Brugada Syndrome and Anesthesia: A Systematic Review

Zafar Aleem Suchal[1], Ahmad Afzal[1], and Amin H. Karim[2]

[1]The Aga Khan University Hospital
[2]Houston Methodist Academic Institute

December 25, 2022

Abstract

Brugada Syndrome is an inherited disorder causing specific changes on electrocardiogram (ECG) pattern of right bundle branch block and persistent ST elevation in right precordial leads increases the risk of cardiac arrest and fatal arrhythmia. Patients with brugada are prone to abnormal cardiac rhythms which can be induced by alcohol, stress, vagal stimulation, and certain medications. Thus medications are divided into different classes from I to III with I carrying the most evidence for potential arrhythmia while III being the least likely. Exceptional care needs to be taken to avoid anesthetic and analgesic during surgeries for such patients as several of the known anesthesia medications can lead to arrhythmia in these patients. In this review we aimed to study the effect different anesthetic and analgesic medication could have on patients with brugada syndrome. We conducted a systematic review following PRISMA guidelines to query PubMed, Embase, Cochrane library and ProQuest electronic databases. Mesh combinations and synonyms of "Brugada Syndrome", "Anesthesia", "Analgesics" were used. We included all original human studies that focused on outcomes of anesthetic and analgesics on patients with brugada. After screening 1149 studies, we included 49 articles consisting of a total of 1414 subjects for qualitative analysis. We found local analgesics to be least likely to lead to potential arrhythmic complications with other systemic and inhaled agents having a risk although the risk varied because of multitude of reasons ranging from type of drug to patient factors like the patient's condition and type of Brugada. We concluded that anesthetic although could be used for individuals with Brugada the type of anesthetic to be used should be selected keeping the potential cardiac risk under consideration.

Brugada Syndrome and Anesthesia: A Systematic Review

Zafar Aleem Suchal MBBS[1], Ahmad Afzal MBBS[1], Amin H. Karim MD[2]

[1] College of Medicine, Aga Khan University, Karachi, Pakistan

[2] Assistant Professor of Clinical Cardiology, Academic Institute of Houston Methodist Hospital, Houston, Texas, USA

Corresponding Author

Name: Zafar Aleem Suchal

Email: zafar.suchal21@alumni.aku.edu

Brugada Syndrome and Anesthesia: A Systematic Review

Zafar Aleem Suchal, Ahmad Afzal, Amin Karim

Abstract

Brugada Syndrome is an inherited disorder causing specific changes on electrocardiogram (ECG) pattern of right bundle branch block and persistent ST elevation in right precordial leads increases the risk of cardiac arrest and fatal arrhythmia. Patients with brugada are prone to abnormal cardiac rhythms which can be

induced by alcohol, stress, vagal stimulation, and certain medications. Thus medications are divided into different classes from I to III with I carrying the most evidence for potential arrhythmia while III being the least likely. Exceptional care needs to be taken to avoid anesthetic and analgesic during surgeries for such patients as several of the known anesthesia medications can lead to arrhythmia in these patients. In this review we aimed to study the effect different anesthetic and analgesic medication could have on patients with brugada syndrome.

We conducted a systematic review following PRISMA guidelines to query PubMed, Embase, Cochrane library and ProQuest electronic databases. Mesh combinations and synonyms of "Brugada Syndrome", "Anesthesia", "Analgesics" were used. We included all original human studies that focused on outcomes of anesthetic and analgesics on patients with brugada.

After screening 1149 studies, we included 49 articles consisting of a total of 1414 subjects for qualitative analysis. We found local analgesics to be least likely to lead to potential arrhythmic complications with other systemic and inhaled agents having a risk although the risk varied because of multitude of reasons ranging from type of drug to patient factors like the patient's condition and type of Brugada.

We concluded that anesthetic although could be used for individuals with Brugada the type of anesthetic to be used should be selected keeping the potential cardiac risk under consideration.

Keyword: Brugada Syndrome, Anesthesia, Analgesia, Arrhythmia

Introduction

To function properly the heart needs its own electrical circuit that can keep the heart functioning with minimum input from the rest of the body, however there are instances when the flow of current can be disturbed due to a variety of causes making the heart prone to cardiac arrest and fatal arrhythmias (1). One such condition first described in 1992 is Brugada Syndrome, an inherited disorder causing specific changes on electrocardiogram (ECG) pattern of right bundle branch block and persistent ST elevation in right precordial leads (2). A disease that has only been known for 30 years there are several factors regarding the syndrome that are still unknown and the methods of treatments for the individuals affected is still debated. Over the years several studies have come forward shedding light on the inheritable nature of the syndrome, in one such recent study Marina et al discusses that how out of the 23 genes known to be associated with the syndrome, only SCN5A, a gene coding for cardiac sodium channels, has shown to be have clinical action (3).

The diagnosis of the disease is further made difficult by its heterogenetic nature and variable expression even in individuals from the same family as it has an autosomal dominant inheritance and incomplete penetrance (4). The syndrome has been further divided into three subtypes according to ECG pattern, type 1, 2 and 3 according to the degree of ST elevation (5). Out of these, individuals with type 1 ECG pattern have shown to be most susceptible to sudden ventricular fibrillations, fatal arrhythmias, and cardiac deaths (6). Even in people with a similar ECG pattern of brugada the symptoms can vary from dizziness, fainting, shortness of breath, palpitations, and seizures to even some people being completely asymptomatic with the diagnosis of brugada being only an incidental ECG finding (7). Furthermore, it has come to light recently that brugada pattern can sometimes be unmasked in individuals who have inherited the disorder because of other conditions such a fever, injuries, COVID and other viral illnesses, stress and even certain medications and anesthetic agents (8).

Due to the nature and presentation of the syndrome the treatment guidelines are still something debated on as despite the higher than average risk of life threatening cardiac events many patients can live most of their life without facing any issue and without any symptom (9). Furthermore the main treatment of Brugada, an implantable cardiac defibrillator (ICD) has the patient undergo invasive procedure presenting with its own medical and financial complications (10). Thus currently it is agreed upon that treatment with ICD should only be undergone after the patient undergoes risk stratification for fatal cardiac events where a decision by physician is to be made after evaluating the patient's symptoms, previous history of arrhythmias, risk factors that can lead to arrhythmia and comorbities (11).

Furthermore as individuals with brugada syndrome are more susceptible to arrhythmia care must be taken when prescribing them medications as several medicines can increase the risk of adverse cardiac events. An extensive review by Postema et al showed that medications are divided from class I to III in accordance with their potential of leading to life threatening arrhythmias (12). However the effect anesthesia agents can have on patients is a topic that still needs further research so that a guideline can be made showing the anesthetic to avoid or give depending on the type of surgery and patient condition so the treatment for each patient can be patient centric and individualized. The purpose of this review is to summarize and discuss current literature and studies on the effect of anesthesia on brugada patients.

Materials and Methodology

Search Strategy and Selection Criteria

The review was conducted in accordance with the guidelines laid out by Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) (13) and the Cochrane Handbook for Systemic Reviews and Interventions V 5.1.0 (14). We included all the studies done on a human population irrespective of age, gender or ethnicity that explored the outcomes for anesthetic agents on patients with Brugada syndrome. Our review included case reports, case series and clinical trials that discussed this particular issue. Furthermore the studies done on non-human subjects, any reviews and those with no mention of outcome were excluded from our review. We also excluded studies that were not in English language.

The literature search was performed on PubMed, Embase, Cochrane Library and Proquest electronic database. In an attempts to include unpublished studies and trials Clinical Trials and National Research Register were also searched. In the cases of studies with incomplete data attempts were made to contact the authors and if not possible the data was excluded from our review. Depending on the search requirement for different databases various combination for the following search term were used without any restriction in terms of publication date or publication status: Brugada Syndrome, Brugada, Anesthesia, Anesthetic Agents and Anesthesia Drugs. The MESH term used for PubMed was ("Brugada Syndrome"[Mesh] OR "Brugada"[Mesh]) AND ("Anesthesia"[Mesh] OR "Anesthesia Agent"[Mesh]). Cross Checking for repeat articles was done manual after the literature search.

Data Extraction and Standardization

Data extraction on the selected studies was performed by an author and then independently reviewed by another author to minimize the chances of error. Study related data collected included the name of the first author, the year of publication, the type of study, the number of patients included in the study, the ethnicity/country of the participants. Data was also collected on the type of Brugada, if the syndrome had been previously diagnosed, the agent used for anesthesia and the outcomes after the administration of anesthesia.

Outcome Analysis

The outcome analysis was performed in accordance with our eligibility criteria. We looked sat ECG findings after the administration of anesthesia as our primary outcome. Where specified the type of surgery, the operating time and follow up period were also considered as well as the type of brugada pattern seen on ECG. The clinical picture of patient after the surgery and any resuscitation measures needed post anesthesia were considered the secondary outcome.

Quality Assessment and Risk of Bias

For the randomized control trials in our review, Cochrane Collaborations Risk of Bias tool (ROB 2.0) (15) was used for quality assessment. Each study was assigned as possessing a low, unclear, or high risk of bias by checking five domains: randomization process, deviation from intended intervention, missing outcome data, measurement of selected outcome and selective outcome reporting.

For non-randomized studies the Cochrane library tool Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) (16) was used with the study being assigned low, moderate, serious, or critical risk of

bias unless there was an indeterminate amount of information. Seven domains were assessed: confounding, selection of participants, classification of intervention, deviation from intended interventions, missing data, measurement of outcomes and selection of reported results.

In the case of case reports and case series, it was not possible to apply the above-mentioned tools as risk of bias is inheritably high in such articles. The results for the bias assessment have been summarized in Figures 1 & 2.

Figure 1. ROB 2.0 for RCTs

Figure 2. ROBIN-1 for non-randomized trials

These risks of biases were evaluated by two authors and then reviewed by a third author to ensure accuracy.

Results

After a thorough literature search of the online databases and identifying, screening and selecting studies based on our eligibility criteria a total of 48 studies were selected for the purpose of our review. All studies were published in medical journals and were in English. These included twenty-nine case reports (18-45), nine case series (46-54), eleven clinical trials out of which four were randomized (55-58) and seven were non-randomized (59-65). The process of study selection has been summarized in Figure 3.

Figure 3. Flow Diagram for Study Selectio

Study Characteristics

The total number of patients included in our review were 1414 with 28 of these patients being from case reports, 299 being from case series, 318 being from non-randomized control trials and 769 from randomized control trials. The data included effect of anesthetic agents observed in various different surgeries. The characteristics of the studies selected, and the data extracted from them has been summarized in Table 1-4. The adverse events occurring in different patients and the agents leading to adverse events have been summarized in Figures 4 and 5.

Author	Country	Year	Anesthetic Agent	Outcome
Mónica Nunes Ferreira **(18)**	Portugal	2019	Intrascalene Plexus Block & Propofol	No arrythmia found
Pasquale Loiudice **(19)**	Italy	2020	Lidocaine	No arrythmia found
Shayla Mena **(20)**	USA	2022	Lidocaine	No arrhythmia found
Kevin Vernooy **(21)**	Netherlands	2006	Bupivacaine	Induced Brugada Pattern
Carla Gould **(22)**	Korea	2021	Remifentanil	Pregnant Patient, Brugad
Chandra M Kumar **(23)**	Singapore	2021	Bupivacaine & Lidocaine	No arrythmia found
Ebru Biricik **(24)**	Turkey	2016	Rucoronium & Sugammadex	No arrythmia found
Bahattin Tuncalı **(25)**	Turkey	2021	Thiopental, Sevoflurane & Sugammadex	No arrythmia found
Cengiz Sahutoglu **(26)**	Turkey	2018	Sugammadex, Sevoflorane & Tramadol	Arrythmia temoprally
Haruyuki Yuasa **(27)**	Japan	2021	Remifentanil	No arrythmia found
Tariq Alzahrani **(28)**	Saudi Arab	2016	Propofol	Cardiac Arrest
Sally A Corey **(29)**	Georgia	2017	Bupivacaine	Ventricular Fibrilation
B Oliván **(30)**	Spain	2016	Lidocaine	Induced Brugada Pattern
Junpei Konishi **(31)**	Japan	2012	Rocuronium & Sugammadex	No arrythmia found
Halide Hande Şahinkaya **(32)**	Turkey	2016	Remifentanyl	No arrythmia found
Pietro Paolo Martorano **(33)**	Italy	2013	Remifentanyl & Midazolam	No arrythmia found
Shwetal Goraksha **(34)**	India	2010	Propofol & Remifentanyl	Ventricular Fibrillation
J Bramall **(35)**	UK	2011	Bupivicaine	No arryhtmia found
Duygu Uzun **(36)**	USA	2020	Propofol	Ventricular arrhythmia
Yoshihiro Fujiwara **(37)**	Japan	2006	Propofol & Remifentanyl & Vecuronium	Ventricular Fibrillation
Laura Baty **(38)**	USA	2008	Propofol	Ventricular arrhythmia

Author	Country	Year	Anesthetic Agent	Outcome
A Vaccarella (39)	Italy	2008	Propofol &, Remifentanyl & Atracurium	No arrhythmia found
Hande Gurbuz Aytuluk **(40)**	Turkey	2018	Bupivacaine	Cardiac Arrest
Masaki Fuyuta **(41)**	Japan	2010	Propofol &, Remifentanyl & Atracurium	Cardiac Arrest
Keith A Candiotti **(42)**	USA	2004	Propofol	No arrhythmia found
Ozgur Canbay **(43)**	Turkey	2008	Propofol	Cardiac Arrest
Tomoaki Yatabe **(44)**	Japan	2011	Propofol	Ventricular Fibrillation
Nicole Phillips **(45)**	Australia	2003	Bupivacaine	Induced Brugada Pattern

Table No 1. Characteristics of Case reports

Author	Country	Year	Sample Size	Sample Size	Anesthesia A
Mélanie Duque **(46)**	Portugal	2017	31	Propofol & Tramadol	Propofol & Tr
Benjamin Kloesel **(47)**	USA	2011	8	Oxymetazoline & Propofol	Oxymetazolin
Panagiotis Flamée **(48)**	Belgium	2021	135	Propofol	Propofol
Fabio Dell'Olio **(49)**	Italy	2021	3	Diazepam	Diazepam
Hye-Mee Kwon **(50)**	Korea	2018	53	Propofol	Propofol
Mihoko Inamura **(51)**	Japan	2005	6	Propofol & Sevoforane	Propofol & Se
Panagiotis Flamée **(52)**	Belgium	2013	57	Propofol	Propofol
J S Kim **(53)**	Korea	2004	2	Propofol	Propofol
Luisa G Santambrogio **(54)**	Italy	2005	4	Propofol & Remifentanyl & Sevoflurane	Propofol & Re

Table No. 2 Characteristics of Case Series

Author	Country	Year	Sample Size	Anesthesia Agents	Outcome
Giuseppe Ciconte **(59)**	Italy	2017	36	Propofol & Ajmaline	ST elevation and J wav
Ai Goto **(60)**	Japan	2020	4	Halothane	Elevation of J waves, H
Kanemori T (61)	Japan	2008	26	Flecainide	Induced Brugada
Arnalsteen-Dassonvalle E (62)	France	2010	32	Ajmaline	Ventriicular Premature
Calvo D (63)	Spain	2014	59	Flecainide	Induced Brugada
A. Adler **(64)**	Netherlands	2008	152	Quinidine	Decreased incidence of
Belhassen B (65)	Israel	2009	9	Quinidine	Decreased incidence of

Table No. 3 Characteristics of Non-Randomized Control Trial

Author	Country	Year	Sample Size	Anesthesia Agents	Outcome
Panagiotis Flamée **(55)**	Belgium	2020	80	Propofol & Etomidate	ST depression in 11
Moisés Rodríguez-Mañero **(56)**	Belgium	2013	611	Propofol & Ajmaline	35 had atrial fibrilat
Ana Carolina Guimarães Oliveira **(57)**	Brazil	2019	28	Lidocaine	No arrythmia found
Antoine Andorin **(58)**	France	2017	50	Quinidine	Decreased incidence

Table No. 4 Characteristics of Randomized Control Trial

Figure No. 4 Number of Incidence Observed

Figure No. 5 Agents used

Discussion

Overview of Existing Studies

This systemic review included in-vivo studies performed on human patients to evaluate the effect different anesthetic and analgesic agents can have on a patient with Brugada syndrome. Only studies evaluating patient outcomes after anesthetic application were included in our review to get a better understanding of possible safety of using various agents in Brugada patients. Due to Brugada being a relatively new syndrome with not many clinical trials done on the subject, case series and reports on the subject had to be included. The studies included in the review focused on several agents including propofol, lidocaine, rocuronium, remifentanil, bupivacaine, and several others. This review shoed that despite most patients not experiencing any complication the risk of arrhythmia is still present, thus giving valuable insight on safety of these medication.

Risk in Brugada Syndrome

It has been well established in previous studies that Brugada syndrome places an individual at a much higher risk for sudden cardiac deaths, fatal arrhythmias, and ventricular fibrillation (66) and since its first diagnosis a comprehensive list of medication has been made on the level of risk of arrhythmia such patient can face when a certain drug is administered. In a review discussing the pathophysiology behind Brugada, Meregalli et al have discussed how it is not a monofactorial syndrome but rather its physiology can vary greatly from one person to another and thus the targeting therapies need to be tailored for each individual patient (67).

In brugada patients previous studies have divided the drugs into different classes depending on the level of evidence available to show its potential to cause arrhythmia (12). These classes are:

- Class I – Evidence showing potential to cause arrhythmia
- Class IIa – Evidence showing conflicting data with more studies suggesting arrhythmic potential
- Class IIb – Evidence showing conflicting data with fewer studies suggesting arrhythmic potential
- Class III – Evidence still unclear

On analyzing the outcomes from the use of several medication in patients in brugada patients from our selected studies we arrived at a similar conclusion. Below we have discussed briefly our findings from different studies.

Propofol

Propofol is a very popular IV anesthetic used in a lot of surgeries and procedures. It is a hypnotic agent which has rapid onset and offset along with fast elimination from the body. It is metabolized by the hepatocyte CYP450 system and is excreted in the urine as glucuronide conjugates. (68)The rapid onset of recovery is considered as the major advantage in the medical world. Propofol works by acting on the GABA receptors. There are two main types of GABA receptors, GABA-A and GABA -B and they are the major inhibitory neurotransmitters in the CNS. Propofol mainly acts on the GABA-A receptor by potentiating its effects in the CNS, while at the same time, reducing the transmission of glutamate. (69) Several studies have suggested to avoid the use of propofol in Brugada syndrome. (51) It has been listed as a Class IIa drug for Brugada syndrome (12). In the studies we reviewed we found that there were instances where patients suffered cardiac arrest (28, 38, 40, 41, 43) or ventricular fibrillation (24, 34-38, 44) after propofol administration. In some patients it also showed conflicting ECG changes with some studies showing ST elevation (59) in a few patients while other showing ST depression (55).

Lidocaine

Lidocaine is a local anesthetic agent and also a class IB anti-arrhythmic that has been used for local nerve blockade for a long time. It works by blocking the voltage gated sodium channels. By deactivating these channels, lidocaine works by blocking the nerve action potential and hence reduces pain. (70) A study by Barajas-Martínez et al showed that Lidocaine has the potential to induce Brugada syndrome, particularly in patients who have double mutations of SCN5A.(71) It has been listed as a class IIb drug for brugada

showing a potential risk of arrhythmia (12). In our literature review we found its local application to be showing no potential harm with only concern being induction of brugada pattern in one patient (30).

Flecainide

Flecainide is a Class IC anti-arrhythmic. Its main mechanism of action is blocking the sodium channels. It prolongs depolarization and increases refractoriness due to slow release from the binding site, and mainly acts on the Bundle of His-Purkinje system. Studies have shown that it can potentially trigger ST elevations in patients with a subtype of Long QT syndrome and Brugada syndrome, particularly the LQT 3 syndrome patients. (72) It is also a class IIb drug for patients with brugada (12) with the studies in our review showing it inducing brugada pattern on ECG in an otherwise asymptomatic patient (63).

Bupivacaine

Bupivacaine is a local anesthetic used to relieve pain over a local area through the blockade of nerve impulse generation and conduction. It exerts its action by crossing the neuronal membrane and blocking sodium channels intracellularly (73). Furthermore, it is known to act on EP1 subtype of prostaglandin E2 and reducing inflammation and hyperalgesia (74).It has been listed as a class IIa drug for patients with brugada with the studies having shown it to be pro arrhythmic for such patients (12). In our review we observed patients previously having masked brugada pattern showing a classical brugada pattern on ECG without any symptom after administration (21, 45), however there were studies showing ventricular fibrillation (29) and cardiac arrest (40) in patients thus highlighting its potential risk.

Ajmaline

Ajmaline is a class 1a anti-arrhythmic agent known to improve abnormal rhythms of the heart. It has a particularly high affinity for sodium channels of the heart and lengthens the action potential of cardiac pacemaker nodes by interfering with the activity of these receptors (75). Being a class I drug it has been proven to be having an arrhythmic potential in patients with brugada (12). Its use for diagnosing masked or hidden brugada has also been seen with patients undergoing ajmaline test to observe if brugada ECG pattern could be induced (76). In studies we reviewed no potential life threatening arrhythmia were observed after the use of ajmaline (56, 59, 62) making it one of the safer drugs that could potentially be used alongside anesthetic agents to lower the risk of arrhythmia.

Quinidine

Quinidine is an isomer obtained from quinine present in bark of several pant species and is considered to be the first anti-arrhythmic to be used (77). It functions by prolonging cellular action potential by blocking sodium and potassium currents and has been used in treatment of a wide variety of arrhythmias including atrial and ventricular fibrillation (78). It is also used as an antimalarial drug (79). It has been widely recognized as a potential treatment for patients suffering from symptomatic brugada reducing the risk and incidence of arrhythmias and other symptoms (80). In our study we found three clinical trials that have shown it to be an effective medication that can be safely used in symptomatic brugada patients (58, 64, 65).

Conclusion

In our review we found that patients with brugada syndrome have a very clear risk for fatal arrhythmias and cardiac arrest when administrating analgesics and anesthetics. We found it particularly risky to give propofol in patients with symptomatic brugada, especially those with type 1 ECG pattern. We also concluded that giving topical analgesics is relatively safe with little risk of cardiac complications. However we concluded that the analgesic and anesthetic selection for brugada patients should be decided to cater for each individual patient depending on patient's condition, symptoms and comorbidities as well as physician preference and the type of surgery to be done. In each case it should always been kept in mind that the risk of arrhythmias is there and measures to handle an adverse cardiac situations should be kept ready for such patients.

Reference

1. Sieira J, Brugada P. The definition of the Brugada syndrome. European heart journal. 2017 Oct 21;38(40):3029-34.
2. Brugada R, Campuzano O, Sarquella-Brugada G, Brugada J, Brugada P. Brugada syndrome. Methodist DeBakey cardiovascular journal. 2014 Jan;10(1):25.
3. Cerrone M, Costa S, Delmar M. The Genetics of Brugada Syndrome. Annual Review of Genomics and Human Genetics. 2022 May 13;23.
4. Watanabe H, Minamino T. Genetics of Brugada syndrome. Journal of human genetics. 2016 Jan;61(1):57-60.
5. Tondo C. The Brugada syndrome: How many types?. Heart Rhythm. 2008 Nov 1;5(11):1565-6.
6. Yan S, Wei G, Shah C. Type 1 Brugada Syndrome. Journal of Education and Teaching in Emergency Medicine. 2018;3(2).
7. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present status of Brugada syndrome: JACC state-of-the-art review. Journal of the American College of Cardiology. 2018 Aug 28;72(9):1046-59.
8. Korlipara H, Korlipara G, Pentyala S. Brugada syndrome. Acta Cardiologica. 2021 Nov 10;76(8):805-24.
9. Gourraud JB, Barc J, Thollet A, Le Marec H, Probst V. Brugada syndrome: diagnosis, risk stratification and management. Archives of cardiovascular diseases. 2017 Mar 1;110(3):188-95.
10. Bayrak F, Brugada P. Recent Status in Brugada Syndrome. Turk Kardiyoloji Dernegi Arsivi. 2022 Mar 1;50(2):137.
11. Krahn AD, Behr ER, Hamilton R, Probst V, Laksman Z, Han HC. Brugada Syndrome. Clinical Electrophysiology. 2022 Mar 1;8(3):386-405.
12. Blok M, Boukens BJ. Mechanisms of arrhythmias in the brugada syndrome. International Journal of Molecular Sciences. 2020 Sep 25;21(19):7051.
13. M C, T L, MJ P, J C, VA W, JP H, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane database Syst Rev 2019; 10:ED000142.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Med 2009; 6:e1000097.
15. JAC S, J S, MJ P, RG E, NS B, I B, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366
16. JA S, MA H, BC R, J S, ND B, M V, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355
17. RK B, C S. Critical Appraisal Tools and Reporting Guidelines for Evidence-Based Practice. Worldviews evidence-based Nurs 2017; 14:463–72.
18. Ferreira MN, Fontes S, Machado H. Interscalene plexus block and general anesthesia in Brugada syndrome. Saudi Journal of Anaesthesia. 2019 Oct;13(4):371.
19. Loiudice P, Monitillo F, Nardi M, Iacoviello M, Casini G. Local peribulbar anesthesia before glaucoma filtering surgery in a patient with Brugada syndrome. European Journal of Ophthalmology. 2021 Mar;31(2):NP39-42.
20. Mena S, Costa A, DeLemos M, Schabel J, Factor M. Labor Analgesia in Brugada Syndrome and the Importance of Contingency Planning. Case Reports in Anesthesiology. 2022 Jul 15;2022.
21. Vernooy K, Sicouri S, Dumaine R, Hong K, Oliva A, Burashnikov E, Timmermans C, Delhaas T, Crijns HJ, Antzelevitch C, Rodriguez LM. Genetic and biophysical basis for bupivacaine-induced ST segment elevation and VT/VF. Anesthesia unmasked Brugada syndrome. Heart Rhythm. 2006 Sep 1;3(9):1074-8.
22. Gould C, Bhatia K. Remifentanil labor analgesia in a parturient with Brugada syndrome. Korean Journal of Anesthesiology. 2021 Feb 1;74(1):76-8.
23. Kumar CM, Vohra SB, Rad RF. Vitreoretinal Surgery Under Sub-Tenon's Block and Conscious Sedation in a Patient with Brugada Syndrome: A Case Report and Literature Review. Anesthesiology and Pain Medicine. 2021 Oct;11(5).
24. Biricik E, Hatipoğlu Z, Küçükbingöz Ç. Sugammadex in a patient with Brugada syndrome. Turkish

Journal of Anaesthesiology and Reanimation. 2016 Apr;44(2):99.
25. Tuncalı B, Kökten G, Altın C. Anaesthetic Management of a Patient with Brugada Syndrome in Total Knee Arthroplasty. Turkish Journal of Anaesthesiology and Reanimation. 2021 Feb;49(1):70.
26. Sahutoglu C, Kocabas S, Askar FZ. Tramadol use in a patient with Brugada syndrome and morphine allergy: a case report. Journal of pain research. 2018;11:191.
27. Yuasa H, Kitaura A, Kitayama C, Fuyuta M, Mino T, Okamoto K, Nakao S. A 32-Year-Old Man Diagnosed with Type II Brugada Syndrome on Preoperative Electrocardiogram 1 Week Before Elective Tympanoplasty. The American Journal of Case Reports. 2021;22:e927756-1.
28. Alzahrani T. Near miss in a patient with undiagnosed Brugada syndrome: a case report and literature review. Journal of Clinical Anesthesia. 2016 Dec 1;35:427-9.
29. Corey SA, Varkey S, Phillips DR, Gay GL. Brugada Syndrome Induced by an Interscalene Block: A Case Report. JBJS Case Connector. 2017 Dec 1;7(4):e96.
30. Oliván B, Arbeláez A, de Miguel M, Pelavski A. Diagnosis of Brugada's syndrome after subarachnoid injection of prilocaine. Revista Espanola de Anestesiologia y Reanimacion. 2016 Jan 9;63(8):483-6.
31. Konishi J, Suzuki T, Kondo Y, Baba M, Ogawa S. Rocuronium and sugammadex used effectively for electroconvulsive therapy in a patient with Brugada syndrome. The Journal of ECT. 2012 Jun 1;28(2):e21-2.
32. Şahinkaya HH, Yaşar E, Tekgül ZT, Horsanalı BÖ, Özeroğlu E. Anaesthetic management of a patient with Brugada syndrome. Turkish Journal of Anaesthesiology and Reanimation. 2016 Apr;44(2):96.
33. Martorano PP, Barboni E, Buscema G, Di Rienzo A. A novel anaesthetical approach to patients with brugada syndrome in neurosurgery. Case Reports in Anesthesiology. 2013 May 28;2013.
34. Goraksha S, Bidaye S, Gajendragadkar S, Bapat J, Butani M. General anaesthesia for insertion of an automated implantable cardioverter defibrillator in a child with Brugada and autism. Indian journal of anaesthesia. 2010 Nov;54(6):562.
35. Bramall J, Combeer A, Springett J, Wendler R. Caesarean section for twin pregnancy in a parturient with Brugada syndrome. International Journal of Obstetric Anesthesia. 2011 Apr 1;20(2):181-4.
36. Uzun D, Hassan N, Kohli U. Post-operative Brugada electrocardiographic pattern, polymorphic ventricular tachycardia, and sudden death in a child after administration of propofol anaesthesia. Cardiology in the Young. 2020 May;30(5):724-7.
37. Fujiwara Y, Shibata Y, Kurokawa S, Satou Y, Komatsu T. Ventricular tachycardia in a patient with Brugada syndrome during general anesthesia combined with thoracic paravertebral block. Anesthesia & Analgesia. 2006 May 1;102(5):1590-1.
38. Baty L, Hollister J, Tobias JD. Perioperative management of a 7-year-old child with Brugada syndrome. Journal of Intensive Care Medicine. 2008 May;23(3):210-4.
39. Vaccarella A, Vitale P, Presti CA. General anaesthesia in a patient affected by Brugada syndrome. Minerva anestesiologica. 2008 Apr 1;74(4):149-52.
40. Aytuluk HG. Cardiac arrest during spinal anaesthesia in a patient with undiagnosed Brugada syndrome. European Journal of Anaesthesiology| EJA. 2018 Sep 1;35(9):711-4.
41. Fuyuta M, Nakao S, Takai N, Shiba M, Tanaka Y, Iwamoto T, Kurita T. Sudden cardiac arrest during general anesthesia in an undiagnosed Brugada patient. Journal of Cardiothoracic and Vascular Anesthesia. 2013 Dec 1;27(6):1334-6.
42. Candiotti KA, Mehta V. Perioperative approach to a patient with Brugada syndrome. Journal of clinical anesthesia. 2004 Nov 1;16(7):529-32.
43. Canbay O, Erden IA, Celebi N, Aycan IO, Karagoz AH, Aypar U. Anesthetic management of a patient with Brugada syndrome. Pediatric Anesthesia. 2007 Dec;17(12):1225-7.
44. Yatabe T, Hirohashi M, Takeuchi S, Maeda Y, Yamashita K, Yokoyama M. Case of ventricular fibrillation in patients with brugada type electrocardiogram during surgery. Masui. The Japanese Journal of Anesthesiology. 2011 Jun 1;60(6):728-32.
45. Phillips N, Priestley M, Denniss AR, Uther JB. Brugada-type electrocardiographic pattern induced by epidural bupivacaine. Anesthesia & Analgesia. 2003 Jul 1;97(1):264-7.
46. Duque M, Santos L, Ribeiro S, Catré D. Anesthesia and Brugada syndrome: a 12-year case series.

Journal of Clinical Anesthesia. 2017 Feb 1;36:168-73.
47. Kloesel B, Ackerman MJ, Sprung J, Narr BJ, Weingarten TN. Anesthetic management of patients with Brugada syndrome: a case series and literature review. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2011 Sep;58(9):824-36.
48. Flamée P, Viaene K, Tosi M, Nogueira Carvalho H, de Asmundis C, Forget P, Poelaert J. Propofol for induction and maintenance of anesthesia in patients with Brugada syndrome: a single-center, 25-year, retrospective cohort analysis. Anesthesia & Analgesia. 2021 May 11;132(6):1645-53.
49. Dell'Olio F, Lorusso P, Barile G, Favia G. Brugada Syndrome Updated Risk Assessment and Perioperative Management in Oral Surgery: A Case Series. Journal of Oral and Maxillofacial Surgery. 2021 Nov 1;79(11):2269-e1.
50. Kwon HM, Kim SH, Park SU, Rhim JH, Park HS, Kim WJ, Nam GB. Propofol for implantable cardioverter defibrillator implantation in patients with Brugada syndrome. Pacing and Clinical Electrophysiology. 2018 Jun;41(6):656-60.
51. Inamura M, Okamoto H, Kuroiwa M, Hoka S. General anesthesia for patients with Brugada syndrome. A report of six cases. Canadian Journal of Anesthesia. 2005 Apr;52(4):409-12.
52. Flamee P, De Asmundis C, Bhutia JT, Conte G, Beckers S, Umbrain V, Verborgh C, CHIERCHIA GB, Van Malderen S, CASADO-ARROYO RU, Sarkozy A. Safe single-dose administration of propofol in patients with established Brugada syndrome: a retrospective database analysis. Pacing and Clinical Electrophysiology. 2013 Dec;36(12):1516-21.
53. Kim JS, Park SY, Min SK, Kim JH, Lee SY, Moon BK, Chae YJ. Anaesthesia in patients with Brugada syndrome. Acta anaesthesiologica scandinavica. 2004 Sep;48(8):1058-61.
54. Santambrogio LG, Mencherini S, Fuardo M, Caramella F, Braschi A. The surgical patient with Brugada syndrome: a four-case clinical experience. Anesthesia & Analgesia. 2005 May 1;100(5):1263-6.
55. Flamee P, Varnavas V, Dewals W, Carvalho H, Cools W, Bhutia JT, Beckers S, Umbrain V, Verborgh C, Forget P, Chierchia GB. Electrocardiographic effects of propofol versus etomidate in patients with Brugada syndrome. Anesthesiology. 2020 Mar;132(3):440-51.
56. Oliveira AC, Neves IL, Sacilotto L, Olivetti NQ, Santos-Paul MA, Montano TC, Carvalho CM, Wu TC, Grupi CJ, Barbosa SA, Pastore CA. Is it safe for patients with cardiac channelopathies to undergo routine dental care? Experience from a single-center study. Journal of the American Heart Association. 2019 Aug 6;8(15):e012361.
57. Rodriguez-Manero M, Namdar M, Sarkozy A, Casado-Arroyo R, Ricciardi D, De Asmundis C, Chierchia GB, Wauters K, Rao JY, Bayrak F, Van Malderen S. Prevalence, clinical characteristics and management of atrial fibrillation in patients with Brugada syndrome. The American journal of cardiology. 2013 Feb 1;111(3):362-7.
58. Andorin A, Gourraud JB, Mansourati J, Fouchard S, Le Marec H, Maury P, Mabo P, Hermida JS, Deharo JC, Delasalle B, Esnault S. The QUIDAM study: hydroquinidine therapy for the management of Brugada syndrome patients at high arrhythmic risk. Heart Rhythm. 2017 Aug 1;14(8):1147-54.
59. Ciconte G, Santinelli V, Brugada J, Vicedomini G, Conti M, Monasky MM, Borrelli V, Castracane W, Aloisio T, Giannelli L, Di Dedda U. General anesthesia attenuates Brugada syndrome phenotype expression: clinical implications from a prospective clinical trial. JACC: Clinical Electrophysiology. 2018 Apr;4(4):518-30.
60. Goto A, Hagiwara-Nagasawa M, Izumi-Nakaseko H, Kitta K, Hoshiai K, Chiba K, Ando K, Akie Y, Naito AT, Sugiyama A. Use of microminipigs for unveiling unknown mechanisms of azithromycin-induced cardiovascular death. Journal of Pharmacological Sciences. 2018 Nov 1;138(3):198-202.
61. Kanemori T, Shimizu H, Oka K, Furukawa Y, Hiromoto K, Mine T, Masuyama T, Ohyanagi M. Sodium channel blockers enhance the temporal QT interval variability in the right precordial leads in Brugada syndrome. Annals of Noninvasive Electrocardiology. 2008 Jan;13(1):74-80.
62. Arnalsteen-Dassonvalle E, Hermida JS, Kubala M, Six I, Quenum S, Leborgne L, Jarry G. Ajmaline challenge for the diagnosis of Brugada syndrome: which protocol?. Archives of cardiovascular diseases. 2010 Nov 1;103(11-12):570-8.
63. Calvo D, Rubin JM, Perez D, Gomez J, Florez JP, Avanzas P, Garcia-Ruiz JM, de la Hera JM, Reguero

J, Coto E, Moris C. Time-dependent responses to provocative testing with flecainide in the diagnosis of Brugada syndrome. Heart Rhythm. 2015 Feb 1;12(2):350-7.
64. Adler A, Nordkamp LO, Crotti L, Schwartz P, Castelletti S, Veltmann C, Schimpf R, Shimizu W, Antzelevitch C, Belhassen B, Tan H. Empiric quinidine for asymptomatic Brugada syndrome—preliminary results of an international registry. Heart Rhythm. 2012 Nov 1;9(11):1918-9.
65. Belhassen B, Glick A, Viskin S. Excellent long-term reproducibility of the electrophysiologic efficacy of quinidine in patients with idiopathic ventricular fibrillation and Brugada syndrome. Pacing and clinical electrophysiology. 2009 Mar;32(3):294-301.
66. Rojas R, Kaul R, Frenkel D, Hoch EG, Iwai S, Jacobson JT, Aronow WS. Brugada syndrome clinical update. Hospital Practice. 2021 Aug 8;49(4):255-61.
67. Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more?. Cardiovascular research. 2005 Aug 15;67(3):367-78.
68. Marik P. Propofol: Therapeutic Indications and Side-Effects. CPD. 2004 Nov 1;10(29):3639–49.
69. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties. CNS neuroscience & therapeutics. 2008 Jun;14(2):95-106.
70. Yang X, Wei X, Mu Y, Li Q, Liu J. A review of the mechanism of the central analgesic effect of lidocaine. Medicine. 2020 Apr;99(17):e19898.
71. Barajas-Martinez HM, Hu D, Cordeiro JM, Wu Y, Kovacs RJ, Meltser H, et al. Lidocaine-Induced Brugada Syndrome Phenotype Linked to a Novel Double Mutation in the Cardiac Sodium Channel. Circulation Research. 2008 Aug 15;103(4):396–404.
72. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L, Ronchetti E. The Elusive Link Between LQT3 and Brugada Syndrome: The Role of Flecainide Challenge. Circulation. 2000 Aug 29;102(9):945–7.
73. Babst CR, Gilling BN. Bupivacaine: a review. Anesthesia progress. 1978 May;25(3):87.
74. Blair HA. Bupivacaine/meloxicam prolonged release: a review in postoperative pain. Drugs. 2021 Jul;81(10):1203-11.
75. Ilyas M. Ajmaline in the management of cardiac arrhythmias. J Pak Med Assoc. 1981 Jul 1;31:153-5.
76. Rizzo A, Borio G, Sieira J, Van Dooren S, Overeinder I, Bala G, Pappaert G, Maj R, Osorio TG, Terasawa M, Galli A. Ajmaline testing and the Brugada syndrome. The American Journal of Cardiology. 2020 Nov 15;135:91-8.
77. Yang F, Hanon S, Lam P, Schweitzer P. Quinidine revisited. The American journal of medicine. 2009 Apr 1;122(4):317-21.
78. Mason JW, Hondeghem LM. Quinidine. Annals of the New York Academy of Sciences. 1984 Dec;432(1):162-76.
79. White NJ. The treatment of malaria. New England journal of medicine. 1996 Sep 12;335(11):800-6.
80. Serdoz LV, Rittger H, Furlanello F, Bastian D. Quinidine—a legacy within the modern era of antiarrhythmic therapy. Pharmacological Research. 2019 Jun 1;144:257-63.