The Effect of Ketamine on Depth of Hypnosis Indices During Total Intravenous Anesthesia – a Comparative Study Using a Novel Case Replay System

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Background: Processed electroencephalogram (EEG) monitors provide clinical information by deriving a single depth-of-hypnosis (DoH) index from a complex EEG signal comprising a multitude of frequency components. The reliability of DoH indices can be influenced by many factors, including the unanticipated EEG effects of co-administered drugs. Ketamine, frequently used to reduce postoperative pain [2], is known to affect high frequency EEG power [1]. We have previously reported the development of an EEG simulator for comparison of three common DoH monitors [3]. We recently completed a randomized study of total intravenous anesthesia with propofol and remifentanil in the presence of ketamine (Ketamine trial; NCT02908945). Patients were randomized to one of three groups: Group 0.5 received a 0.5 $mg \cdot kg^{-1}$ ketamine bolus, followed by a 10 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion [4]; Group 0.25 received a 0.25 $mg \cdot kg^{-1}$ ketamine bolus and a 5 $mcg \cdot kg^{-1} \cdot min^{-1}$ infusion; a control group received no ketamine. The purpose of this study is to compare three common DoH monitors in the presence and absence of ketamine by extending our EEG simulator to allow replay of previously recorded EEG.

Methods: A USB-based audio digital to analog converter (U-PHONO UFO202, Behringer, Willich, Germany) was modified by replacing the integrated 22 µF capacitors in the high-pass filter with 1000 µF capacitors, to improve low-frequency replay. Replay behavior was verified with sine waves over the clinically relevant frequency range (0.1-50.0 Hz) and by re-replaying both synthetic and previously recorded EEG. Signals were compared and analyzed in the time and frequency domain. Next, EEG data from the Ketamine trial were extracted at 900Hz, converted into audio files, scaled to adjust amplitude, and replayed to three monitors: NeuroSENSE (NeuroWave Systems, DoH index=WAV), BIS (Medtronic, DoH index=BIS) and Entropy (GE Healthcare, DoH index=RE). Differences in DoH indices during the surgical preparation phase (first 20 min of case), in which peak ketamine DoH effect was expected to be observed in the absence of surgical stimulation, were compared as violin plots, in 5 minute increments, for the three devices. DoH differences between the 2 ketamine groups and the control group were compared using Wilcoxon rank-sum tests for each monitor.

Results: Data from 29 cases were available for analysis. The presence of ketamine significantly increased the median DoH index for all three monitors: compared to the control group, median DoH difference (MD), calculated over a 1 minute window, for Group 0.5 were 14.0, 8.9, and 19.5 for BIS, RE, and WAV respectively; similarly, MD for Group 0.25 were 12.5, 17.2, and 8.2 for BIS, RE, and WAV respectively (Figure 1; all $p<0.025$). Comparing the three monitors at each time point, significant differences were found only when comparing BIS to RE, and WAV to RE for awake data (minute 1).

Conclusion: We observed a ketamine dose-dependent increase in the DoH index for all three monitors. Future work will include other processed EEG parameters such as Burst Suppression Ratio (BSR) and electromyography (EMG) in the monitor comparison. A limitation of this method is that replay of pre-recorded EEG is affected by the input filters applied during the original recording, and detailed filter characterization may be needed to fully reconstruct the raw EEG signal. Once perfected, replay technology can facilitate systematic evaluation of DoH monitors in the presence of adjunct drugs such as ketamine, and contribute to establishing a more widely accepted standard for quantitative measures of anesthetic effect.

References: [1] J Nat Sci Biol Med. 2015;6(2):378-82 [2] Anesthesiology. 2015;123(4):937-960. [3] Anesth Analg. 2016;123(5):1136-1140. [4] J Pain. 2016;17(2):131-157.

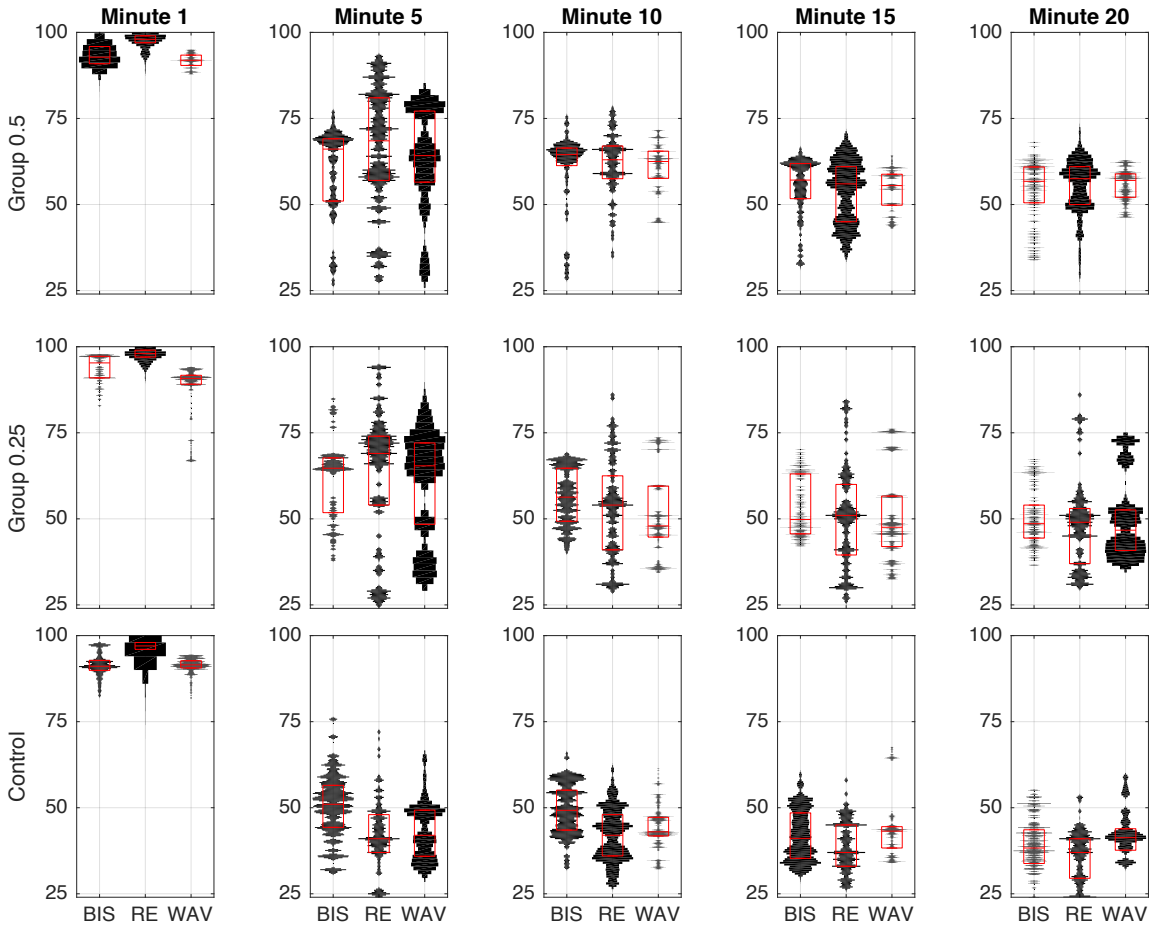

Figure 1: DoH index for Group 0.5, Group 0.25, and the control group, showing a combination of violin and boxplots for the first 20 min of each case, in 5 minute increments for 1 minute of values each, for each monitor-specific DoH index, grouped by ketamine dose.