



A Novel Dosing Algorithm for High-Dose Propofol Administration for the Treatment of Depression

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Background

- High doses of anesthetics produce significant and durable antidepressant effects in those with drug-resistant depression (Fig. 1) [1][2].
- Maintaining a 70-90% EEG burst suppression ratio (BSR) for ~15 minutes seems to yield the strongest antidepressant effects [2].
- Little guidance exists to aid anesthesiologists in achieving these BSR levels with Propofol.

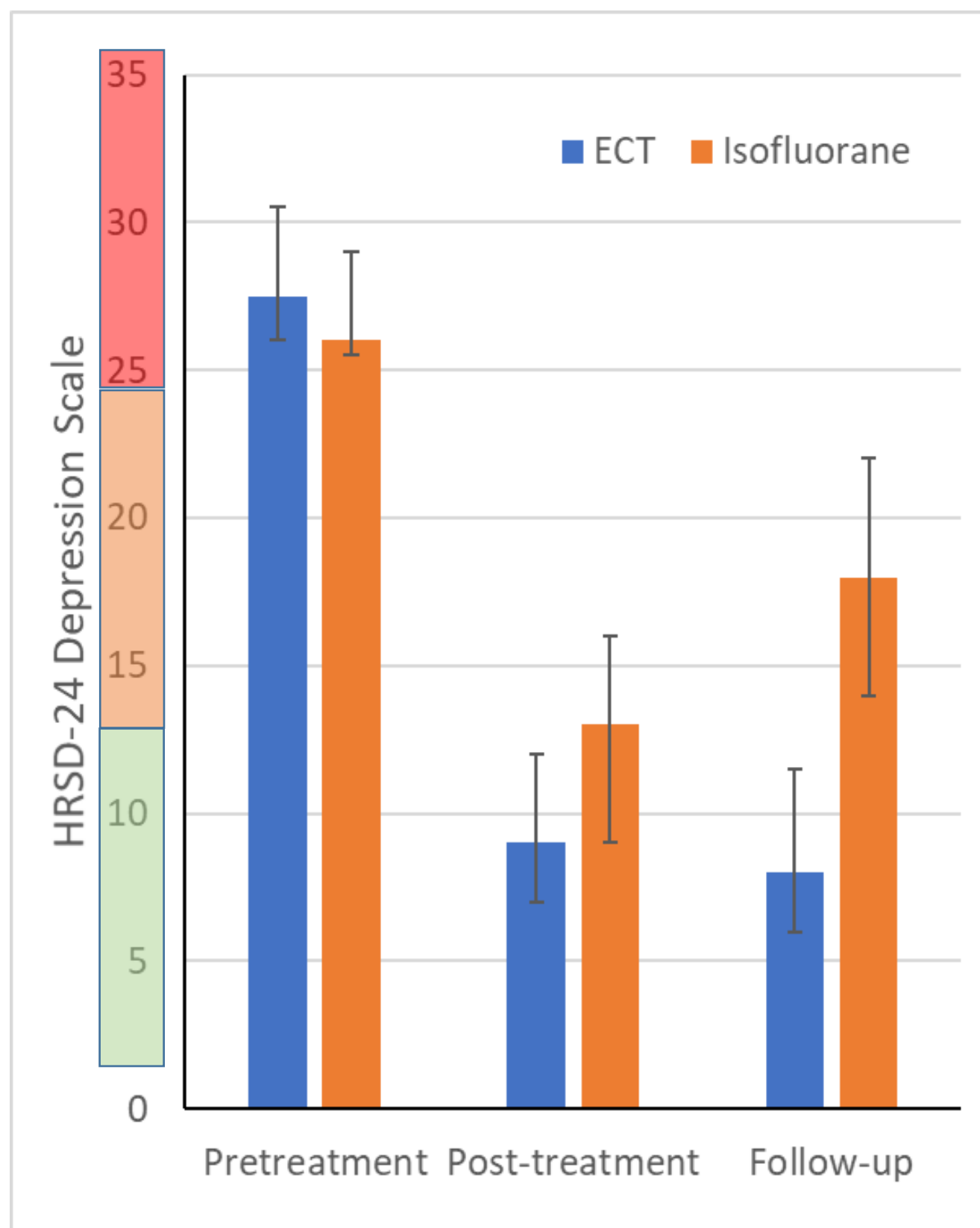


Fig. 1. Comparison of the antidepressant effects of Isoflurane with electroconvulsive therapy (ECT). Data from [2] Tadler and Mickey (2018).

Methods

- 13 participants (69% female, 29-51 years old, 52-119 kg) underwent 3-6 treatments of high doses of Propofol.
- Two dosing algorithms were used:
 - 1) First treatment used participant population mean PK/PD parameters
 - 2) Subsequent treatments used PK/PD parameters estimated based on log-log linear regression of observed BSR of the most recent treatment to the effect site concentration predicted by the Eleveld model [3].
- An iterative approach was then used in both cases to estimate dosing required to achieve 70-90% BSR for 12-15 minutes.

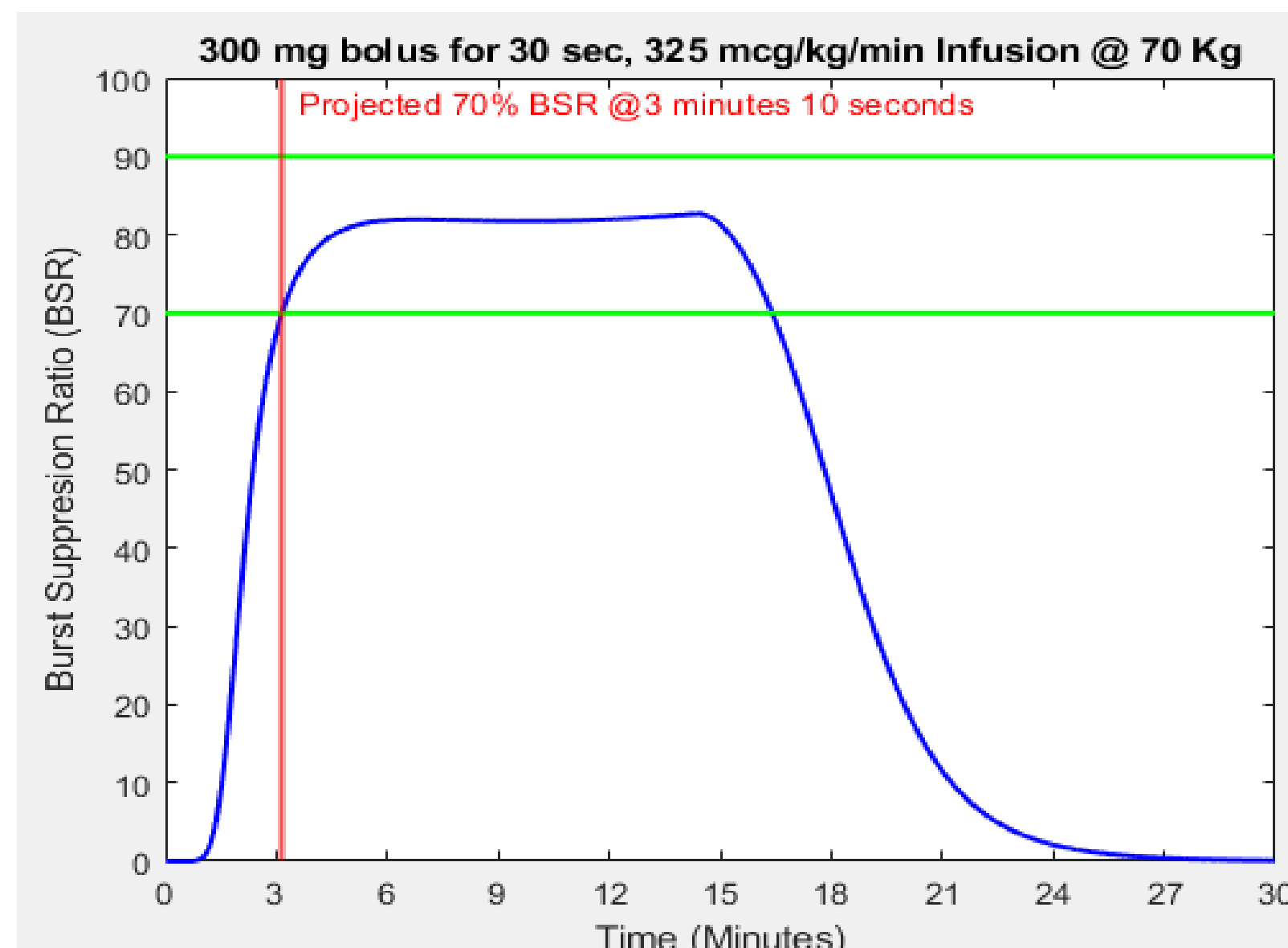


Fig. 2. Example of the output of the dosing algorithm. Projected treatment BSR is on the Y-axis, time is on the X-axis, and the dosing recommendation is at the top.

Results

- Dosing recommendations were then compared to retrospectively determined ideal dosing levels.
- Ideal dosing was actual administered bolus and actual mean infusion rate.
- For treatments with a bolus overshoot, the ideal bolus was considered to be 90% of the administered bolus.
- Median absolute percent error (MdAPE) of 15.1% with an interquartile range (IQR) of 11.4%-16.6% between dosed and ideal bolus.
- MdAPE of 20.4% with an IQR of 15.8%-26.6% between dosed and ideal infusion rate.

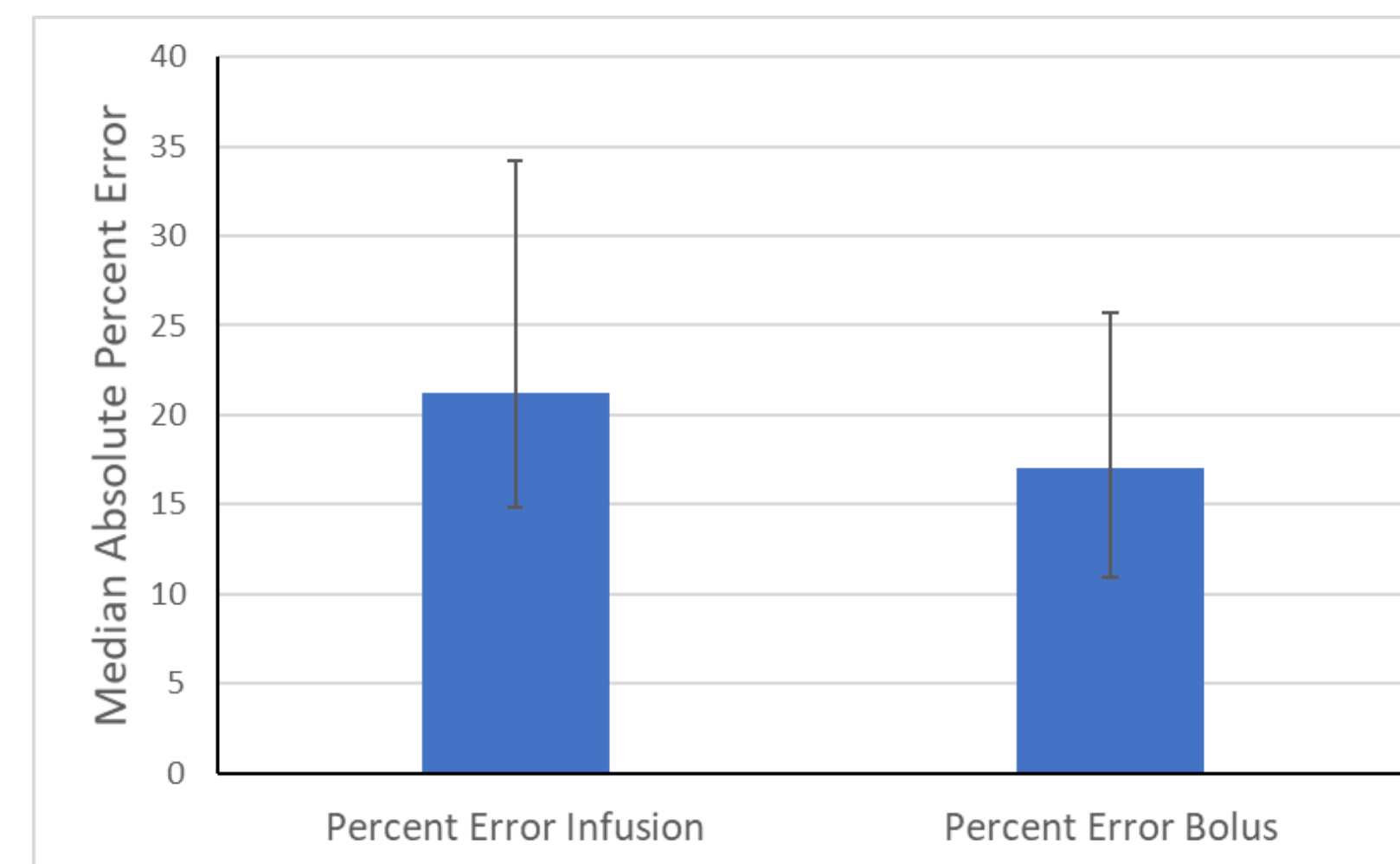


Fig. 3. Median absolute percent error between the dosing recommendation and retrospectively determined ideal dosing level, for the infusion and bolus of all participants (n=13).

Discussion

- Error lies well within the 20% to 30% range that is considered acceptable for MdAPE of PK models alone [4].
- Limitations include:
 - relatively small sample size of participants.
 - secondary analysis of data from a study that was not primarily designed as a PK/PD modeling study.
- This is an imperfect but useful first prototype for dosing Propofol during high-dose anesthetic treatments for depression.

Cited Literature

[1] N. Khalid, M. Atkins, J. Tredget, K. Champney-Smith, and G. Kirov, "The Effectiveness of Electroconvulsive Therapy in Treatment-Resistant Depression: A Naturalistic Study," *J ECT*, vol. 24, no. 2, p. 5, 2008.

[2] S. C. Tadler and B. J. Mickey, "Emerging evidence for antidepressant actions of anesthetic agents," *Current Opinion in Anaesthesiology*, vol. 31, no. 4, pp. 439-445, Aug. 2018.

[3] D. J. Eleveld, P. Colin, A. R. Absalom, and M. M. R. F. Struys, "Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation," *British Journal of Anaesthesia*, vol. 120, no. 5, pp. 942-959, May 2018.

[4] J. P. van den Berg *et al.*, "Influence of Bayesian optimization on the performance of propofol target-controlled infusion," *British Journal of Anaesthesia*, vol. 119, no. 5, pp. 918-927, Nov. 2017.