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REVIEW ARTICLES

Bridging the Gap in Resuscitation Therapies: Centhaquine in Hypovolemic Shock

Sanjay Shah

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ABSTRACT

Hypovolemic shock is a life-threatening condition with high mortality, requiring urgent resuscitative therapy to restore perfusion and prevent irreversible organ damage alongside the definitive management. Current treatments, including fluid resuscitation with initially crystalloids and later blood or its components followed by vasopressors have certain limitations in effectively restoring hemodynamics and improving tissue perfusion besides some safety concerns. This review explores unique features of a novel first-in-class resuscitative agent centhaquine including unique mechanism of action, pure venoconstriction without arterial constriction and wide safety margin. The balanced modulation of venous return and arterial resistance allows centhaquine to increase cardiac output in patients with hypovolemic shock while maintaining the tissue perfusion without compromising microcirculatory flow, offering clinicians a more effective option to improve survival in these critically ill patients. Preclinical and clinical studies demonstrate that centhaquine significantly improves hemodynamic parameters, reduces vasopressor and fluid requirements, lowers blood lactate levels and improves survival in patients with hypovolemic shock. Centhaquine's renoprotective effects further highlight its potential in preventing organ failure following hypovolemic shock. The safety profile of centhaquine has been established across multiple phases of clinical trials and it is currently approved in India for the treatment of hypovolemic shock. Centhaquine represents a promising advancement in the management of shock, offering a novel approach to improving patient outcomes. Further research could evaluate the potential of centhaquine in managing other forms of shock such as neurogenic shock and septic shock.

KEYWORDS

• Centhaquine • Hypovolemic shock • Resuscitation therapy • Hemodynamic stability • Organ protection • Tissue perfusion • Multiorgan failure

AUTHOR'S AFFILIATION:

[1]Senior Consultant Trauma Surgeon and Head, Emergency Department, Apollo Hospitals Int Ltd, Ahmedabad, Gujarat 382428, India.

CORRESPONDING AUTHOR:

Sanjay Shah, Senior Consultant Trauma Surgeon and Head, Emergency Department, Apollo Hospitals Int Ltd, Ahmedabad, Gujarat 382428, India.

E-mail: drsanjayshah2002@yahoo.com

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Key Messages:

- Centhaquine is a novel resuscitative agent with a unique mechanism of action, pure venoconstriction without arterial constriction, primarily enhancing venous return and tissue perfusion with wide safety margin.
- Centhaquine's innovative therapeutic approach addresses limitations of current treatments, marking a significant advancement in the management of critical shock states.

INTRODUCTION

Hypovolemic shock is a life-threatening condition caused by a critical reduction in circulating blood volume (BV) due to hemorrhage or severe fluid loss, leading to inadequate tissue perfusion and organ dysfunction.[1] Approximately 1.9 million people globally succumb to hemorrhagic shock annually, with most deaths occurring within the first 6 hours.[2,3] Severe hypovolemia significantly reduces cardiac preload, leading to a sharp decline in cardiac output (CO), impairing the tissue perfusion and if left untreated, results into organ failure, acute kidney injury (AKI), coagulopathy and multi-organ dysfunction syndrome (MODS), which further increases mortality and long-term morbidity in survivor.[1,4,5]

Early and effective resuscitation is crucial to restoring perfusion and preventing irreversible damage. Current treatment modalities for hypovolemic shock primarily include fluid resuscitation and vasopressors to maintain blood pressure (BP).[1,6-8] However, despite aggressive fluid resuscitation and the use of vasopressors, outcomes remain poor for many patients due to certain residual mortality.[9,10] Therefore, there is an urgent need for novel resuscitative agents that can effectively improve hemodynamics, improve the tissue perfusion and reduce the burden of fluid and vasopressor administration.

In this context, centhaquine, a novel resuscitative agent, has emerged as a promising therapy for hypovolemic shock and its discovery represents a major advancement.[4] The objective of this review article is to provide a comprehensive overview of centhaquine's role in hypovolemic shock, summarizing its unique mechanism of action, efficacy, clinical benefits and safety, offering clinicians a more effective option to improve survival in these critically ill patients.

HYPOVOLEMIC SHOCK

Hypovolemic shock results from a significant loss of intravascular volume, leading to reduced cardiac preload, CO, stroke volume (SV), circulating BV, BP and inadequate tissue perfusion ultimately resulting in multi-organ failure (MOF) if left untreated.[1,7,11] The primary causes of hypovolemic shock can be broadly categorized into hemorrhagic (e.g. trauma, gastrointestinal bleeding, postpartum hemorrhage, perioperative blood loss) and nonhemorrhagic type (e.g. burns, excessive vomiting, severe diarrhea).[12-14] Regardless of the etiology, the hallmark feature of hypovolemic shock is the failure of oxygen delivery to tissues, initiating a series of compensatory mechanisms aimed at maintaining perfusion and preserving vital organ function.[2]

Compensatory Mechanisms in Hypovolemic Shock

In response to acute fluid loss, the body activates several compensatory systems through the arterial baroreflex activating the autonomic nervous system, sympathetic stimulation while suppressing parasympathetic responses and the cardioinhibitory center. Consequently, peripheral vascular resistance (PVR) and heart rate (HR) increase to maintain mean arterial pressure (MAP) and circulation.[15] Additionally, sympathetic activation leads to constriction of major capacitance veins, enhancing venous return to the heart. It also triggers the adrenal glands to release epinephrine and norepinephrine, which further increase vasoconstriction and HR.[15] These combined baroreflex responses and physiological autoregulation work together to stabilize BP and ensure adequate blood flow to vital organs.[15]

α-adrenergic receptors (AR) play a key role in the sympathetic response by inducing vasoconstriction, which helps to increase the effective circulating volume (ECV).[16] However,

this also reduces renal blood flow (RBF), triggering compensatory activation of the renin-angiotensin-aldosterone system which promotes sodium and water retention, further elevating ECV.[17] Simultaneously, β-ARs enhance cardiac inotropy and chronotropy, as well as increase plasma renin levels, thereby improving CO and contractility.[18,19] These compensatory mechanisms are generally effective in mild to moderate shock but soon begin to fail leading to decompensation and worsening of shock.

Decompensation in Hypovolemic Shock

As blood or fluid loss continues, the compensatory mechanisms eventually fail, leading to decompensated shock.[20] In this phase, the mismatch between oxygen delivery and demand worsens, leading to metabolic acidosis due to anaerobic glycolysis and increased lactate production.[21] Prolonged tissue hypoxia and the resulting metabolic acidosis mark the transition into the uncompensated phase. This ultimately triggers cell death and results in MOF, exacerbating the critical state of hypovolemic shock and significantly increasing the risk of mortality.[22]

CURRENT RESUSCITATION THERAPIES IN HYPOVOLEMIC SHOCK

The primary goal in managing hypovolemic shock is to restore circulating BV, improve tissue perfusion and stabilize hemodynamics. Given that a significant proportion of deaths occur within the first six hours of shock, rapid and efficient treatment is essential.[23] Resuscitation strategies focus on correcting hypovolemia, maintaining cardiovascular function, supporting ventilation and ensuring adequate blood perfusion to vital organs.[23] Accordingly, the current management approach broadly includes fluid therapy, blood products, ventilatory support, and vasopressors.[7,8]

Fluid Therapy

Since the main driving force of hypovolemic shock is a significant reduction in BV, prompt restoration of BV to stabilize hemodynamics by fluid resuscitation is the cornerstone of management.[23] Rapid volume replacement using crystalloids and later on colloids is a standard practice.[24] Crystalloids, such as normal saline (NS) and lactated Ringer's solution, are the first-line agents due to their effectiveness in quickly expanding the intravascular compartment.[25] Balanced electrolyte solutions offer an alternative to NS, as they are associated with a lower risk of hyperchloremic acidosis.[24]

Blood Products

Utilizing blood products in a balanced ratio of plasma, platelets and red blood cells is also beneficial for effective resuscitation.[26] In cases of hemorrhagic shock, blood transfusions are essential to restore both volume and oxygen-carrying capacity. Packed red blood cells (PRBCs) improve tissue oxygenation, but transfusions come with risks like transfusion-related acute lung injury, infections and immune reactions.[26,27] Moreover, logistics related to availability and storage in emergency settings pose significant challenges.

Vasopressors

When fluid therapy alone is insufficient to maintain adequate perfusion, vasopressors are employed.[28] The most commonly used vasopressor is norepinephrine, followed by phenylephrine, epinephrine and dopamine.[29] Infusing catecholamines improves cardiac contractility and vascular tone across arteriolar, venous and renal vascular beds, thereby affecting arterial, venous, and capillary pressures as well as blood flow.[29] But vasopressors should be used only after adequate fluid resuscitation to restore volume, else, it increases PVR and may further aggravate shock physiology if circulatory volume is inadequate.

Limitations of Current Resuscitation Modalities

While the above therapies are integral to managing hypovolemic shock, they come with limitations. The use of large volumes of crystalloids, can lead to adverse outcomes such as abdominal compartment syndrome, pulmonary edema and cardiac dysfunction.[25,30] While colloids (e.g., albumin, hydroxyethyl starch) offer a more sustained volume expansion due to their higher oncotic pressure, they carry risks such as kidney injury and coagulopathy.[31] As such, their use remains controversial. Additionally, crystalloids and colloids can dilute coagulation factors, exacerbating hemorrhage.[32,33] Patients receiving crystalloids often develop coagulopathy, oxidative stress,

systemic inflammation, irreversible loss of capillary perfusion, acidosis, hypothermia, immune suppression all of which can lead to MOF.[11] Vasopressors carry the risk of ischemia due to excessive vasoconstriction, worsening of tissue perfusion, especially in the microcirculation, arrhythmias, and fluid extravasation.[10,34,35] Thus, the debate around the optimal resuscitation methods highlights the pressing need for newer, more effective treatment strategies.[9]

CENTHAQUINE: A MULTIFACETED-ACTION SAVIOR IN HYPOVOLEMIC SHOCK

Centhaquine, a novel pharmacological agent has revolutionized the treatment of hypovolemic shock. Unlike traditional vasopressors and volume expanders, centhaquine aims to improve hemodynamics and tissue perfusion without the adverse effects associated with current therapies.

Improvement in Venous Return

The venous system plays a crucial role in the aftermath of hemorrhage, as it serves as a reservoir to mobilize pooled (unstressed) blood toward the systemic (stressed) circulation.[36,37] A significant volume of blood stored in the venous system can be redirected to the heart and subsequently shifted to the arterial side, enhancing tissue perfusion and oxygenation.[36,37]

Under normal physiological conditions, a considerable amount of blood is sequestered in the venous system, which has a high vascular capacitance. However, during hypovolemic shock, the accumulation of blood in the veins increases further, resulting in a substantial volume that fails to contribute to tissue perfusion.[38] Therefore, strategies aimed at redirecting this pooled venous blood to the arterial circulation are vital, as they can augment circulating BV and overall tissue perfusion.

Centhaquine's primary mechanism is mediated through its action on α2B Ars.[11] The distribution of α2 ARs differs based on the vascular bed. While α2A receptors are abundant in large arteries, α2B ARs predominate in peripheral veins.[39-41] At low doses (0.015–0.02 mg/kg), centhaquine stimulates particularly the α2B ARs, inducing peripheral venoconstriction, mobilizing the blood pooled in the venous system towards systemic circulation, thereby increasing venous return to the heart. The redistribution of this venous blood enhances cardiac preload, SV and CO, which are critical for maintaining MAP and tissue perfusion.[6,11,36,42] This preferential action of centhaquine on venous return is unique compared to traditional vasopressors, which focus more on arterial constriction, often at the expense of tissue perfusion.

Central Sympatholytic Action

Additionally, centhaquine's minor action on the presynaptic α2A ARs in the brain further contributes to its resuscitative effect. During compensatory phase, centhaquine by reducing sympathetic overactivity from the ventrolateral medulla, slightly decreases PVR, which improves blood flow to vital organs while reducing the afterload on the heart.[43,44] Moreover, centhaquine slightly reduces HR in the state of reflex tachycardia, which prolongs diastolic time and enhances ventricular filling, further contributing to increased SV and CO.[11,43]

Cardiovascular Effects

Centhaquine enhances cardiac function by increasing cardiac preload and CO.[45] Moreover, centhaquine has no significant binding to β-ARs, further reducing the risk of arrhythmias, thus distinguishing it from other resuscitative agents like epinephrine.[4]

Furthermore, fluid infusion during resuscitation increases circulating BV and when combined with centhaquine as an adjunct therapy, it can substantially enhance CO and improve overall blood circulation.[11] Figure 1 illustrates key mechanisms of action of centhaquine in the management of hypovolemic shock.

This balanced modulation of venous return and arterial resistance allows centhaquine to increase CO while maintaining tissue perfusion without compromising microcirculatory flow, thereby minimizing the required resuscitation volume and reducing the risk of fluid extravasation and complications like pulmonary edema.[4,11] Its potential to improve survival outcomes while reducing the need for vasopressors represents a significant advancement in shock management.[11] This multi-faceted action makes centhaquine an ideal candidate for the resuscitation of patients with hypovolemic shock.[36] Figure 2 highlights the unique actions of centhaquine which work synergistically to improve tissue perfusion and organ protection during hypovolemic shock.

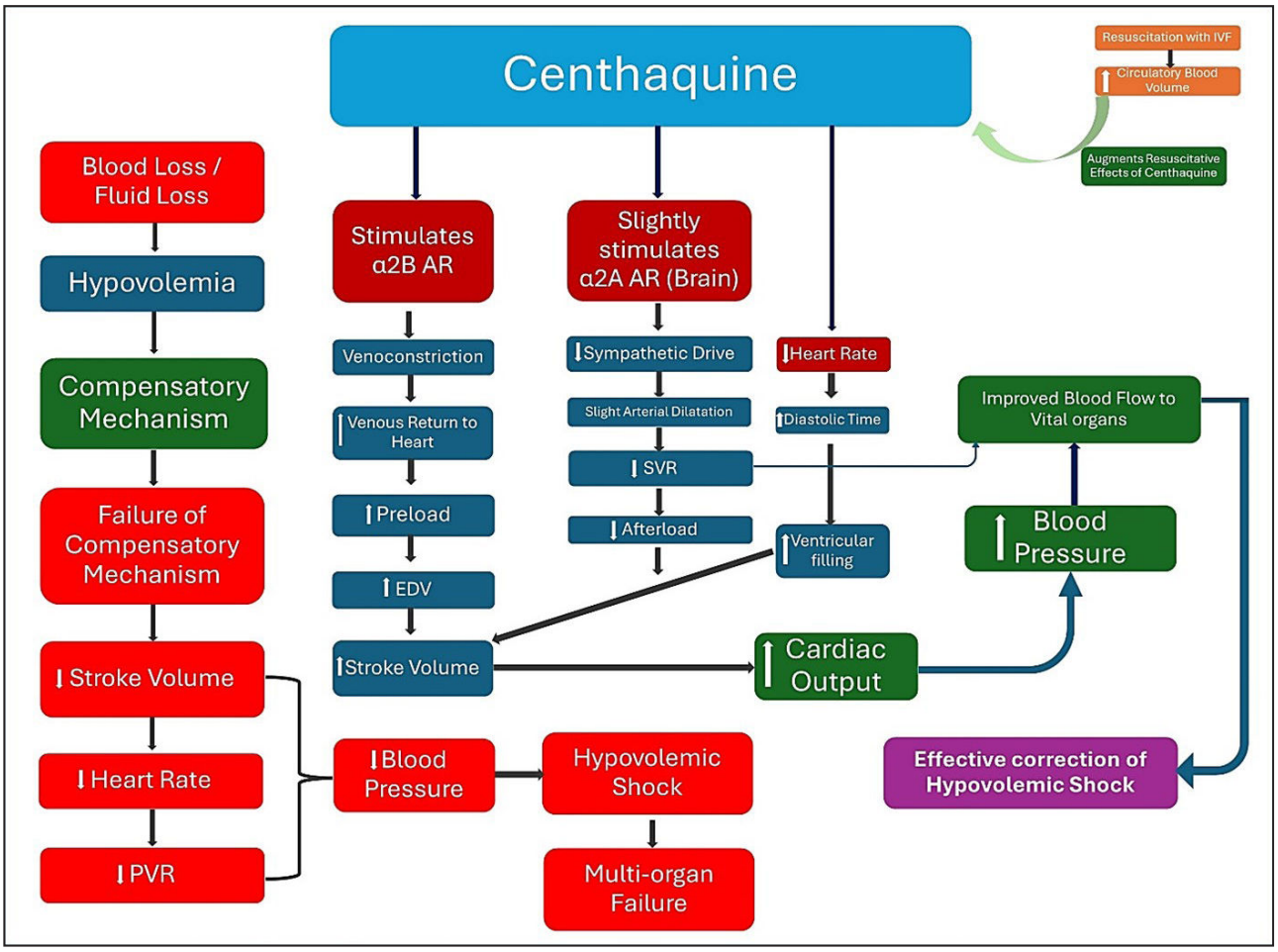


Figure 1: Unique mechanisms of action of centhaquine in the management of hypovolemic shock

PVR – Peripheral vascular resistance, AR – Adrenergic receptors, EDV – End diastolic volume, SVR – Systemic vascular resistance

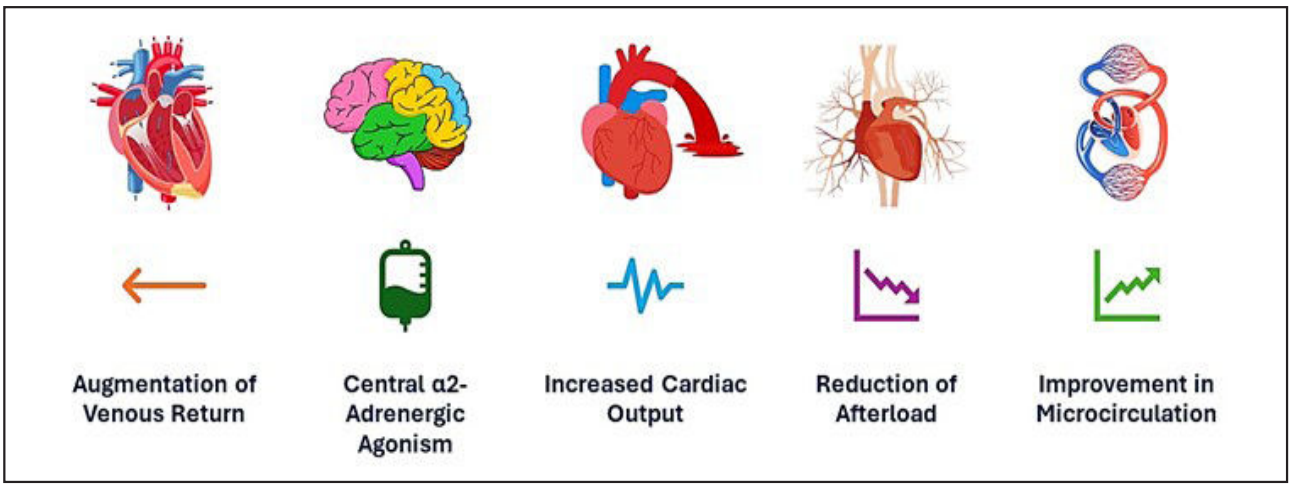


Figure 2: Unique Actions of Centhaquine in Hypovolemic Shock

PRECLINICAL EVIDENCES

Centhaquine has undergone extensive preclinical evaluation in various animal models of hemorrhagic shock. These preclinical proof-of-concept studies have demonstrated its potential as a resuscitative agent, showing a significant improvement in hemodynamics with reduced mortality.

Gulati *et al*. (2011) explored the effects of centhaquine in hemorrhaged rats.[46] The study showed that centhaquine significantly reduced blood lactate levels (1.65±0.23 mmol/L) compared to the NS group (4.10±1.02 mmol/L) at 60 minutes post-resuscitation. Moreover, the norepinephrine requirement to maintain a MAP of 70 mmHg was considerably lower in centhaquine-treated rats (17.5µg) than in the NS group (175µg). In a subsequent set of experiments, blood lactate levels were 44% lower in the centhaquine-treated group compared to hypertonic saline (HS) group. This is a crucial finding, as elevated blood lactate levels are strongly linked to poorer clinical outcomes and an increased risk of mortality.[47] These results demonstrate that centhaquine is a potent resuscitative agent, likely enhancing vascular responsiveness and thereby reducing the need for norepinephrine. Moreover, rats in the HS group survived for 53±7 minutes, whereas those treated with centhaquine survived for 78±8 minutes (P=0.046) suggesting improved survival with centhaquine.[47]

Similarly in another study by Gulati A *et al*. (2013), centhaquine significantly reduced blood lactate, improved CO and MAP, maintained MAP for longer duration (161±14 minutes vs 55±6 minutes) and had prolonged total survival time (266±16 minutes vs 134±12 minutes) compared to HS in hemorrhaged rats.[48] In a rabbit model of uncontrolled hemorrhagic shock with tissue injury, Gulati *et al*. (2013) demonstrated that animals that did not receive resuscitation did not survive beyond 5 minutes. However, both saline and centhaquine-resuscitated animals survived for 2 hours. The volume of fluid required for resuscitation was significantly lower in the centhaquine-treated group (133.60±11.91 ml) compared to the saline group (207.82±9.08 ml, p=0.0011).[49]

Papapanagiotou *et al*. (2016) investigated centhaquine's effect in a swine model of hemorrhagic shock. The centhaquine group achieved target MAP significantly faster (7.10±0.97 min) compared to the control group (36.88±3.26 min), with a reduced total fluid requirement (P<0.001). All animals treated with centhaquine survived the 24-hour period, while only 3 animals in the control group survived (P=0.002).[50]

Thromboelastographic studies have demonstrated that centhaquine does not interfere with key aspects of coagulation, including platelet aggregation, fibrin formation, or clot lysis.[51] Instead, it enhances clot strength, leading to reduced blood loss and a lower need for fluid resuscitation. Additionally, the anticoagulant effects of medications such as heparin or aspirin remain unaffected by centhaquine administration.[52] This highlights that centhaquine is the first resuscitative agent that does not interfere with coagulation.

RENO-PROTECTIVE EFFECTS OF CENTHAQUINE

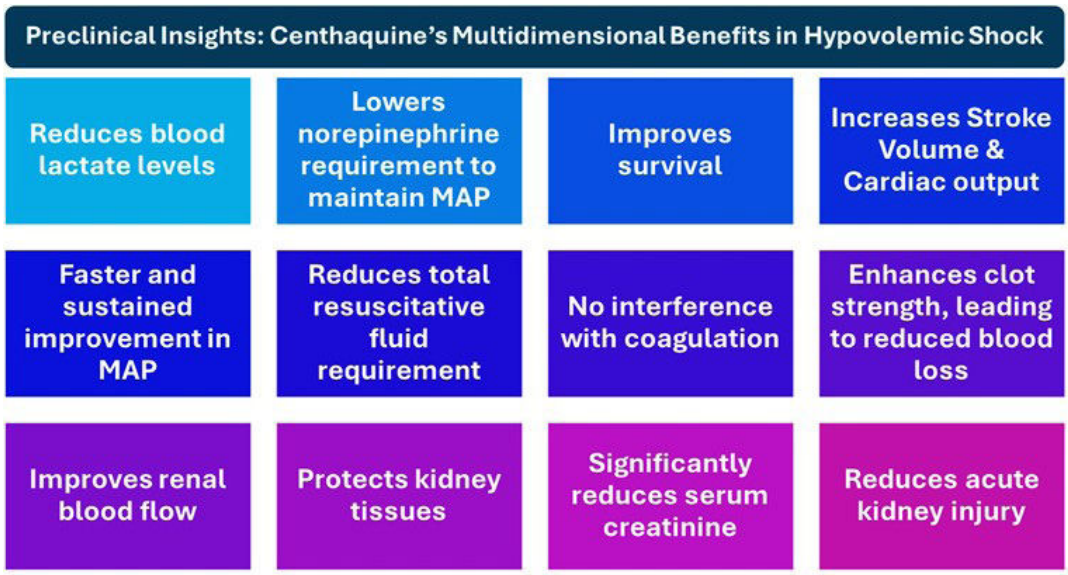
In hemorrhagic shock patients, mortality is often linked to MOF, with acute kidney failure being the most common organ dysfunction observed.[53] The kidneys are among the first organs to sustain damage, more prone to failure at a much earlier stage than other organs following hemorrhage.[54] This early onset of kidney failure triggers a cascade of homeostatic disturbances, exacerbating organ dysfunction and accelerating the failure of other vital systems.[55] Hence, there is a significant clinical need for resuscitative agents capable of providing renal protection to improve outcomes.

Centhaquine has shown promise in mitigating kidney damage post-hemorrhage. Ranjan *et al*. (2020, 2021) conducted preclinical studies in a rat model of hemorrhagic shock.[56,57] In these studies, centhaquine administration resulted in improved RBF, significant reduction in blood lactate levels and protection of kidney tissues. Additionally, centhaquine-treated rats exhibited a significant upregulation of hypoxia-inducible factor 1α (p=0.024) and reduced mitochondrial DNA damage (p=0.03) compared to controls, suggesting a protective effect on renal tissue integrity. Centhaquine reduced both AKI and apoptosis in renal tissues, highlighting its novel role in improving RBF, hypoxia survival response and renal protection during haemorrhagic shock.

Centhaquine's mechanism of reno-protective action may be attributed to its α-adrenergic effects, as the kidney is rich in α-ARs, primarily located in renal arterioles, glomeruli and tubules. These receptors regulate vital renal functions, including RBF, glomerular filtration, renin release and sodium reabsorption.[58,59] Stimulation of α-adrenergic signalling by centhaquine likely

contributes to restoring renal perfusion. This increase in RBF is independent of an increase in CO and BP, indicating that centhaquine's renoprotective effect may stem from selective renal vasodilation.[56]

Moreover, centhaquine has demonstrated significant reduction in serum creatinine levels. In a study by Gulati *et al*. (2019), creatinine levels in the centhaquine cohort dropped from 1.16±0.12 mg/dL at baseline to 0.68±0.05 mg/dL (p=0.0021) by the end of the study, a more pronounced decrease than in the control group.[60] Overall, centhaquine has emerged as a promising resuscitative agent, providing renal protection by enhancing blood flow to the kidneys, reducing lactate buildup, and preventing structural damage. *Figure 3* illustrates the key benefits of centhaquine observed in preclinical studies.



Figures 3: Summary of Preclinical Evidence of Centhaquine Supporting Enhanced Resuscitation and Organ Protection

MAP – Mean arterial pressure

CLINICAL TRIAL EVIDENCES

Phase II Clinical Trial

A prospective, multicentric, randomized, double-blind, phase II clinical trial was conducted to assess the safety and efficacy of centhaquine in hypovolemic shock caused by excessive blood loss.[61] Fifty patients were randomized in a 1:1 ratio to receive either 100 ml of NS over 1 hour, or centhaquine 0.01 mg/kg in 100 ml of NS over 1 hour. Both groups were given standard of care (SOC) and were followed for 28 days.

Hemodynamic Stability and Lactate Clearance

Centhaquine significantly improved hemodynamic parameters, with a more pronounced increase in systolic and diastolic BP over the 48-hour period compared to the control group (P<0.0001) with significant reduction blood lactate levels. Patients treated with centhaquine spent less time in the ICU and required less ventilator support compared to the control group. Notably, the total vasopressor requirement within the first 48 hours was lower in the centhaquine group than in the control group (Table 1).

Table 1: Summary of Phase II Clinical Trial Results[61]

Efficacy Parameters	Centhaquine (N = 23)	Control (N = 22)	Between group Difference
Change in Systolic Blood Pressure from baseline	34.13 mmHg (p<0.0001)	18.41 mmHg (p=0.0261)	
Change in Diastolic Blood Pressure from baseline	18.13 mmHg p<0.0001)	7.273 mmHg (p=0.1812	
Change in Blood Lactate from baseline	- 2.902 ± 0.7865 (p=0.0012)	- 1.110 ± 1.437 (p=0.4441)	- 1.752 ± 1.077 (95% CI - 3.988 to 0.4839, p=0.1183)

Efficacy Parameters	Centhaquine (N = 23)	Control (N = 22)	Between group Difference
% Reduction in Lactate levels from baseline	66.8%	25.8%	p = 0.1183
Change in Base Deficit from baseline	4.823 ± 2.054 (p=0.0237)	7.114 ± 1.439 (p<0.0001)	
Total vasopressor requirement	3.12 ± 2.18 mg	9.39 ± 4.28 mg	- 6.272 ± 4.805, 95% CI - 16.07 to 3.524, p = 0.2013.
Duration of ventilator support	0.89 ± 0.45 days	1.96 ± 1.10 days	- 1.063 ± 1.186, 95% CI - 3.493 to 1.367, p = 0.3778.
Percent stay in ICU	41.89%	48.93%	
Patients needing vasopressors*	26.09%	40.91%	

** first 48 h of resuscitation*

Organ Function and Mortality

There were greater improvements in base deficit, reduced MODS scores and decreased adult respiratory distress syndrome (ARDS) severity. All cause mortality at 28 days was 0/23 in the centhaquine group compared to 2/22 in the control group.

Phase III Clinical Trial

A prospective, multicentric, randomized phase III study was conducted to evaluate the safety and efficacy of centhaquine in 105 patients with hypovolemic shock.[4] Participants were randomized in a 2:1 ratio to receive centhaquine 0.01 mg/kg in 100 mL of NS infusion over 1 hour (n = 71) or NS (n = 34). Both groups received SOC and were followed up for 28 days.

Hemodynamic Stability

Patients treated with centhaquine exhibited significantly greater increases in SBP at all time points compared to the control group. The mean SBP increase was 15.2 mmHg in the centhaquine group versus 11.0 mmHg in the control group at 1 hour of resuscitation and this difference remained consistent at 12,24, and 48 hours. Notably, more patients in the centhaquine group achieved an SBP> 90 mmHg at 12 hours (96.9% vs. 87.5%), and significantly more patients reached SBP≥110 mmHg at 24 hours (79.7% vs. 60.6%; p=0.04).

Improved Cardiac Functions

Centhaquine-treated patients showed a 12.9% increase in the area under the curve (AUC 0–48) for SBP compared to the control group, suggesting improved venous return and CO in centhaquine group than in the control group. Additionally, pulse pressure was significantly increased, with a 48.1% rise in AUC 0–48 in the centhaquine group, indicating enhanced SV. A 7.4% decrease in AUC 0–48 for DBP in the centhaquine group suggested improved ventricular filling.

Shock Index

The shock index (SI), an important prognostic indicator showed significant improvement in the centhaquine group. SI was significantly lower in the centhaquine group from 1 to 4 hours post-resuscitation (p<0.0001), highlighting better hemodynamic stability in these patients.

Lactate Clearance and Base Deficit

Blood lactate levels, a key marker of tissue hypoperfusion, showed significant improvement in the centhaquine group, with 69.3% of patients achieving improvement compared to 46.9% in the control group (p=0.03). Centhaquine also significantly improved base deficit, with 69.8% of patients showing improvement compared to 43.7% in the control group (p=0.01).

Meta-analysis of Phase II and Phase III Data

Additionally, Gulati A *et al*. conducted a meta-analysis of the mortality data from Phase II and Phase III studies. The analysis revealed a mortality rate of 10.71% in the control group compared to 2.20% in the centhaquine group (odds ratio 5.34 (95% CI 1.27–26.50); p=0.03), indicating a statistically significant reduction in mortality in the centhaquine group.[4]

Phase IV Post-marketing Clinical Study

A prospective, Phase IV post-marketing multicenter, open-label pilot study was conducted on 12 randomly selected patients with hypovolemic shock to further

evaluate the efficacy of centhaquine using transthoracic echocardiography in real-world clinical settings.[6] A marked increase in SV was observed at 60, 120 and 300 minutes after centhaquine initiation, with a ~40% increase in SV compared to typical increases of 10–25% seen in studies that rely solely on fluid resuscitation.[62] In addition, there was a significant increase in CO, inferior vena cava diameter and left ventricular outflow tract velocity-time integral (LVOT-VTI), reflecting improved venous return.

Case Report

Wasir AS *et al*. reported 3 cases of adult male patients who presented with hemorrhagic shock.[63] Despite receiving multiple vasopressors, inotropes and transfusions, their hemodynamics continued to deteriorate. As a last resort, each patient received an infusion of centhaquine (0.01 mg/kg in 100 ml NS over 1 hour) after 2, 5 and 7 hours of presentation. Hemodynamic improvement began within 15–20 minutes post-infusion in all cases. Centhaquine provided a critical hemodynamic window, acting as a bridge to definitive surgical intervention by stabilizing the life-threatening bleeding.

REGULATORY STATUS OF CENTHAQUINE

Based on robust data, Pharmazz Inc. (Willowbrook, IL, USA) has successfully obtained marketing authorization for centhaquine in India in 2020 for the treatment of hypovolemic shock as a frontline adjuvant to SOC. This approval marks an important milestone in the availability of a novel resuscitative agent for hypovolemic shock in the clinical setting. In addition, Pharmazz Inc. has also received the green signal from the U.S. Food and Drug Administration (FDA) to conduct a Phase III clinical trial of centhaquine for treating hypovolemic shock without the need for Phase I and Phase II clinical trials. The trial (NCT05251181) is expected to start in October 2023, with an estimated completion date of October 2025. This regulatory approval highlights the ongoing global clinical development of centhaquine and its potential to significantly improve outcomes for patients with hypovolemic shock.

SAFETY PROFILE OF CENTHAQUINE

Centhaquine has demonstrated a favorable safety profile across early-phase and late-phase clinical trials. In the Phase I study, centhaquine was generally well-tolerated at various doses. Mild adverse reactions were observed at 10 times the recommended doses of centhaquine; hypotension and elevated lactic acid in one subject at the highest dose (0.15 mg/kg), and drowsiness, dry mouth, and a decrease in respiratory rate in another subject at the 0.1 mg/kg dose. All events were mild in severity, resolved without intervention, and had no lasting effects. In Phase II and Phase III clinical trials, centhaquine did not show any clinically significant effects on vital signs, hematology, lipid profile, kidney and liver functions, or serum electrolytes.[4,61,64]

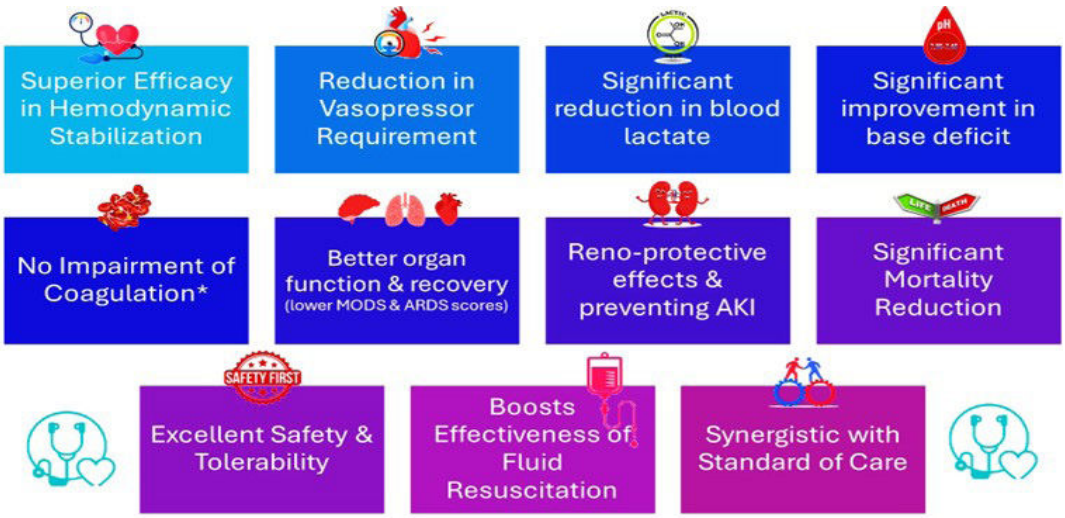


Figure 4: Key Clinical Benefits of Centhaquine in Hypovolemic Shock

***preserving clot** formation and strength allowing safer resuscitation in hemorrhagic shock without increasing bleeding risk. **AKI** - acute kidney injury, **MODS** - multi-organ dysfunction syndrome, **ARDS** - Adult respiratory distress syndrome

Unlike traditional vasopressors, which can increase the risk of arrhythmias, and myocardial ischemia, centhaquine has shown a lower propensity for such complications.[4,61] Unlike vasopressors, which can lead to renal vasoconstriction and AKI, centhaquine preserves RBF, reduced both AKI and apoptosis in renal tissues.[56,57,60,65] In trauma patients, hypocalcemia is a common complication, affecting approximately 55% of cases and can aggravate coagulopathy, worsening hemorrhage.[66,67] In Phase III Clinical trial, centhaquine did not negatively impact serum calcium levels.[4] Figure 4 illustrates the major clinical advantages of centhaquine in hypovolemic shock.

FUTURE RESEARCH DIRECTIONS

Further research could evaluate the potential of centhaquine in managing other forms of shock characterized by hemodynamic instability or refractory hypotension, which often lead to MOF and death. One such area of interest could be distributive shock, where the ability of centhaquine to enhance CO and improve tissue perfusion may offer significant therapeutic benefits. Centhaquine's mechanisms could be explored in septic and neurogenic shock.

CONCLUSION

Centhaquine represents a promising advancement in the management of hypovolemic shock, offering unique resuscitative benefits by enhancing venous return, improving CO and promoting tissue perfusion without compromising safety. Its demonstrated efficacy in mitigating organ dysfunction, particularly in the kidneys and reducing mortality, sets it apart from current resuscitation therapies. Future research will further clarify its role in other forms of shock and expand its therapeutic potential. Centhaquine could revolutionize the treatment landscape, providing a critical option in the resuscitative care of shock patients.

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