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Utility of Oral Quinine Sulfate for the Treatment of Brugada Syndrome Presenting As Electrical Storm in Remote Areas: Resilience in the Coronavirus Disease 2019 (COVID-19) Era

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ABSTRACT
Electrical storm is a malignant presentation of Brugada syndrome (BrS). Pharmacologic antiarrhythmic therapy is mandatory for this condition, followed by implantation of an implantable cardioverter–defibrillator to prevent sudden cardiac death. We report a case of a BrS patient presenting with electrical storm in a remote area. A referral to tertiary healthcare services was turned down due to the capacity demands of coronavirus disease 2019 cases. Oral quinine was used as a bailout therapy and successfully maintained the arrhythmia suppression. Our case confirms that quinine is a reliable option to suppress electrical storm in BrS.

ABSTRACT
L’orage rythmique est une manifestation néfaste du syndrome de Brugada (SBr). Une pharmacothérapie antiarythmique s’avère incontrôlable dans ce contexte et doit être suivie de l’implantation d’un défibrillateur cardioverteur afin de prévenir la mort subite par arrêt cardiaque. Nous présentons le cas d’un patient atteint du SBr ayant subi un orage rythmique dans une région éloignée. Son orientation vers des services de soins de santé tertiaires a été refusée en raison de la mobilisation des ressources par les cas de COVID-19. Un traitement de sauvetage par la quinine administrée par voie orale a été instauré et a permis de maintenir la suppression des arythmies. Le cas de ce patient confirme que la quinine représente une option fiable pour arrêter un orage rythmique chez un patient atteint du SBr.

Brugada syndrome (BrS) is one of the most common etiologies of malignant ventricular arrhythmia and sudden cardiac death (SCD) in the absence of structural heart abnormalities. The estimated incidence is 1-5 cases per 10,000 in the Asian male population in the age range of 25-55 years.1 Quinidine is a potent antiarrhythmic agent that effectively suppresses malignant ventricular arrhythmias in BrS, but in many regions, it is not widely available.2 Urgent defibrillation and referral for implantable cardioverter–defibrillator (ICD) implantation to prevent SCD is a common practice in remote healthcare facilities. Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic in early 2020, there has been a progressive decline in hospital admission of non—COVID-19 cases, which is largely attributable to fear of contagion in health facilities. We present a case of electrical storm in BrS, occurring in a remote area, that was successfully treated with quinine, in the absence of quinidine and timely referral to tertiary care.

Case
A 50-year-old man with no previous history of cardiovascular disease presented to the emergency department in our hospital in a remote area in August 2020, following a witnessed sudden loss of consciousness and an episode of seizure after having dinner with his family. Upon arrival, he was unresponsive, with no palpable pulse and no spontaneous breathing. Subsequently, cardiopulmonary resuscitation was initiated, and cardiac monitoring detected ventricular fibrillation (VF; Fig. 1A) He was immediately defibrillated with 200 J (biphasic), with successful conversion to sinus rhythm with multifocal premature ventricular complexes (Fig. 1B) and return of spontaneous circulation. The patient was initially hemodynamically stable but had a recurrence, with polymorphic ventricular tachycardia (VT) (Fig. 1C). Immediate defibrillation and cardiopulmonary resuscitation was performed, which again resulted in return of spontaneous circulation. The patient was somnolent, with a blood pressure of 90/60 mm Hg, heart rate of 80 beats per minute, and spontaneous breathing. Other
physical findings were unremarkable. A 12-lead electrocardiogram (ECG) was obtained, which showed a sinus rhythm with 2-mm coved-type ST elevation in lead V1-2, compatible with the ECG pattern for type I BrS (Fig. 2A). The initial laboratory studies showed a normal complete blood count, renal function, and metabolic panel. A rapid IgG/IgM antibody test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was also done, with a nonreactive result. A brief history from the patient’s family revealed no episodes of fever and no alcohol consumption before the event, which commonly lead to the unmasking of BrS. There was no family history of sudden cardiac death, nor any family member known to be diagnosed with BrS.

A chest x-ray was unremarkable. Echocardiography showed normal cardiac structures with good ventricular systolic and diastolic function. No regional wall motion abnormality was identified, making an arrhythmia etiology of coronary artery disease unlikely. An initial diagnosis of BrS was made. The patient was then prepared for urgent transfer to the intensive cardiac care unit (ICCU), at which time he developed sustained monomorphic VT, with unstable hemodynamics (carotid pulse was palpable, blood pressure was unmeasurable, and heart rate was 180 beats per minute). Synchronized cardioversion (biphasic) with 100 J was immediately done, which successfully converted him into sinus rhythm. An Intravenous bolus of amiodarone was initially considered, but then was postponed, owing to its potential arrhythmogenicity and lack of efficacy in BrS.

The patient was then urgently transferred to the ICCU. Upon arrival, he again developed a monomorphic VT, which was immediately cardioverted. Given the recurrence of ventricular arrhythmias, urgent maintenance antiarrhythmic therapy was deemed mandatory. Unfortunately, quinidine and isoproterenol were not available at the facility. After a brief telemedicine consult with the cardiologist in the tertiary-care facility, an alternative measure was proposed, which was to use quinine sulfate, an antimalarial drug commonly used in the local area, as a bailout therapy. Quinine sulfate, in the form of a 200-mg tablet every 8 hours, was given via a nasogastric tube.

The hospital was located in a rural area, and given the lack of resources, a referral to a tertiary-care facility was initially arranged, but then was delayed because the tertiary-care facility was operating at overcapacity, owing to COVID-19 cases.

Over the next 2 hours, the patient slowly regained consciousness and eventually was able to communicate well. The 12-lead ECG tracing on the fourth day showed resolution of the BrS pattern, without any QTc prolongation (Fig. 2B) No episodes of ventricular arrhythmia occurred after the initiation of therapy. The rest of his ICCU care was uneventful, and on the fifth day of care, he was discharged and prescribed a maintenance dose of quinine at 200 mg, 3 times daily. A referral through the outpatient clinic for ICD implantation was offered, but the patient declined due to his concerns regarding the risk of spread of COVID-19 at a tertiary-care facility.

After 7 months of follow-up visits, no episodes of syncope, arrhythmias, or BrS-pattern ECG were encountered. Despite receiving a recommendation for ICD implantation for each visit, the patient preferred to be continued on pharmacologic therapy. The quinine dose was reduced to 200 mg, twice a day, to lower the risk of side effects. No recurrence of symptoms was reported with the use of the reduced dose. Switching to quinidine was not considered, due to its lack of availability in the region.

**Discussion**

BrS commonly presents as malignant arrhythmia, notably polymorphic VT and VF. The underlying mechanism for this
arrhythmia is mutations in the gene encoding the sodium channel SCN5A, which lead to overactivity of the transient outward current.\textsuperscript{1} This overactivation results in an imbalance of the electrical current across cardiac cells. Notably, our patient developed electrical storm, which is reported to occur in < 10\% of all the arrhythmic presentations of BrS.\textsuperscript{3}

ICD implantation is indicated to prevent SCD in BrS, notably in those patients with a history of aborted SCD or documented spontaneous VT/VF.\textsuperscript{1} Pharmacologic antiarrhythmic therapy, on the other hand, suppresses the arrhythmia burden.\textsuperscript{1,4} Hence, antiarrhythmic agents still play a vital role irrespective of the availability of ICD implantation. ICD implantation in our patient was initially deferred because the tertiary-care facility was operating at overcapacity, and outpatient implantation was declined by the patient due to pandemic-related concerns.

The acute presentation of our patient, combined with the recurrent arrhythmia, clearly warranted prompt antiarrhythmic management. Quinidine is highly effective in terminating acute arrhythmia in BrS and suppressing recurrence of arrhythmia.\textsuperscript{3} Moreover, long-term oral quinidine as a single agent has been reported to be effective for secondary prevention of malignant arrhythmia in patients who have already received an ICD, with frequent shocks.\textsuperscript{4} However, quinidine is not widely available in Indonesia, especially in rural areas. This scarcity has been reported in many countries,\textsuperscript{5} potentially creating difficulties in managing malignant arrhythmia in BrS, especially in the pandemic era, in which referral to a higher-level healthcare facility is often not feasible.

Quinine, a stereomer of quinidine, has been commonly used as an antimalarial agent in areas where it is endemic. In human studies, quinine has been shown to be as effective as quinidine in preventing and treating arrhythmia. Quinine may have an antiarrhythmic mechanism similar to that of quinidine—suppression of transient outward current activity in the epicardial cells, leading to stabilization of the epicardial electrical current and preventing arrhythmia.\textsuperscript{6} However, reports on its use in clinical arrhythmia settings are still limited. Shenthar et al. reported the effectiveness of oral quinine sulfate as a monotherapy for the prevention of recurrent ICD shocks due to electrical storm in BrS.\textsuperscript{4} Mehrrota et al. reported the successful use of intravenous quinine, in combination with cilostazol, for the treatment of electrical storm in a pediatric patient for whom quinidine was not available. In our case, the electrical storm and the unavailability of quinidine led to the use of oral quinine sulfate as the only available bailout therapy.

A commonly reported side effect of the long-term use of quinine is cinchonism, which includes tinnitus, visual impairment, nausea, vertigo, and diarrhea. A high-tryptophan

Figure 2. (A) A 12-lead electrocardiogram (ECG) tracing showed a coved-type ST elevation in lead V1-2, suggestive of the ECG pattern of type 1 Brugada syndrome. (B) A follow-up, 12-lead ECG tracing on the fourth day showed a partial resolution of ST-segment elevation in lead V1-2, without prolongation of the QTc interval.
diet containing beans, meat, and milk may prevent these side effects.

As previously reported, the use of quinine results in less QTc-interval prolongation, compared with use of quinidine, a difference that may be attributable to the stereoselective blockage of quinine, as compared to quinidine.6 The absence of QTc prolongation on serial follow-up ECGs of our patient during routine visits reflected this finding. In our case, we used an oral dose of 200 mg, 3 times daily, which effectively suppressed the electrical storm. However, further studies are needed to validate this efficacy.

Conclusion
In remote settings where quinidine and ICD implantation facilities are not available, quinine sulfate may act as a reliable alternative therapy for terminating electrical storm and maintaining long-term ventricular arrhythmia suppression in BrS patients.

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References
1. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome. Report of the Second Consensus Conference. Circulation 2005;111:659-70.
2. Viskin S, Wilde AAM, Guevara-Valdivia ME, et al. Quinidine, a lifesaving medication for Brugada syndrome, is inaccessible in many countries. J Am Coll Cardiol 2013;61:2383-7.
3. Jongman JK, Jepkes-Bruin N, Ramdat Misier AR, et al. Electrical storms in Brugada syndrome successfully treated with isoproterenol infusion and quinidine orally. Neth Heart J 2007;15:151-4.
4. Shenthar J, Chakali SS, Acharya D, Parvez J, Banavalikar B. Oral quinine sulfate for the treatment of electrical storm and prevention of recurrent shocks in Brugada syndrome after failed cilostazol therapy. HeartRhythm Case Rep 2017;3:470-4.
5. Belhassen B, Rahkovich M, Michowitz Y, et al. Management of Brugada syndrome: thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarrhythmic drugs. Circ Arrhythm Electrophysiol 2015;8:1393-402.
6. Sheldon RS, Duff HJ, Koshman ML. Antiarrhythmic activity of quinine in humans. Circulation 1995;92:2944-50.
7. Mehrotra S, Juneja R, Naik N, Pavri BB. Successful use of quinine in the treatment of electrical storm in a child with Brugada syndrome. J Cardiovasc Electrophysiol 2011;22:594-7.