Clinics in Surgery

Research Article
Published: 14 May, 2021

Target Controlled Infusion *via* Smartpilot® view for Neuromonitoring in Neurosurgical Patients: A Novel Technology

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Abstract

Background: Intravenous anesthetic administration utilizing pharmacokinetic/pharmacodynamic models during Intraoperative Neurophysiologic Monitoring (INM) has never been investigated. SmartPilot® View (SPV) is a software that takes into account hypnotic-opioid interactions and produces Noxious Stimulation Response Index (NSRI) to determine various levels of anesthesia. The goal was to investigate whether the efficacy of Target Controlled Infusion (TCI) could be optimized without affecting INM parameters *via* SPV technology.

Methods: Patients underwent neurosurgery with INM between January 1st, 2018 to January 1st, 2019 were retrospectively documented. The subjects were divided into two groups following data scanning: Those monitored with SPV (Group SPV) and those undergone standard anesthesia follow-up (Group Control). The analysis included hemodynamic parameters, BIS, anesthesia and surgery times, extubation time, and anesthesia consumption. For Group SPV, the relationship between hypotensive episodes as well as anesthesia time spent in each isobole and alterations of neuromonitoring signals was analyzed.

Results: Data from 43 patients were included in this analysis (n=20 SPV; 23 control). Both groups had similar demographic data. Extubation time (p=0.013) and total anesthesia time spent with mean arterial pressure <60 mmHg (p=0.008) was longer in Group Control. Propofol was consumed more in Group Control (p=0.036). There was a linear correlation between anesthesia time spent with MAP<60 mmHg (p<0.0001), anesthesia time spent with TOL (tolerance of laryngoscopy) >90 (p=0.0011) and prolongation in latency and decrease in amplitude of neuromonitoring signals.

Conclusion: By reducing intraoperative hypotension time, SPV-guided TCI improved intraoperative hemodynamics and was effective in optimizing intravenous anesthesia without influencing INM signals during neuromonitoring.

Keywords: Intraoperative neurophysiologic monitoring; Anesthetics; Intravenous; Consciousness monitors; Monitoring; Intraoperative

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Received Date: *09 Apr 2021*
Accepted Date: *10 May 2021*
Published Date: *14 May 2021*

Citation:
Inan G, Satirlar Ozkose Z. Target Controlled Infusion via Smartpilot® view for Neuromonitoring in Neurosurgical Patients: A Novel Technology. Clin Surg. 2021; 6: 3165.

Introduction

Over the last decades, intraoperative neuromonitoring has been widely used and subsequently has become a routine monitorization for most of the neurosurgical procedures [1]. The Intraoperative Neuromonitoring (INM) is essentially used to diagnose imminent neurological injury such as a permanent neurological deficit [2]. Commonly utilized INM techniques include Somatosensory Evoked Potentials (SSEP), Motor-Evoked Potentials (MEP), transcranial electrical motor evoked potentials, Electromyography and Electroencephalography (EEG), which can be used either alone or in combination depending on the procedure [3].

The proper functioning of INM can be impaired depending on the choice of the anesthetic drugs and the technique [3,4]. The best technique for anesthesia during INM remains an issue. Total Intravenous Anesthesia (TIVA) without muscle relaxants has been suggested for INM during neurosurgery [5,6]. However, as opposed to TIVA with muscle relaxants, it may result in higher and/or extended propofol dosing regimens. In this regard, higher propofol consumption can contribute to hypotension, which is independently linked to suppression of evoked responses, hemodynamic instability and delayed recovery.

Therefore, by using propofol-sparing adjuncts such as lidocaine, dexmedetomidine and

desflurane, various solutions have been advocated to minimize the overall dose of propofol [7-12]. However, to our knowledge, none of the studies have taken Pharmacokinetic and Pharmacodynamic (PK/PD) responses into account in order to maintain adequate depth of anesthesia and analgesia by optimizing drug administration throughout the practice of neuroanesthesia.

SmartPilot® View (SPV) software is a novel integrated monitoring system that demonstrates the effects of the interactions of combined hypnotic-analgesic drugs and displays actual and predicted levels of anesthesia [13]. This is the first study of neuroanesthesia using SPV. Although there is little clinical evidence of SPV, recent research has shown that SPV-guided anesthesia reduces anesthetic consumption [14]. Thus, for patients undergoing neuromonitoring, will SPV be relevant?

In this retrospective research, we aimed to evaluate whether SPV was correlated with optimal anesthetic agent titration as a decision support device in anesthesia management and to investigate its usefulness and efficacy on intraoperative hemodynamic stabilization and attainment of neuromonitoring signals.

Material and Methods

After obtaining Institutional Ethics Committee approval, records of patients who underwent neurosurgery with INM between January 1st, 2018 and January 1st, 2019 at Gazi University Department of Anesthesiology and Reanimation were reviewed. The subjects were divided into two groups following data scanning: Those monitored with SPV (Group SPV) and those undergone standard anesthesia follow-up (Group Control).

Data were obtained from anesthesia records, the electronic database of SmartPilot® View (SPV) and intraoperative monitoring recordings. Following investigation, patients who underwent elective surgery and those with ASA physical classification I-III were included in the study. Exclusion criteria were awake craniotomies, patients with ASA physical classification >IV, Glasgow coma grade <8, BMI>35 kg/cm^2, who underwent emergency surgery and whose records could not be reached.

All patients were monitored perioperatively with Electrocardiogram (ECG), invasive arterial blood pressure, End-tidal Carbon dioxide ($EtCO_2$), Pulse Oximetry (SpO_2), and Bispectral Index (BIS) (Infinity Delta XL, Drager Medical, Lübeck, Germany). SmartPilot® View (software version 3.00.12, Drager Medical, Lübeck, Germany) was connected to the anesthesia ventilator (Perseus A500, Drager Medical, Lübeck, Germany), hemodynamic and anesthesia depth monitor (Infinity Delta XL) and Braun Space Station for infusion pumps (Perfusor Space, Braun Medical, Germany).

For all subjects, induction was achieved with Target Controlled Infusion (TCI) of propofol; Schnider effect-site Concentration (Ce) model and remifentanil; Minto effect-site Concentration (Ce) model. In patients who underwent SPV-guided surgery (Group SPV) anesthesia was maintained with TCI propofol and remifentanil targeting the predefined Noxious Stimulation Response Index (NSRI) isobole graphs showing the specific anesthesia levels on the SPV monitor; the dark grey isobole for intubation, incision and surgery and the light-grey isobole for surgical closure. Standard anesthesia follow-up (Group Control) was achieved by maintaining BIS between 40 and 60.

Data for anesthesia and surgery durations, extubation times, and amount of propofol consumed were obtained from anesthesia records. Anesthesia duration time was defined as the time from the induction to cessation of intravenous infusions of propofol and remifentanil. Extubation time was defined as time needed for patients to be extubated from the cessation of anesthetics.

Electrophysiological monitoring was conducted using a Deltamed system (Paris, France). The increase in latency 10% with the prolongation being almost 1 msec and the decrease of amplitude 50% was considered as the threshold to be clinically significant alert. Time spent with attainment of neuromonitoring signals due to non-surgical causes was recorded during electrophysiological monitoring.

Duration of hypotension (total anesthesia time spent with mean arterial pressure <60 mmHg in minutes) was calculated. Hypotension, in case of indication was treated using ephedrine or noradrenaline; the need for vasopressors and number of repetitive administration of vasopressors was also recorded.

The study data was analyzed using IBM SPSS 20. A p value ≤ 0.05 was considered statistically significant. Descriptive statistics was expressed displayed as mean ± standard deviation. Differences between both groups were analyzed with 2-tailed Student t test and chi-square test. Linear regression was performed to determine the relationship between attainment of neuromonitoring signals and MAP, BIS or target isobole of SPV (Tolerance of laryngoscopy - TOL 50 to 90 or TOL >90). All the physiological variables at different time points during the study were analyzed by repeated measures - analysis of variance.

Results

The data of 43 patients in total, 20 patients in Group SPV and 23 patients in Group Control were retrospectively analyzed. Both groups had similar demographic data. Twenty patients who undergone SPV-guided neurosurgery (7 cranial, 4 cervical, 5 thoracic, 4 lumbar surgery) were 9 females and 11 males, their age ranging from 25 to 79 years, and ASA physical status 6 ASA I, 11 ASA II, 3 ASA III. In Group Control (6 cranial, 5 cervical, 6 thoracic, 6 lumbar surgery) there were 10 females and 13 males between 27 to 83 years old with 4 ASA I, 14 ASA II and 5 ASA III.

Details of the intraoperative data are shown in Table 1. Seventeen patients in Group Control experienced hypotensive episodes, in 10 of them vasopressors were administered 3 times, in 4 of them 3 times, in 1 of them 5 times and in 2 of them once. Six patients in Group SPV needed vasopressors for the treatment of hypotension. In 3 of them 3, in 1 of them 1, in 1 of them 2, and in 1 of them 6 times vasopressor administration was repeated. Total anesthesia time spent with mean arterial pressure <60 mmHg was longer in Group Control (p=0.008). Extubation time prolonged (p=0.013) and propofol was consumed more in Group Control (p=0.036).

There was a linear correlation between anesthesia time spent with MAP<60 mmHg and attainment of neuromonitoring signals (p<0.0001) (Figure 1). Increase in anesthesia time spent with MAP<60 mmHg increased the likelihood of influencing neuromonitorization. The statistically significant correlation (p=0.0011) between anesthesia time spent with TOL>90 (min) and attainment of neuromonitoring signals is shown in Figure 2. There was no statistically significant correlation between anesthesia time spent with BIS 40 to 60 or anesthesia time spent with TOL 50 to 90 and attainment of neuromonitoring signals (p=0.3686, p=0.3475, respectively) (Figure 3, 4).

Table 1: Intraoperative data.

	Group SPV	Group Control	p
Duration of surgery (min)	198.15 ± 83.628	224.44 ± 86.48	0.728
Duration of anesthesia (min)	225.60 ± 87.384	255.75 ± 91.7	0.854
Extubation time (min)	4.70 ± 2.319	10.2 ± 1.85	0.013
Anesthesia time spent with MAP <60 mmHg (min)	18.70 ± 30.663	62 ± 18.2	0.008
Anesthesia time spent with BIS 40-60 (min)	192.80 ± 80.876	204.78 ± 14.5	0.483
Propofol consumed (mg)	2325.80 ± 716.296	3967 ± 623.9	0.036
Anesthesia time spent with TOL 50-90 (min)	175.25 ± 75.739		
Anesthesia time spent with TOL >90 (min)	14.25 ± 7.319		

Values are expressed as mean ± standard deviation, MAP: Mean Arterial Pressure; BIS: Bispectral Index; TOL: Tolerance of Laryngoscopy

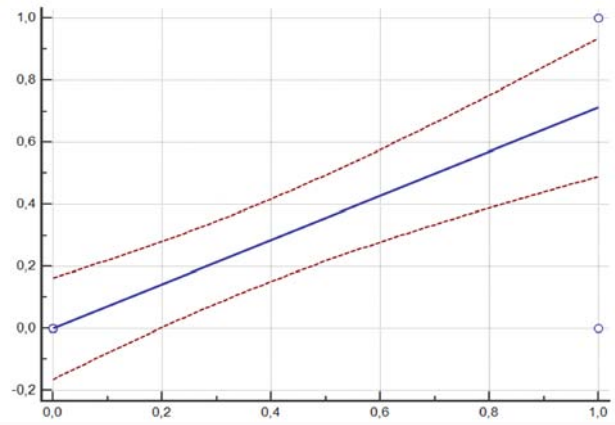

Figure 1: Relation between probability of attenuating neuromonitor signals and probability of hypotension. Dotted lines show the 95% confidence intervals.

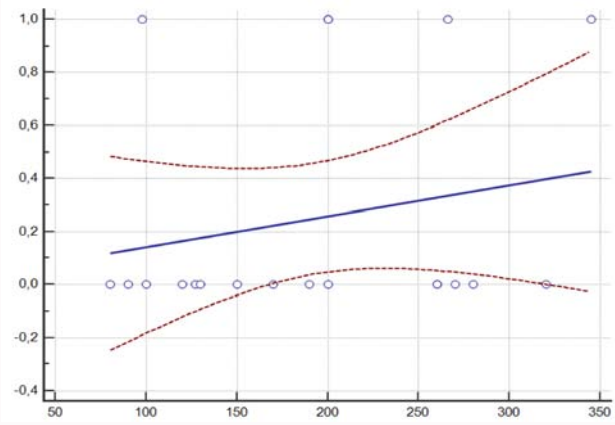

Figure 3: Relation between probability of attenuating neuromonitor signals and anesthesia time spent with BIS 40 to 60 in minutes. Dotted lines show the 95% confidence intervals. BIS indicates bispectral index.

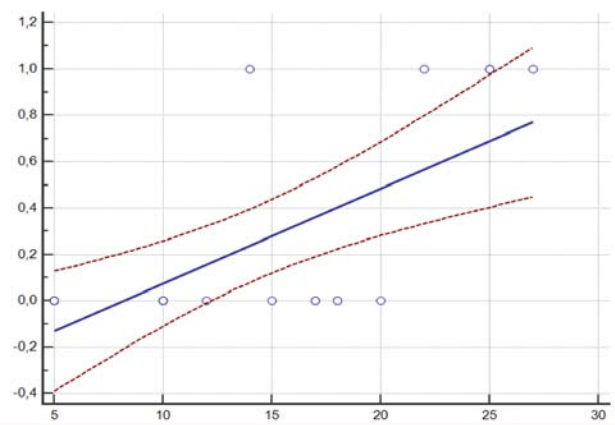

Figure 2: Relation between probability of attenuating neuromonitor signals and anesthesia time spent with TOL >90 in minutes. Dotted lines show the 95% confidence intervals. TOL indicates tolerance of laryngoscopy.

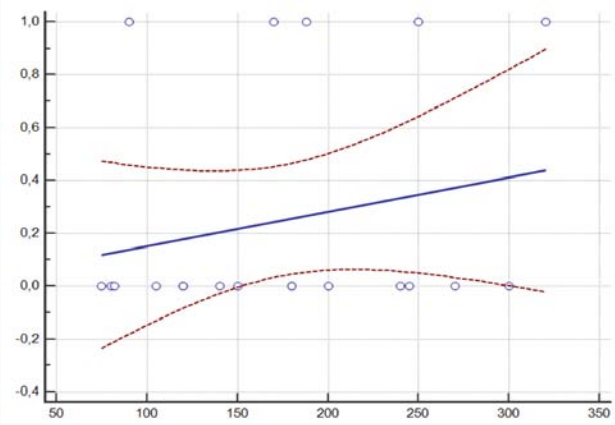

Figure 4: Relation between probability of attenuating neuromonitor signals and anesthesia time spent with TOL 50 to 90 in minutes. Dotted lines show the 95% confidence intervals. TOL indicates tolerance of laryngoscopy.

Discussion

The primary findings of the current retrospective study suggest that, under intraoperative neuromonitoring, target controlled infusion anesthesia *via* SPV for neurosurgical procedures improved intraoperative hemodynamics by minimizing intraoperative hypotension period. With less hypotension, SPV guidance undoubtedly made it possible to minimize anesthesia-related attainment of neuromonitoring signals.

For several neurosurgical procedures, the use of intraoperative monitoring significantly improves the quality of healthcare. In general, however, well-known anesthetic agents have an effect on neurophysiologic intraoperative responses [15]. Inhalational anesthetic agents by their synaptic effects causes marked reductions in amplitude and increases in latency. Similarly, intravenous agents also reduce the amplitude and increase latency, but to a lesser degree in a dose-dependent manner [4,16,17].

Anesthetic agents affect SSEP less than MEP [18]. The effect of propofol on SSEP latency and amplitude has already been

discussed, but remifentanil also causes significant changes in SSEP [18], especially in high doses. As a result, optimal intravenous agent titration is gaining importance [7,18,19]. The main focus of the studies was to reduce the dosage of propofol with the concomitant administration of adjunctive agents.

Without taking into account the inter-individual variability of PK/PD responses, anesthesia drug administration is often focused on clinical parameters. In comparison, optimizing the administration of intravenous drugs based on pharmacological models is the mechanism of action of recent monitors, which seem promising to improve intraoperative decision-making and prevent drug overdose [20].

To demonstrate the combined clinical effects of two or more drug concentrations, response surface models have been developed [21-23]. This is a three-dimensional interaction model; the x and y-axes are the predicted hypnotic and opioid concentrations, and the z-axis displays synergic drugs' effects called isoboles. Predicted hypnotic and analgesic effect site concentrations on respond surfaces form the isoboles for the probability of "nonresponse" to a series of stimuli. The interaction between different hypnotics and analgesics has been studied by using response surface methodology [21,24-26]. In a response surface modeling study of intraoperative propofol and remifentanil, both drugs reduced the other's requirement in a synergistic manner [27].

A similar response surface model for propofol and remifentanil has been described by Bouillon et al. [28]. Based on Bouillon's model, Schumacher et al. [24] have defined a new anesthetic depth index the Noxious Stimulation Response Index (NSRI) ranging between 100 and 0. NSRI has been proposed as a derivative of probability to tolerate and to predict intraoperative response to a noxious stimulus [29,30]. NSRI 100 means 100% probability of response and if NSRI approaches to it reflects 0% probability of responding to laryngoscopy [24]. Fifty percent probability to Tolerate Laryngoscopy (TOL) is equal to NSRI 50, and 90% TOL is equal to NSRI 20 [29]. In 44 subjects, NSRI performed better prediction of response to noxious stimulation than EEG-derived parameters and drug effect site concentrations [29].

SmartPilot® View is based on the same PK/PD model concept that provides estimated past, present and future drug effect site concentrations. In order to monitor intraoperative reaction to a noxious stimulus during surgery, SPV uses NSRI that integrates the synergistic effects of a hypnotic combined with an opioid. The SPV evaluates and predicts the current level of anesthesia and for the next 10 min the expected depth of anesthesia. The SPV displays a priori anesthesia level prediction, enabling anesthesia depth to be adjusted, whereas the EEG-derived anesthesia depth monitor BIS can only provide a posteriori information, usually after a delay in response.

Nonetheless, by considering the synergistic relationship of hypnotics and opioids, SPV with NSRI enables individualized anesthetic treatment and reduction in anesthetic dose. Clinical validation of SPV, however, is not enough yet. Cirillo et al. [14] in their prospective non-randomized study demonstrated that SPV-guided anesthesia decreases anesthetic consumption, but they have not study effects on either intraoperative hemodynamics or postoperative outcomes. In another prospective, randomized, blinded, controlled trial patient results of SPV-guided general anesthesia were contrasted with normal practice in vulnerable patients undergoing hip fracture surgery. SPV-guided general anesthesia in vulnerable patients decreased incidence of intraoperative hypotension, postoperative complications, and duration of hospital stay [13].

Actual and expected anesthesia levels are depicted as dots on isoboles graphically on SPV display. Anesthetic doses are determined to produce predefined isoboles. There are 3 layers of isoboles, the dark grey isobole reflects anesthesia depth to tolerate intubation and surgical incision, the mild-grey isobole for the remainder of surgery and the light-grey isobole for surgical closure. The administrator may decide individualized anesthetic level depending on the surgery and the patient.

It may be difficult to maintain adequate depth of anesthesia that will prevent patients from moving during neurosurgical procedures involving INM when muscle relaxants are not used. Furthermore, high-dose anesthesia may be needed to prevent the patient's movement, and as anesthesia is deepened, the response to monitoring is disturbed even more. We didn't aim anesthetic depth under the mild-grey isobole zone (NSRI>50) at any point of surgery as we felt it wouldn't be the ideal anesthetic zone during intraoperative neuromonitoring. An anesthetic zone between TOL 50 to 90 and NSRI 20 to 50 was targeted *via* SPV. Deepening the anesthetic depth (TOL>90 or NSRI<20) resulted in positive association with an increase and prolongation in latency and at least 50% decrease in amplitude of neuromonitoring signals because of increased anesthesia time spent with hypotension (MAP<60 mmHg). As reported in the literature, hypotension affects not only the quality of evoked potentials but neurologic outcome as well [31]. Although intraoperative hypotension is a multifactorial issue, the fact that more patients in the control group had hypotensive episodes, consumed more propofol, and took longer to recover led us to assume that using SPV-guided anesthesia reduced the hypotensive period. Besides perioperative hemodynamic control, SPV enabled enhanced recovery, in line with a recent article [32].

As a limitation, this is a single-center analysis in retrospective style with low sample size therefore verification of our findings would be needed. In order to assess the impact of an anesthesia regimen on overall hemodynamic performance, a more strict elimination of the confounding factors such as comorbidities of the participants, intraoperative blood losses, positioning etc. might be mandatory. Moreover, the evaluation of short-term neurological outcomes would be valuable.

Conclusion

Compared to usual practice, SPV-guided anesthesia management decreased intraoperative hypotension duration, thereby reducing possible adverse impact of hypotension on neuromonitoring in patients undergoing neurosurgery. The idea that SPV-guided TCI anesthesia improves the effectiveness of neuromonitoring during neurosurgery is supported by our results. SmartPilot® View has been a helpful tool for improving the efficiency of standardized TCI regimens and enhancing our anesthetic management during INM by reducing the anesthetic effects on neurophysiological responses. In terms of perioperative hemodynamic control and enhanced recovery, SPV-guided anesthesia was considered clinically superior to our previous experience. Further research, however, is needed to determine whether SPV has beneficial effects on patient outcomes.

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