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Case Series

Centhaquine Citrate – A Composite Perspective in Managing Refractory Hemorrhagic Shock in Non-identical Etiologies

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ABSTRACT

Centhaquine (CQ) citrate is a vascular resuscitative agent, not a vasopressor. Hemorrhagic shock due to severe poly-trauma injuries is life-threatening and requires intensive care and surgical intervention. Such an emergency scenario can be even more challenging if the patient is on high vasopressor and inotropic support and needs shifting from the emergency room for imaging to radiology, to the intensive care unit, or operation theater (OT). Patients need hemodynamic stabilization for safe transport. Even some window periods of improving hemodynamics can save a patient through early surgical intervention and help in decision-making and prognostication if appropriate imaging is possible. We discuss here three patients who presented to our hospital's emergency with hemorrhagic shock due to non-identical etiologies such as fall from height, gunshot injuries, and blunt abdominal trauma. All three patients were requiring vasopressors in high dosages. Despite multiple blood product transfusions, they had severe hemodynamic instability. We gave injection CQ at 0.01 mg/kg dosage and diluted in 100 mL saline to the patients after 2, 5, and 7 hour of presentation, respectively. Hemodynamics stabilized in all of them allowing definitive intervention in the OT. Two patients later got discharged, and one succumbed to injuries 2 days later. Hemodynamics had improved within 15–20 min of CQ administration in all three patients. CQ, temporarily arresting hemorrhage, gave a window of opportunity for definitive intervention. CQ is a vascular resuscitative agent rather than a vasopressor allowing a vasopressor-free resuscitation transiently. This may help emergency physicians, intensivists, trauma surgeons, orthopedics, and anesthetists who are handling patients of trauma in hemorrhagic shock with severe hemodynamic instability despite following standard advanced trauma life support (ATLS) protocol. The timely use of CQ in anticipating refractory hemorrhagic shock in these patients provided a relatively stable hemodynamic status enabling better clinical decision and intervention, enabling better clinical clinical outcome. Robust randomized controlled trials need to be performed to establish the most appropriate time and use of CQ in patients with hemorrhage.

Keywords: Centhaquine, Hemorrhagic shock, Polytrauma, Severe hemodynamic instability

INTRODUCTION

Hemorrhagic shock is a form of hypovolemic shock in which severe bleeding leads to inadequate oxygen delivery at the cellular level. Polytrauma causing bleeding is life-threatening and requires treatment in the intensive care unit (ICU), and often surgical intervention, and is associated with high mortality rates reaching 20%.[1] Treatment approaches include intravenous fluid replacement, appropriate blood product transfusion, and definitive surgery.

Vasopressors are required along with simultaneous blood product transfusion but the risk of arrhythmias, fluid extravasation, transfusion-related pulmonary complications, infection, fluid overload, and ischemia is there.

Centhaquine (CQ) was the first tested drug as antihypertensive drug in India.[2,3] CQ is undergoing clinical trials as a resuscitative agent for managing circulatory shock.[2] It acts as a venous constrictor agent by stimulating beta-adrenergic receptors in the venous system. It is also an arterial dilator as it stimulates α2A-adrenergic receptors in the brain, inhibiting the sympathetic drive. CQ has been found in various studies to be a suitable resuscitative agent in patients with hypovolemic shock, though its potential in treating distributive shock is still being studied.[4] CQ was found to be a highly effective resuscitative agent in animal models of hemorrhagic shock and is currently in the clinical development phase.[2,5,6] It has been shown to improve perfusion pressures, cardiac index, and S. lactate levels with increased survival in animals.[2] For the optimal timing of hemodynamic status to administer CQ. Robust randomized controlled trial need to be performed to establish the most appropriate time and use of CQ in patients of hemorrhagic shock. We report three patients with trauma who were given CQ as a measure in the situation of ongoing life-threatening bleeding.

CASE SERIES

Case 1

A 43-year-old man was referred to our emergency room (ER) from a primary care center with multiple gunshot injuries and shock almost 22 h after the injury. A computed tomography (CT) trauma protocol was initiated, which showed right subdural hematoma with a depressed fracture of the skull, bilateral hemopneumothorax, right 11th and 12th rib fractures, left lower chest blunt injury, metallic foreign bodies (bullets) noted at bodies of L3 and D10 vertebrae, right supraclavicular area, transverse process fracture of D10 and 11 vertebrae, right elbow fracture, right superior ala comminuted fracture, perisplenic subcapsular hematoma with grade 2 laceration, and pelvic hematoma. On evaluation, the Glasgow coma scale (GCS) was E3V5M6, heart rate (HR) was 141 beats/min, and respiratory rate (RR) was 40/min. He was hypotensive requiring norepinephrine infusion at 0.4 mcg/kg/h and vasopressin at 2.4 units/min. Fluid resuscitation was continued, and a massive transfusion protocol was initiated as his hemoglobin (Hb) was 4 mg/dL. The patient was then shifted to the ICU for stabilization. Despite receiving 3 packed red blood cell (PRBC) units, his Hb remained at 3.4 g/dL. Arterial blood gas (ABG) showed pH= 7.2, $pCo_{2=}$ 52.2 mmHg, $pO_{2=}$ 77.2 mmHg, $HCO_{3=}$ 20.1, and lactates= 10 mmol/L. At this stage, Inj. CQ was administered at 0.01 mg/kg in 100 mL of normal saline over 1 h. Over the next 3 h, vasopressors were gradually reduced and serial ABG showed improvement in acidosis and lactate levels. Hb levels also stabilized. The patient was then moved to the operating theater (OT) for exploration and splenectomy. Postoperatively, the patient stabilized and was discharged after 15 days.

Case 2

A 20-year-old man presented to the ER with a history of fever for 4 days, generalized weakness, and dizziness on standing. He also gave a history of falls in the washroom by falling on the commode the same day which resulted in blunt abdominal trauma. He was admitted to a primary healthcare facility where he received first aid but was referred to our facility due to worsening shock despite fluid resuscitation with falling Hb and thrombocytopenia. In the ER, GCS = 15, HR = 122/min, blood pressure (BP) = 80/30 mmHg, and RR = 33/min with left flank tenderness and guarding. Investigations showed Hb = 5.6 mg/dL, platelets = 4600/mcL, international normalized ratio = 3.49, and activated partial thrombin time = 200. He had to be intubated for worsening shock and mentation. ABG showed pH = 7.19, pcO_2 = 33.8 mmHg, pO_2 = 218.87Hg, $HcO_{3=}$ 713, and lactates = 7.66 mmol/L, on assist control mode with an $FiO_{2=}$ 50%. CT abdomen showed grade 3 splenic laceration and peri-splenic hematoma. His Hb was 5.3 mg/dL even after 4 units of PRBC transfusions, coagulopathy correction with fresh frozen plasma, and platelet transfusions. Injection CQ was administered at this juncture. Within 20 min, for a brief period (approximately 45 min), hemodynamics improved, giving some time to shift the patient to the OT for splenectomy. Although the patient seemed to stabilize initially, he deteriorated 2 days later and could not be revived.

Case 3

A 25-year-old man presented to the ER with an alleged history of fall from height (4th floor). He was first spotted by a watchman lying in an unconscious state with bleeding from both his ears. On arrival at the ER, he was immediately intubated for low GCS (E1V1M1), and the vitals recorded were HR = 133/min, BP = 90/46 mmHg, and RR = 32/min. After initial fluid and blood product resuscitation, he was shifted for imaging. He was found to be dengue positive. CT trauma protocol showed grade III liver laceration with hemoperitoneum, cumminuted pelvic fracture, left shaft femur fracture, multiple facial fractures, bilateral multiple fractures in the mandible, and bilateral orbit fractures. He was then shifted to the ICU on high doses of vasopressors and inotropic support with persistently low Hb of 4.5 mg/dL despite the ongoing massive transfusion protocol. After 7 hour of observation, the patient was administered injection CQ. For the next hour, hemodynamics gradually improved, and the patient was shifted to the OT for exploration and management. He underwent angioembolization for the hepatic bleed. He was later moved to the general ward after

15 days. [Table 1] outlines the details of all three cases(1,2,3) outlying their injuries and management, including administration, onset of action, and duration of effects of CQ.

DISCUSSION

CQ is a vascular resuscitative drug rather than a vasopressor. It serves as a primary resuscitative agent for the treatment of hypovolemic shock.[2,4] It limits the use of vasopressors and helps achieve a "vasopressor-free-resuscitation window." When administered by α2β adrenergic receptors (periphery), CQ produces venous vasoconstriction so increasing the right ventricular preload and hence the cardiac output. By stimulating central α2β adrenergic receptor in the brain, it produces mild arterial vasodilation (decreased sympathetic stimulation) and reduces the left ventricular afterload thereby further increasing the stroke volume.[3]

CQ citrate resuscitation preserves cerebral blood flow and reduces oxidative damage to the brain following hemorrhagic shock.[7]

Although CQ citrate was given once standard resuscitative protocols were followed, further studies are needed on – at which point of clinical status during resuscitation CQ should be given, e.g., vasopressin is considered noradrenaline-sparing resuscitative agent.

Types of shock with non-identical etiologies

- Cardiogenic shock: Caused by heart problems, such as a heart attack, heart disease, or valve disorders.
- Hypovolemic shock: Caused by too little blood volume.
- Anaphylactic shock: Caused by a severe allergic reaction.
- Septic shock: Caused by infections, such as *Escherichia coli*.
- Neurogenic shock: Caused by damage to the nervous system, such as a spinal cord injury.
- Obstructive shock: Caused by something outside of the heart that prevents the heart from pumping enough blood, such as a blood clot in the pulmonary artery.
- Endocrine shock: Caused by a severe hormonal disorder, such as hypothyroidism, in a critically ill person.
- All the above types of shock have different approaches of initial and maintenance resuscitation, respectively. What is the place of centaquine in all these clinical states and at which stage of resuscitation it should be given - needs further systematic studies.

CQ citrate versus other vasopressors - What's the difference?

CQ increases the cardiac output without increasing the HR, in contrast to vasopressors which constrict arteries and veins to increase the HR, also leading to an increased oxygen demand of the heart. Vasopressors increase afterload due to arterial constriction and may continue to result in tissue hypo-perfusion. In contrast, CQ has a unique mechanism of action (described above) that does not cause tissue hypo perfusion or increased metabolic demands. Administration of vasopressors also requires dose titration and bears the risk of cardiac arrhythmias/ischemia. In contrast, there is no need for dose titration with CQ; it is free from any cardiac risk. CQ seems to be an effective resuscitative agent when added to the standard of care. Therefore, CQ is of interest to physicians and paramedics involved in the resuscitation of patients in

Table 1: Details of patients with management including administration, onset of action, and duration of effects of centhaquine.

Sr. No.	Management and centhaquine citrate study parameters	Case 1	Case 2	Case 3
1	Injury sustained	Poly-trauma - multiple gunshot injuries	Blunt abdominal trauma in dengue with thrombocytopenia	Polytrauma - fall from height
2	Treatment before administering CQ	Norepinephrine, vasopressin (maximum doses)	Norepinephrine, vasopressin, Adrenaline (maximum doses)	Norepinephrine, vasopressin, adrenaline (maximum doses)
3	Massive transfusion protocol followed	Yes	Yes	Yes
4	CQ was given after how many hours of presentation	2 h	5 h	7 h
5	Onset of action (positive impact on hemodynamics)	Within 15–20 min	Within 15–20 min	Within 15–20 min
6	Duration of hemodynamic improvement post-CQ administration	3 h	45 min	3 h

CQ: Centhaquine citrate

hypovolemic shock. Several animals and human studies have shown good pk/pd profile and safety.[5,6,8]

Effect of CQ on coagulation profile-risk of bleeding or thrombosis was studied.[9] They found no risk of bleeding or risk of thrombosis after its use in uncontrolled bleeding.

In 2021, Gulati A *et al.*[4] carried out a metacentric, randomized, controlled Phase III study to assess the effectiveness of CQ as a resuscitative agent in patients with hypovolemic shock from trauma or gastroenteritis, who had a systolic BP ≤90 mm Hg and blood lactate levels ≥2 mmol/L. Their study showed that patients who were administered CQ (0.01 mg/kg in 100 mL normal saline) required lesser vasopressor support in the first 48 h of resuscitation showed an improved systolic BP, pulse pressure, and stroke volume and also had an improved 28-day mortality with better multiorgan dysfunction scores in comparison to those patients with a normal saline infusion. Following such studies, CQ was approved to treat hypovolemic shock in India. A phase III investigational new drug application has been approved by the United States Food and Drug Administration for a trial on 430 patients.[10] CQ may also reduce the requirement of fluids and blood products which can play a key role in reducing the duration of ventilator support, thereby reducing the overall length of ICU and hospital stay.[8]

Recent patient blood management (PBM) guidelines recommend the implementation of viscoelastic testing-guided bleeding management algorithms with a 1B or 1A recommendation. This is also addressed in the World Health Organization policy brief about the urgent need to implement PBM in all member states in a timely manner.[11] CQ may also reduce the requirement of fluids and blood products which can play a key role in reducing the duration of ventilator support, thereby reducing the overall duration of ICU and hospital stay. Therefore, it may be cost effective as compared to cost of multiple blood products and intravenous fluid administration and its consequences on clinical outcome. As it is available in India, now, there is an ever-growing need to explore the benefits of this drug more.

Potential areas for future research

1. Can CQ be given immediately after resuscitation with fluid and blood products or should we wait for vasopressors and inotropes to work?
2. Can the CQ dose be repeated if a patient does not respond to the first?
3. Can a CQ be used in postoperative bleeding complications?
4. Can CQ be used in cases with intra-operative hemorrhagic shock?
5. Can CQ be given as soon as the patient is received in the ER in hemorrhagic shock?
6. Scope of CQ in hemorrhagic complications of different organ dysfunctions like decompensated chronic liver disease with bleeding esophageal varices.
7. The use of CQ in bleeding is related to different invasive procedure complications.
8. Role of CQ in infectious disease-related hemorrhagic states like bleeding in dengue with hemorrhagic complications.
9. Role of CQ in hemorrhagic shock due to anticoagulation overdose with bleeding.
10. Role of CQ in DIC – at which stage it can be useful?
11. Role of CQ in central nervous system hemorrhagic states such as traumatic brain injury or intracranial hemorrhage.
12. Role of CQ in post-operative coagulopathy/hemorrhagic shock such as post-coronary bypass grafting, valvular, or aortic surgeries.
13. Role of CQ in disseminated intravascular coagulation.
14. Role of CQ in post-partum hemorrhage.
15. Role in ENT bleeds.
16. Role in solid organ malignancy and tumor-related bleeding or hemorrhagic shock.
17. Long-term outcomes such as its use and length of ICU stay, overall operative and non-operative mortality, and delayed adverse effects in non-identical etiologies.

CONCLUSION

Administration of CQ citrate in patients with hemorrhagic shock improved transient hemodynamics. Thus, CQ served as a temporary bridge to specific treatment interventions by momentarily halting life-threatening bleeding.

CQ may limit the use of vasopressors and help achieve a "vasopressor-free-resuscitation window." Future research is needed to determine this molecule's precise role and identify the optimal stage of hemorrhagic shock for administering CQ in appropriate doses.

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