surgical visits. Indeed, one must consider either a placebo or even a Hawthorne effect as confounders.

Generalizing the Academic Medical Center ERAS Experience

The bulk of the ERAS literature has come out of major academic medical centers, and we challenge investigators to expand and test whether and how these protocols are applicable to community and even small critical-access rural hospitals. In that process, we must recognize a number of barriers to generalized adoption of ERAS, including the following:

- Cost. Additional resources are needed to initiate and maintain protocols, rewrite standard order sets in your electronic medical record, provide sufficient monitors for protocol-driven algorithms, and hire data collection and analytic personnel to continually monitor quality outcomes within the institution.
- Robust informatics. Measuring pathway improvements is vital to both intelligently modify the protocols for maximum benefit as well as sustain support from hospital leadership. This requires both a sophisticated functional data system as well as skilled informatics practitioners to analyze the outcomes. At the University of Minnesota, more than $150,000 per year is spent tracking these quality metrics (personal communication, Richard C. Prielipp, M.D., Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota; verbal communication as of June 2020).
- A new team culture. Although a local champion is key to initiating an ERAS pathway, the long-term success requires sustained collaboration of anesthesia, surgery, nursing, and hospital administration. Any breakdown in this network exposes impediments to sustained compliance.

Summary

We applaud Sessler and Memtsoudis for sounding the alarm about the unbridled enthusiasm for ERAS protocols.[1,3,4] As Sessler opined: "There is no basis for giving clinical pathways a 'free pass' on evidence."[1] Indeed, we applaud Anesthesiology for increasing the volume of the alarm bell with publications like the randomized, controlled trial by Maheshwari *et al.*[2] Publication of such "negative" trials[4] is vital to separating valid ERAS elements from unnecessary or perhaps even detrimental components of proposed pathways. "Great expectations" for ERAS may indeed prove to be true, but in 2020 we still don't know whether the reality equates to the hype. Regardless, it is time to put the evidence in ERAS.[1,5]

Competing Interests

Dr. Prielipp is a member of the Board of Directors of the Anesthesia Patient Safety Foundation (APSF; Rochester, Minnesota) and serves on the speakers' bureau for Merck Co., Inc. (Kenilworth, New Jersey). Dr. Rice declares no competing interests.

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This letter was sent to the author of the original article referenced above, who declined to respond.—Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief.

DOI: 10.1097/ALN.0000000000003466

References

1. Sessler DI: Implications of practice variability. Anesthesiology 2020; 132:606–8
2. Maheshwari K, Avitsian R, Sessler DI, Makarova N, Tanios M, Raza S, Traul D, Rajan S, Manlapaz M, Machado S, Krishnaney A, Machado A, Rosenquist R, Kurz A: Multimodal analgesic regimen for spine surgery: A randomized placebo-controlled trial. Anesthesiology 2020; 132:992–1002
3. Memtsoudis SG, Poeran J, Kehlet H: Enhanced recovery after surgery in the United States: From evidence-based practice to uncertain science? JAMA 2019; 321:1049–50
4. Sessler DI: Negative trials, and what to do with them?: First, stop calling them "negative". Anesthesiology 2020; 132:221–4
5. Joshi GP, Kehlet H: Enhanced recovery pathways: Looking into the future. Anesth Analg 2019; 128:5–7

(Accepted for publication June 19, 2020. Published online first on July 13, 2020.)

Impact of Closed-loop Anesthesia on Cognitive Function: Comment

To the Editor:

Joosten *et al.* are to be congratulated on their deployment of technically complex closed-loop systems to support patients during anesthesia and surgery.[1] The possibility of experiencing impaired neurocognitive function in association with a surgical episode is a concern to patients and those who care for them. It makes sense to establish whether changes in clinical technologies might diminish or abolish these unwelcome syndromes.

Nevertheless, we have concerns about the Primary Outcome Measure and its analysis.

On clinical trials.gov (https://clinicaltrials.gov/ct2/show/NCT03148730) the Primary Outcome Measure is "*Incidence* of postoperative cognitive dysfunction." This implies a definition of postoperative cognitive dysfunction. The authors chose the Montreal Cognitive Assessment score (maximum 30), so we need to consider what a meaningful change is. Reduction by a single point is very unlikely to be clinically significant and certainly does not represent a reduction of more than 1 SD less than normative published data.[2] A decline of two points? Five points? Falling from more than 26 to less than 26? Each patient either does or does not have postoperative cognitive dysfunction and the incidence would be the proportion of patients with the condition in each of the two treatment groups; then we can compare the incidence after control and closed-loop treatments.

In the article, the primary outcome was the *change* of the cognition score. This is an important alteration because incidences, group differences, and individual *change* are not the same thing. The authors have concluded there is a difference in cognitive outcome based on a screening test (the Montreal Cognitive Assessment) and ignored the results of the more robust cognitive assessment tools that returned no difference between groups.

Not all the primary outcome data is shown. The Montreal Cognitive Assessment has been treated as parametric (normally distributed) in the power calculation, but is (partially) reported as nonparametric in the results. Baseline scores are set out in table 1. We looked for, but cannot find, any summary of the data after baseline; the values at 1 week and 90 days are not reported. Instead we are given what is probably the median (it is not defined) and the interquartile ranges of the change from baseline. It would be helpful to see the raw data perhaps presented as a scattergram with lines to show the individual trajectories. In addition, summary statistics (*i.e.* the median and interquartile ranges of the scores at 1 week and 90 days for each of the treatment groups) would be helpful.

Regarding the analysis and statistical significance, we note the 95% CI of the differences include zero at both 1 week and at 3 months? How can these results be significant?

In addition the *post hoc* sensitivity analysis showed no difference between the treatment groups when the absolute values were analyzed. What was the reason for the decision to use change in scores from baseline as the primary analysis? Was any statistical correction made for multiple testing? Bonferroni correction or similar?

The abstract will be widely read. The conclusion is not based on the prespecified primary outcome measure. In addition, none of 18 secondary outcome measures defined on clinicaltrials.gov were reported (understandable because of space constraints). However, the authors include three additional measures of which two are similar to, but not the same as, those prespecified.

Overall we are worried that Joosten *et al.* have overstated their findings. An alternative interpretation is that the high-tech technique made no difference to outcome.

Competing Interests

The authors declare no competing interests.

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DOI: 10.1097/ALN.0000000000003468

References

1. Joosten A, Rinehart J, Bardaji A, Van der Linden P, Jame V, Van Obbergh L, Alexander B, Cannesson M, Vacas S, Liu N, Slama H, Barvais L: Anesthetic management using multiple closed-loop systems and delayed neurocognitive recovery: A randomized controlled trial. Anesthesiology 2020; 132:253–66
2. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, Oh ES, Crosby G, Berger M, Eckenhoff RG; Nomenclature Consensus Working Group: Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Anesthesiology 2018; 129:872–9

(Accepted for publication June 19, 2020. Published online first on July 13, 2020.)

Impact of Closed-loop Anesthesia on Cognitive Function: Reply

In Reply:

We would like to thank Dr. Sneyd and Prof. Evered for their interesting comments regarding our recent article which assessed the feasibility and potential impact of automated closed-loop anesthesia management on short- and mid-term cognitive function after noncardiac surgery.[1,2]

We agree with these authors that an alternative interpretation of our results could be that automated anesthetic management using the combination of three controllers had no impact on delayed neurocognitive recovery. In

correspondence with the Journal's Statistical Editor, the most valid treatment estimate for change in cognition score (the 30-item Montreal Cognitive Assessment) from baseline would be an analysis of covariance, using preoperative cognition score as a covariate and group assignment as a fixed effect. In line with Journal policy, this analysis was labeled as a *post hoc* sensitivity analysis, as it was requested after examining the data. When analyzed in this manner, there was no statistical difference between the two groups at 1 week (point of estimate 0.7 with 95% CI, −0.2 to 1.6; $P = 0.14$) and 3 months (point of estimate 1.1 with 95% CI, 0.0 to 2.2; $P = 0.056$) postsurgery follow-up. The difference between this analysis and the originally planned analysis is that the groups were somewhat imbalanced at baseline, and this imbalance could account for approximately 30% of the treatment effect when analyzed as a change score. As requested by the letter authors, we have added herein the median cognition scores in both groups at their baseline, short-term (1 week) follow-up, and mid-term (3 months) follow-up (table 1), and we have added figure 1 that describes changes from baseline cognition score for the two groups. It is worth noting that the point estimate from the analysis of covariance approach is similar in magnitude to the original approach, but with increased imprecision (*i.e.*, wider CIs).

Competing Interests

Dr. Joosten reports being a consultant for Edwards Lifesciences (Irvine, California). Dr. Van der Linden has received, within the past 5 yr, fees for lectures and consultancies from Fresenius Kabi GmbH (Bad Homburg, Germany), Aguettant Medical SA (Lyon, France), Nordic Pharma (Paris, France), and Vifor Pharma (Antwerp, Belgium). Dr. Rinehart reports ownership interest in Sironis, a company developing closed-loop systems and consulting for Edwards Lifesciences. Dr. Barvais declares no competing interests.

Table 1. Cognition Score

Variables	Control Group (N = 44)	Closed-loop Group (N = 45)	*P* Value
Cognition score at baseline	27 [25–29]	27 [25–28]	0.345
Cognition score at one week postsurgery	27 [26–29]	27 [24–29]	0.549
Cognition score at 3-months postsurgery	27 [25–28]	27 [25–29]	0.253
Cognition score difference (baseline to 1 week postsurgery)	−1 [−2 to 1]	0 [−1 to 1]	0.033
Cognition score difference (baseline to 3-months postsurgery)	−1 [−3 to 0]	0 [−2 to 2]	0.017

Cognition score is the score obtained at the 30-item Montreal Cognitive Assessment test.

Data are presented as median [25th to 75th percentiles].

Values are rounded to the nearest whole value in line with their original precision of measurement.

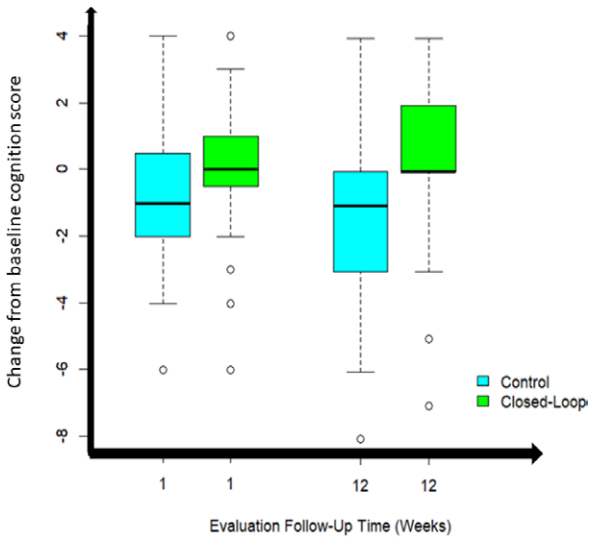

Fig. 1. Changes from baseline cognition score at 1 and 12 weeks in the control (*blue*) and the closed-loop (*green*) groups. Boxplots are shown for change in cognition score at 1-week and 12-week follow-up. The box shows the 25th to 75th percentile with median shown as the *solid line* inside the box. Whiskers extend to the minimum/maximum scores or 1.5× the interquartile range, whichever is less. If there are points outside of 1.5× the interquartile range they are shown as *dots* ("outliers").

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DOI: 10.1097/ALN.0000000000003469

References

1. Sneyd JR, Evered LA: Impact of closed-loop anesthesia on cognitive function: Comment. Anesthesiology 2020; 133:945–6
2. Joosten A, Rinehart J, Bardaji A, Van der Linden P, Jame V, Van Obbergh L, Alexander B, Cannesson M, Vacas S, Liu N, Slama H, Barvais L: Anesthetic management msing multiple closed-loop systems and delayed neurocognitive recovery: A randomized controlled trial. Anesthesiology 2020; 132:253–66

(Accepted for publication June 19, 2020. Published online first on July 13, 2020.)