019; 130:63–71
2. Gupta SK, Nayak RP: Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. J Pharmacol Pharmacother 2014; 5:88–92
3. Kharasch ED, Eisenach JC: Wherefore gabapentinoids? Was there rush too soon to judgment? Anesthesiology 2016; 124:10–2
4. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL: Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17:131–57
5. Mishriky BM, Waldron NH, Habib AS: Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. Br J Anaesth 2015; 114:10–31
6. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR: Different cognitive profiles for single compared with recurrent fallers without dementia. Neuropsychology 2009; 23:500–8
7. Rapport LJ, Hanks RA, Millis SR, Deshpande SA: Executive functioning and predictors of falls in the rehabilitation setting. Arch Phys Med Rehabil 1998; 79:629–33
8. Hippocrates, Jones WHS, Potter P, Smith WD: Hippocrates: 2. Cambridge, Massachusetts, Harvard University Press, 1923

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Crystalloid/Colloid Renal and Disability Outcomes: Comment

To the Editor:

The recent article in Anesthesiology compared intraoperative fluid management by crystalloids *versus* colloids.[1] The authors analyzed postoperative sequelae 1 yr

after surgery of the same group of patients whose early postoperative results were reported in a previous publication.[2] Fluid management was based on hemodynamic optimization according to noninvasive cardiac output measurements, and it was provided by a closed-loop system. The study groups were defined by the type of fluids infused by means of a goal-directed fluid therapy strategy that consisted of multiple 100-ml mini-fluid challenges using either a crystalloid solution or a synthetic colloid solution (hydroxyethyl starch).

Eight of the 80 patients in the crystalloid group had anastomotic leakage and five had bleeding that required reoperation in comparison with none of the 80 patients in the colloid group.[2] In addition, the operation took longer in the crystalloid group.

The power analysis that the authors performed was based on changes in Post-Operative Morbidity Survey under the hypothesis that the only difference between treatment groups will be the type of fluid management. However, there could hardly be any argument that a patient's recovery from surgery depends on numerous factors other than fluid management.

A recent review that appeared in Anesthesiology suggests that the effect of various types of fluid management should be evaluated in addition to the complexity of the surgery.[3] In the current study, the authors performed the analysis by intention-to-treat, with which we concur. However, when 16% of patients in one group had significant surgery-related events *versus* 0% of patients in the other group, a different analysis is needed to prevent potentially misleading conclusions of the study findings. Although the authors provided a list of the specific sources of surgical complications that were encountered (*i.e.,* bleeding that required reoperation, anastomotic leakage, peritonitis, and reoperation), the data analysis ascribed all of the postoperative sequelae solely to fluid management. Reoperation attributable to bleeding or anastomotic leakage requires prolonged treatment and could affect kidney function as well as the patients' overall health condition no less than—and possibly more than—the type of fluids given intraoperatively. Moreover, the issue of group differences in surgical risk was not addressed.[3]

The second article analyzes patient wellbeing and renal function 1 yr after the surgery, and the authors used the power analysis of the Post-Operative Morbidity Survey on postoperative day 2 from the first study.[1] The intention to connect long-term recovery to intraoperative fluid management is understandable; however, the underlying medical condition and the type of surgery that the patient underwent a year earlier must also be taken into account.

Competing Interests

The authors declare no competing interests.

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References

1. Joosten A, Delaporte A, Mortier J, Ickx B,Van Obbergh L,Vincent JL, Cannesson M, Rinehart J,Van der Linden P: Long-term impact of crystalloid *versus* colloid solutions on renal function and disability-free survival after major abdominal surgery. Anesthesiology 2019; 130:227–36
2. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L,Van Obbergh L, Loi P, Rinehart J, Cannesson M,Van der Linden P: Crystalloid *versus* colloid for intraoperative goal-directed fluid therapy using a closed-loop system: A randomized, double-blinded, controlled trial in major abdominal surgery. Anesthesiology 2018; 128:55–66
3. Miller TE, Myles PS: Perioperative fluid therapy for major surgery. Anesthesiology 2019; 130:825–32

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Crystalloid/Colloid Renal and Disability Outcomes: Reply

In Reply:

We thank Drs. Pizov and Gelman for their interesting comments regarding our two recent publications, which compared the effects of crystalloids and colloids on short- and long-term outcomes in high-risk surgical patients.[1,2] Although we agree that surgical complexity could be a potential confounding factor for immediate postoperative complications and for its long-term consequences, we do not think that patients in the crystalloid group underwent more complex surgeries than those randomized to the colloid group. Indeed, beyond the surgical time, we have no data to support this hypothesis. Surgical procedures and incidences of high-risk surgery were comparable in the two groups, and blood loss, which is often considered as a marker of surgical complexity, was also not different between the two groups. A longer surgical time did