The Effect of Ketamine on EEG and WAV

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Background: The processed electroencephalogram (EEG) depth-of-hypnosis (DoH) indices may not be reliable when multi-modal anesthesia, particularly when ketamine is used. Low dose ketamine administered as a sole anesthetic agent introduces high β- and low γ-band oscillations (25-32 Hz) [1]. The WAV_CNS (NeuroSENSE, NeuroWave Systems) DoH index is predominantly determined by EEG in the γ-band (32–64 Hz), and may therefore be affected by ketamine. If ketamine is co-administered with propofol, the EEG signature resembles the propofol signature, where ketamine shifts the peak of α spindles to higher frequencies [4]. Ketamine had limited effect on the WAV_CNS index during steady-state propofol-remifentanil anesthesia [5]. Conflicting results on the effect of ketamine on other pEEG monitors have been reported. The aim of this study was to evaluate the validity of the WAV_CNS index to guide propofol infusion in the presence of analgesic ketamine dosing as recommended by guidelines on the management of postoperative pain (recommended dose) [2]. We examine the effect of ketamine with propofol-remifentanil anesthesia on the WAV_CNS index and on the raw EEG during induction of anesthesia.

Methods: Following research ethics board approval and written informed consent, 30 ASA I-II adults aged 18-54 years were randomized to one of three groups. Group 0.5 received the recommended dose of ketamine; a bolus of 0.5 mg·kg⁻¹ immediately before induction of anesthesia, followed by a 10 mcg·kg⁻¹·min⁻¹ infusion until last suture. Group 0.25 received a bolus of 0.25 mg·kg⁻¹ followed by a 5 mcg·kg⁻¹·min⁻¹ infusion. The control group received no ketamine. All participants received a bolus of 1.0 mcg·kg⁻¹ remifentanil and a bolus of 1.5 mg·kg⁻¹ propofol for induction of anesthesia. Additional propofol doses (0.5 mg·kg⁻¹) were administered as required. Anesthesiologists were blinded to the WAV_CNS, but not to the ketamine dose. The attending anesthesiologist evaluated adequacy of anesthesia using standard clinical signs. The EEG power spectral density was evaluated using the multi-taper method [3]. Results are expressed as median [Qi, Qi] and compared to the control group using a two-tailed Wilcoxon rank-sum test.

Results: EEG data were available for 28 cases (22 males, 29 [26, 37] years, 84.0 [74.5, 95.8] kg, 180.2 [175.3, 185.4] cm). Total propofol induction dose was 1.5 [1.5,2.5] mg·kg⁻¹ in Group 0.5 (p=0.27), 2 [1.5,2] mg·kg⁻¹ in Group 0.25 (p=0.41) and 2 [2,2] mg·kg⁻¹ in the control group. The peak of the α-spindles (8–16 Hz) shifted to higher frequencies with increasing doses of ketamine (Fig 1A). Normalized power in the β- (16–32 Hz) and γ-band (32–64 Hz) also increased with increasing ketamine doses (Fig 1A). The WAV_CNS trends in Group 0.5 showed temporarily elevated values with a median of over 60 (Fig 1B), while individual blood pressure and heart rate trends showed no significant response to stimulation during airway instrumentation. The
elevated WAV\textsubscript{CNS} values coincided with peak frequency (Fig 1C) and normalized γ-power (not shown) exceeding their respective steady-state values during maintenance of anesthesia. Transient increases were not observed in Group 0.25, where interpatient variability was large (not shown).

**Conclusion:** The recommended dose of ketamine, with propofol-remifentanil anesthesia, does not introduce high β- and low γ-band oscillations seen with ketamine when used as a sole agent. We did observe a dose-dependent shift in the peak frequency, consistent with previous reports [4]. We speculate that the recommended bolus of 0.5 mg/kg of ketamine (Group 0.5) introduces a peak in ketamine EEG effect following induction of anesthesia, which exceeds the effect of the corresponding maintenance infusion of 10 mcg·kg\textsuperscript{-1}·min\textsuperscript{-1}. This observation needs to be confirmed in a larger study. The median of the corresponding WAV\textsubscript{CNS} values in Group 0.5 was also above the recommended [40-60] range.

**Figure 1.** WAV\textsubscript{CNS} trends and EEG spectral characteristics for Group 0.5 (red), Group 0.25 (blue) and the Control group (black). Fig1A shows EEG power, normalized over the 0-64 Hz frequency range, at 5 min after the start of propofol infusion. Fig1B and 1C show the WAV\textsubscript{CNS} and peak frequency trends. Median values are indicated by solid lines, IQR is indicated by dashed lines (10 second averages shown each minute).