PROPOFOL-BASED INTRAVENOUS ANESTHESIA IN PATIENTS WITH BRUGADA SYNDROME. A SINGLE-CENTER, 25 YEAR, RETROSPECTIVE COHORT ANALYSIS.

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Word Count

Abstract: 324

Introduction: 240

Discussion: 1106

Entire body (abstract & references excluded): 2713

Financial Disclosures: None

Conflicts of interest: None

Abbreviated Title: (<50 characters) Total IntraVenous Anesthesia in Brugada Syndrome

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Key Points Summary

- Question: Does the administration of a propofol-based total intravenous anesthesia increase the risk of arrhythmias for patients with Brugada Syndrome?
- Findings: This retrospective analysis could not reveal the occurrence of malignant arrhythmias in patients with Brugada Syndrome when providing clinical doses of propofol-based total intravenous anesthesia.
- Meaning: Patients with Brugada Syndrome who might benefit from a propofol-based total intravenous anesthesia should not be deprived of this option.

ABSTRACT

Background: Propofol administration in patients with Brugada Syndrome is still a matter of debate. Despite lacking clear evidence for its feared arrhythmogenicity based on its sodium-channel blocking properties, up to date, expert cardiologists in the electrophysiologic field still recommend avoiding propofol. However, propofol-based total intravenous anesthesia has many advantages over volatile-based anesthesia. Besides having neuroprotective properties, it is associated with a favorable recovery profile and a better patient experience. Total intravenous anesthesia provides less risk for nausea and vomiting, emergence agitation and postoperative pain. The main aim of this study was to assess the association between propofol-based total intravenous anesthesia in patients with Brugada Syndrome and the occurrence of adverse events during or after administration.

Methods: We performed a retrospective cohort study on the data of patients with Brugada Syndrome, from January 01, 1996 to September 30, 2020, who received continuous propofol infusions. Only patients that received propofol-based total intravenous anesthesia were included. We analyzed the anesthetic and electronic medical records of all eligible patients for the occurrence of malignant arrhythmias, adverse events, need for defibrillation, major hemodynamic support, hospital length of stay and the 30-days mortality.

Results: Thirty-three Brugada Syndrome patients were included in the study. The mean age of the cohort was 48 ± 16 years with a male to female approximate ratio of 1 to 3. Four-teen patients had an automated cardiac defibrillator implanted, therefore considered as high-risk patients. Seven out of twenty-seven genetically screened patients were carriers of the SCN5A mutation. The median duration of propofol infusion was 60 minutes. In the current study, no malignant arrhythmias or defibrillations were reported. The 95% confidence interval, calculated with Hanley's formula, of the estimated risk for malignant arrhythmias was [0, 9.1].

Conclusions: In this retrospective analysis, a propofol-based anesthesia in patients with Brugada Syndrome, was not associated with malignant arrhythmias or adverse events when clinical infusion rates were provided. Prospective evaluation of these findings is necessary and thorough preoperative screening and precautionary measures are still recommended whenever general anesthesia or sedation is deemed necessary.

Glossary of Terms

AICD	Automated Implantable Cardiac Defibrillator
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BrS	Brugada Syndrome
ECG	ElectroCardioGram
GABA	Gamma Aminobutyric Acid
ICU	Intensive Care Unit
IRB	Institutional Review Board
LOS	Length Of Stay
NMDA	N-Methyl D-Aspartate
PONV	Post-operative Nausea and Vomiting
PACU	Post-operative Anesthesia Care Unit
PRIS	Propofol Infusion Syndrome
SCN5A	Sodium Channel 5A subunit
STROBE	Strengthening The Reporting of OBservational studies in Epidemiology
SPC	Summary of Product Characteristics
ST-segment	Electrocardiographic ST-segment
TCI	Target Controlled Infusion
TIVA	Total IntraVenous Anesthesia
WHO	World Health Organization

BODY TEXT

Introduction

Brugada Syndrome (BrS) is an autosomal dominant transmitted arrhythmic disorder with incomplete penetrance and expression.[1] Firstly described in 1992 and acknowledged in 1997 as a distinct arrhythmogenic disease[2], it is diagnosed by an accentuated J-wave or ST-segment elevation of at least 2mm — *coved type 1* ST-elevation — in at least one right precordial lead (V_1 to V_3).[3] The pathophysiology of BrS is still not fully understood. BrS is a rare disease with already more than twenty genes associated.[4] Mutations in the myocardial sodium channel gene SCN5A are believed to be among the most relevant and linked with an increased propensity of malignant arrhythmias.[5]

Propofol, an intravenous short-acting hypnotic, is widely used to induce and maintain general anesthesia for surgery, procedural sedation and sedation for mechanically ventilated patients at the intensive care unit.[6-8] Its pharmacokinetic and pharmacodynamic profile renders it as an advantageous agent in the aforementioned settings. Moreover, propofol is included since 2011 in the "model list of essential medicines" of the World Health Organisation.[9]

Considering the sodium channel blocking properties of propofol[6], the cardiological society of BrS recommends avoiding its administration in patients burdened with this pathology. Nevertheless, up to date no prospective clinical trials have been carried out to investigate its arrhythmogenic potential.[10-13]

This single-center study aimed primarily to investigate whether propofol-based total intravenous anesthesia (TIVA) was associated with the occurrence of malignant arrhythmias and adverse events in patients with BrS the past twenty-five years. The secondary aim was to analyze the length of hospital stay and the 30-day mortality outcome.

Methods

After Institutional Review Board (IRB) approval (Nr. 2020/226) and waiving of informed consent requisite, this retrospective cohort study indexed registered BrS patients admitted to the University Hospital of Brussel receiving propofol-based TIVA, for an elective surgery or procedure. From 1996 on, all consecutive patients diagnosed with BrS are charted in the internal database of the Heart and Rhythm Management Cardiovascular intra-hospital center. In the present study, all BrS patients receiving propofol-based TIVA — from January 01, 1996 to September 30, 2020 — were screened. Additionally, BrS patients admitted at the intensive care unit, necessitating mechanical ventilation and sedation with propofol, were similarly traced.

Our institution's database listed 789 consecutive BrS patients. Their intraoperative period is retrospectively and digitally traceable by means of highly qualitative digital anesthesia charts (Metavision®) based on live time-stamped data feeds from anesthesia workstations. This intra-operative register is further centrally linked to the Electronic Health Record of the hospital (KWS®), facilitating a fluent interchange and overview of perioperative data. However, when patients undergo sedation at an out-of-theatre location, due to compromising infrastructure, the anesthetic charts are filled in manually. At the end of the procedure, those records are scanned and stored into the hospitals' Electronic Health Record. Only adult patients from our local Brugada database with general anesthesia or sedation with propofol-based TIVA were included. The ICU data are also high qualitative digital charts from the same interface (Metavision®) based on live time-stamped data feeds. They are linked to the Electronic Health Record of the hospital (KWS®).

An individual anesthetic- and ICU-chart review of data during the propofol infusion was conducted. Moreover, outcome measures were investigated. Collected data included the duration and dose of propofol infusion and all other intravenously administered drugs. Adverse outcomes during propofol-infusion, subdivided as major hemodynamic support by means of epinephrine administration or defibrillation due to the de novo incidence of malignant arrhythmias, were dichotomically classified (yes/no). Similarly, the incidence of these complications in the post-operative setting (post-operative

adverse outcomes) were investigated by means of an individual analysis of the digitalized post-operative monitoring data at the post-operative anesthesia care unit (PACU) and the ward. Finally, the medical records were assessed for delayed out-of-hospital discharge, hospital readmission within 30-days and mortality within 30-days after anesthesia, all similarly noted as yes/no nominal data. The same data was collected for patients that received propofol-infusions at the ICU.

This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[14]

The demographic and clinical characteristics of the cohort such as the American Society of Anesthesiologists (ASA) physical status classification, body mass index (BMI), rates and duration of propofol-based TIVA, temperature, adjuvant medication, genetic screening, malignant arrhythmias and adverse events were registered.

Propofol-based TIVA was provided by pre-programmed pumps with commonly published Target Controlled Infusion (TCI) protocols (e.g. Marsh©, Schnider©). In some cases, mainly for short procedural sedations, propofol-based TIVA through manually dialed-in rates was used. When procedures took place in the central operating theater, the infusion rate was automatically recorded thanks to a direct connection of the pump with the digital anesthesia workstation. For patients in possession of an AICD, the read-out record of the AICD was investigated postoperatively for the occurrence of malignant arrhythmias.

We defined malignant arrhythmias as registered de novo ventricular or supraventricular arrhythmias with significant hemodynamic deterioration and need for treatment with defibrillation or epinephrine. All post-operative medical files were scrutineered up to the discharge of each patient out of hospital. A follow-up period of thirty days upon the intervention was evaluated through our institution's digital medical records for readmission and mortality.

No power analysis was deemed necessary since all eligible patients were included in the study. Descriptive statistics were used, and values are reported as mean ± standard deviation. In the case of

proportions, the absolute numbers were reported, followed by percentages. Since the incidence of BrS is relatively low, producing a limited cohort size, with a zero numerator for malignant arrhythmias, the estimate of this risk was calculated by the *rule of three (3/n)*[15] with a type-1 error of 0.05.

Results

From the institution's database, 789 patients diagnosed with BrS receiving anesthesia were screened. One hundred and seventy-one of these had undergone at least one surgical procedure under general anesthesia. A sub-analysis revealed that 139 of those patients received propofol as a bolus for induction of a volatile-based anesthesia. In one patient propofol-based TIVA was initiated but there were missing data in the anesthetic chart and was therefore excluded. A total of thirty-three patients with BrS and a propofol-based TIVA were retained for analysis (figure 1). All included patients received continuous propofol infusions for anesthesia or sedation.

This specific cohort's mean age was 48 ± 16 years with a male to female approximate ratio of 1:3. Only nine (27%) patients were male. Seven out of twenty-seven genetically screened patients carried the SCN5A mutation (26%). Twenty-seven (87%) patients had a history of a brutal syncope and fourteen (45%) had an AICD implanted. Despite the small size of the cohort, based on those ratios we considered the cohort representative for BrS patients with a low bias inclusion. All patients but one, were normothermic before their intervention. Nineteen patients (79%) had a history of an uneventful surgical procedure under general anesthesia, as reported at their preoperative consultation. The demographic and perioperative clinical characteristics are summarized in table 1.

The propofol rates are reported either in $mcg.ml^{-1}$, when TCI was provided or in $mg.kg^{-1}.h^{-1}$ for TIVA. Due to the variety of pre-programmed pump protocols (e.g. Marsh©, Schnider©, plasma-concentration, effect-site concentration) available for TCI anesthesia and the study's retrospective nature, we could not differentiate between the selected protocols to report a mean administrated dose.

The median duration of propofol-infusion duration was 60 minutes. Infusion rates varied for TCI between 2 and 6 $mcg.ml^{-1}$ and for TIVA between 0.8 and 10.0 $mg.kg^{-1}.h^{-1}$. (Table.1)

Analysis of the anesthetic charts and medical files, along with the AICD read-outs, revealed no malignant arrhythmias requiring defibrillation intra- or post-operatively. We evaluated the patients for readmission within 30-days upon their initial procedure. Only one patient was re-admitted for a

re-intervention, after his initial treatment of a caustic-induced esophageal-stenosis was deemed insufficient. The 30-day mortality assessment revealed one patient died at the ICU. This ASA 4 patient was initially admitted at the hospital for an acute alcoholic hepatitis. The patient developed severe respiratory insufficiency for which mechanical ventilation, facilitated by propofol-based TIVA, was provided at the ICU. The patient developed Acute Respiratory Distress Syndrome (ARDS) followed by pancreatitis, septic shock with multiple organ failure. The patient died five days after the ICU admission. There was no evidence of malignant arrhythmias. All remaining patients were safely discharged from the hospital.

One postoperative event was registered on the ward four hours after the end of a propofol-based TIVA. It concerned an asymptomatic BrS patient with a negative electro-physiological study, electively planned for a mandibula osteotomy. The patient experienced a vagal reaction after using the bathroom. No syncope was noted. His vital parameters were normal upon subsequent control. There was no suspicion of a malignant arrhythmia and his previous and further perioperative surveillance and 30-days follow up were uneventful.

Due to the zero numerator of malignant arrhythmias (making impossible to use the normal approximation, i.e. the asymptotic/Wald confidence interval), risk estimation was computed with Hanley's formula (3/n). In this line of thought, the 95% confidence interval of the calculated risk for malignant arrhythmias in the present cohort was [0, 9.1].

Discussion

A previously conducted retrospective analysis of volatile-based anesthesia induced by a bolus propofol, in BrS patients, failed to demonstrate the occurrence of perioperative malignant arrhythmias.[16] A recent prospective randomized controlled trial compared propofol versus etomidate in bolus, for induction of anesthesia in BrS. No significant difference in electrocardiographic changes was observed between these groups. No perioperative arrhythmic events were registered either.[17] In the current single-center retrospective trial, we were unable to find evidence that propofol-based TIVA was associated with malignant arrhythmias or adverse outcomes in patients burdened with BrS.

The study's strength is the representative cohort of patients with a disease of low prevalence, with high-quality digital life-feed data registration. The prevalence of BrS varies worldwide, not only geographically, within ethnicities but also between age-groups. The global prevalence is estimated to range from 1 : 5.000 to 1 : 2.000, although the exact prevalence is hard to assess, since the dynamic character of the electrocardiographic pattern if often concealed.[18] Although the *a priori* risk-stratification in BrS is still debatable, judged by the high percentage of patients with an AICD (47%), almost half of our patients were considered high risk. Moreover, the incidence of an SCN5A mutation in the study´s cohort (26%) is similar to the Brugada population's estimated incidence (20 to 30%).[19] Based on those findings, we believe that the cohort was representative with a low risk for inclusion bias from this prospectively collected database.

The present study also comes with limitations, one being it´s retrospective nature. Prospectively controlled studies are ideal for this purpose, although limited by a clear rare disease inclusion bottleneck. Such study is currently undergoing for this purpose (NCT trial register 2019-004750-28). Another weakness relates to the limited size of the cohort, both due to the low incidence of BrS and the well-known preference from anesthesiologists to provide volatile-based anesthesia instead of propofol-based TIVA. The choice of volatile-based anesthesia might stem also from the cardiology consortium endorsements to avoid propofol in BrS. On the other hand, another 139 patients received propofol as an induction agent. Finally, transient electrocardiographic changes or arrhythmias without

a direct hemodynamic impact have the potential to be missed out in a retrospective analysis. On the other hand, the clinical significance of such changes should equally be subject to debate.

Up to date, the physio-pathological mechanism of BrS remains incompletely understood. It´s low prevalence together with a lacking clear-cut risk-stratification makes the treatment of these patients challenging. Moreover, literature relating propofol with BrS is mostly composed of single case observations, small cohorts and retrospective observations within complex circumstances, resulting in conflicting evidence. Concordantly, providing an evidence-based patient-tailored anesthetic plan remains equally challenging.

It is known that patients with BrS are more prone to develop malignant arrhythmias during episodes of fever or increased vagal tone, as well as after the administration of certain medications.[20] Propofol is the most commonly used hypnotic, based on its favorable pharmacokinetic and pharmacodynamic profile.[7, 8] Besides being an excellent hypnotic for induction of anesthesia, with anxiolytic, anti-convulsive and anti-emetic effects, the added value of propofol for the maintenance of anesthesia in specific situations has already been demonstrated. Not only does it hold neuroprotective properties,[21] but similarly leads to a reduced risk of post-operative nausea and vomiting (PONV), as well of coughing/straining during emergence. Moreover, international guidelines put forward propofol as the drug of choice for anesthesia and sedation of mechanically ventilated patients.[22-24]

From a pharmacological perspective, propofol has stimulating properties on the central acting γ-aminobutyric acid A ($GABA_A$) and $GABA_B$ receptors, blocks N-methyl D-aspartate (NMDA) receptors, diminishes calcium influx via slow calcium ion channels and has also been described to have sodium channel blocking properties.[6] Presumably, it is based on its sodium channel blocking properties that propofol's arrhythmogenic potential is derived. In essence, anesthesiologists are currently confronted with a pathophysiological incompletely understood phenomenon, as well as with an unestablished causal clinical relationship. Moreover, some of the abovementioned assumptions are derived from *in vitro* experiments, often with supra-clinical or toxic doses, which should not be directly translated to humans. In fact, Saint et al. demonstrated, *in vitro*, the effects of propofol on

single-channel sodium currents in ventricular myocytes. They also report a significant dissociation between macroscopic current and myocardial single-channel behavior.[25] Few studies exist on propofol's effect on sodium currents, probably due to the complexity of separating the impact of the different ionic currents. Besides that, other ion channels and their respective currents similarly play a role during the different phases of (re-) depolarization. The net effect, in vivo, is presumably even more challenging to predict. Conversely, other studies reported no significant effect of propofol on the myocardial conduction system, rendering it an ideal hypnotic for sedation during electrophysiological studies.[26-28] Finally, Probst et al. already questioned the main role of SCN5A as a causal pathology for BrS.[19]

Despite the findings presented herein, it is primordial to remain prudent when administering propofol-based TIVA for anesthesia purposes. As evidenced by the known propofol infusion syndrome (PRIS)[29], the previous statement applies to all patients. The first putative association of propofol infusion with the cardiac death of a three-year-old was in 1990.[30] In 1992, Park et al. reported the death of five children that were on propofol infusion.[31] The definition of PRIS was then a well-defined complication, characterized by acute bradycardia —unresponsive to therapy— progressing to asystole in association with propofol infusion. Other characteristics were rhabdomyolysis, myoglobinuria, elevated serum creatine kinase, serum urea, serum potassium, lipemic plasma, ketonuria, increased liver enzymes, green or red-colored urine, unexplained metabolic acidosis, fatty liver enlargement, multiple organ failure and eventually cardiac failure. Interestingly, in a comprehensive review, Hemphill et al. found that not all of the aforementioned findings are seen when PRIS is diagnosed.

Prolonged propofol administration can lead to the lethal complication of PRIS. Nonetheless, it is still unclear what its exact pathophysiologic is. In a recent structured literature review from Hemphill et al., it is suggested that the cumulative dose of propofol plays an important role in the etiology of PRIS, either through high infusion rates, prolonged duration, or both. For this purpose, within the maximal dose ranges reported for the patients included in the present study (5mcg.mL^{-1} for TCI and

10mg.Kg^{-1} TBW.mL^{-1} for weigh-time-based dosing schemes) no ventricular arrhythmias have been reported. Other commonly accepted risk factors are critical illness, children, traumatic brain injury, increased catecholamine levels (endo- or exogenous), impaired microcirculation and carbohydrate supply [32]. As finally also reported by the manufacturer in the summary of product characteristics (SPC), the main precautions are adherence to recommended propofol-dosing, adequate glucose control and good hemodynamic and oxygen delivery management.[33]

To summarize, clinical characteristics and data during propofol-based TIVA of thirty-three consecutive BrS patients were retrospectively analyzed in this study. Propofol-based TIVA with a mean duration of 60 minutes, within clinically acceptable infusion rates, was not associated with new malignant arrhythmias or adverse outcomes.

Conclusion

From the current retrospective analysis, we could not reveal malignant arrhythmias occurring with propofol-based total intravenous anesthesia in adult, afebrile, BrS patients. Prospective studies with propofol-based total intravenous anesthesia should be conducted to investigate potential electrocardiographic effects.

Funding: None

References

1. Brugada P. BJ. Right bundle branch block, persistent ST segment elevation and sudden cardiac death A distinct clinical and electrocardiographic Syndrome. A multicenter report. *JACC*. 1992;20(6):1391-6.

2. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation*. Oct 21 1997;96(8):2595-600. doi:10.1161/01.cir.96.8.2595

3. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. Dec 2013;10(12):1932-63. doi:10.1016/j.hrthm.2013.05.014

4. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. *J Am Coll Cardiol*. Aug 28 2018;72(9):1046-1059. doi:10.1016/j.jacc.2018.06.037

5. Lippi G, Montagnana M, Meschi T, Comelli I, Cervellin G. Genetic and clinical aspects of Brugada syndrome: an update. *Adv Clin Chem*. 2012;56:197-208.

6. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties. *CNS Neurosci Ther*. Summer 2008;14(2):95-106. doi:10.1111/j.1527-3458.2008.00043.x

7. Langley MS, Heel RC. Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs*. Apr 1988;35(4):334-72. doi:10.2165/00003495-198835040-00002

8. Pollard BJ, Elliott RA, Moore EW. Anaesthetic agents in adult day case surgery. *Eur J Anaesthesiol*. Jan 2003;20(1):1-9. doi:10.1017/s0265021503000012

9. World Health Organization (WHO) UMC. The use of the WHO-UMC system for standardized case causality assessment. . Updated May 08, 2020. Accessed May 08, 2020, http://www.who.int]

10. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). *Heart Rhythm*. Sep 2009;6(9):1335-41. doi:10.1016/j.hrthm.2009.07.002

11. Vernooy K, Delhaas T, Cremer OL, et al. Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. *Heart Rhythm*. 2006;3(2):131-137.

12. Robinson JD, Melman Y, Walsh EP. Cardiac conduction disturbances and ventricular tachycardia after prolonged propofol infusion in an infant. *Pacing Clin Electrophysiol*. Aug 2008;31(8):1070-3. doi:10.1111/j.1540-8159.2008.01138.x

13. M. I, H. O, M. K, S. H. General anesthesia for patients with Brugada syndrome. A report of six cases. *Can J Anesth*. 2005;52(4):409-412.

14. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. Oct 16 2007;147(8):573-7. doi:10.7326/0003-4819-147-8-200710160-00010

15. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*. Apr 1 1983;249(13):1743-5.

16. Flamée P, De Asmundis C, Bhutia JT, et al. Safe single-dose administration of propofol in patients with established Brugada syndrome: a retrospective database analysis. *Pacing Clin Electrophysiol*. Dec 2013;36(12):1516-21. doi:10.1111/pace.12246

17. Flamée P, Varnavas V, Dewals W, et al. Electrocardiographic Effects of Propofol versus Etomidate in Patients with Brugada Syndrome. *Anesthesiology*. Mar 2020;132(3):440-451. doi:10.1097/ALN.0000000000003030

18. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A meta-analytic review of prevalence for Brugada ECG patterns and the risk for death. *Medicine (Baltimore)*. Dec 2016;95(50):e5643. doi:10.1097/MD.0000000000005643

19. Probst V, Wilde AA, Barc J, et al. SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome. *Circ Cardiovasc Genet*. Dec 2009;2(6):552-7. doi:10.1161/CIRCGENETICS.109.853374

20. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. Feb 08 2005;111(5):659-70. doi:10.1161/01.CIR.0000152479.54298.51

21. Petersen KD, Landsfeldt U, Cold GE, et al. Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: a randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. *Anesthesiology*. Feb 2003;98(2):329-36. doi:10.1097/00000542-200302000-00010

22. Gan T, Diemunsch P, Habib A, et al. Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. *Anesthesia and analgesia*. 01/01 2014;118:85-113. doi:10.1213/ANE.0000000000000002

23. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on post-operative delirium. *Eur J Anaesthesiol*. Apr 2017;34(4):192-214. doi:10.1097/EJA.0000000000000594

24. Barr J, Pandharipande PP. The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. *Crit Care Med*. Sep 2013;41(9 Suppl 1):S99-115. doi:10.1097/CCM.0b013e3182a16ff0

25. Saint DA. The effects of propofol on macroscopic and single channel sodium currents in rat ventricular myocytes. *Br J Pharmacol*. Jun 1998;124(4):655-62. doi:10.1038/sj.bjp.0701876

26. Pires LA, Huang SK, Wagshal AB, Kulkarni RS. Electrophysiological effects of propofol on the normal cardiac conduction system. *Cardiology*. Jul-Aug 1996;87(4):319-24. doi:10.1159/000177113

27. Erb TO, Kanter RJ, Hall JM, Gan TJ, Kern FH, Schulman SR. Comparison of electrophysiologic effects of propofol and isoflurane-based anesthetics in children undergoing radiofrequency catheter ablation for supraventricular tachycardia. *Anesthesiology*. Jun 2002;96(6):1386-94. doi:10.1097/00000542-200206000-00018

28. Lavoie J, Walsh EP, Burrows FA, Laussen P, Lulu JA, Hansen DD. Effects of propofol or isoflurane anesthesia on cardiac conduction in children undergoing radiofrequency catheter ablation for tachydysrhythmias. *Anesthesiology*. Apr 1995;82(4):884-7. doi:10.1097/00000542-199504000-00010

29. Roberts RJ, Barletta JF, Fong JJ, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care*. 2009;13(5):R169. doi:10.1186/cc8145

30. Hatch DJ. Propofol-infusion syndrome in children. *Lancet*. Apr 3 1999;353(9159):1117-8. doi:10.1016/S0140-6736(99)90018-1

31. Parke TJ, Stevens JE, Rice AS, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ*. Sep 12 1992;305(6854):613-6.

32. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth*. Apr 2019;122(4):448-459. doi:10.1016/j.bja.2018.12.025

33. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. *Minerva Anestesiol*. 2009;75:339-44.