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ORIGINAL RESEARCH ARTICLE

A Multicentric, Randomized, Controlled Phase III Study of Centhaquine (Lyfaquin®) as a Resuscitative Agent in Hypovolemic Shock Patients

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Abstract

Introduction Centhaquine (Lyfaquin®) showed significant safety and efficacy in preclinical and clinical phase I and II studies.

Methods A prospective, multicentric, randomized phase III study was conducted in patients with hypovolemic shock, systolic blood pressure (SBP) ≤ 90 mmHg, and blood lactate levels ≥ 2 mmol/L. Patients were randomized in a 2:1 ratio to the centhaquine group ($n = 71$) or the control (saline) group ($n = 34$). Every patient received standard of care (SOC) and was followed for 28 days. The study drug (normal saline or centhaquine 0.01 mg/kg) was administered in 100 mL of normal saline infusion over 1 h. The primary objectives were to determine changes (mean through 48 h) in SBP, diastolic blood pressure (DBP), blood lactate levels, and base deficit. The secondary objectives included the amount of fluids, blood products, and vasopressors administered in the first 48 h, duration of hospital stay, time in intensive care units, time on ventilator support, change in acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and the proportion of patients with 28-day all-cause mortality.

Results The demographics of patients and baseline vitals in both groups were comparable. The cause of hypovolemic shock was trauma in 29.4 and 47.1% of control group and centhaquine group patients, respectively, and gastroenteritis in 44.1 and 29.4%, respectively. Shock index (SI) and quick sequential organ failure assessment at baseline were similar in the two groups. An equal amount of fluids and blood products were administered in both groups during the first 48 h of resuscitation. A lesser amount of vasopressors was needed in the first 48 h of resuscitation in the centhaquine group. An increase in SBP from baseline was consistently higher up to 48 h (12.9% increase in area under the curve from 0 to 48 h [$AUC_{0–48}$]) in the centhaquine group than in the control group. A significant increase in pulse pressure (48.1% increase in $AUC_{0–48}$) in the centhaquine group compared with the control group suggests improved stroke volume due to centhaquine. The SI was significantly lower in the centhaquine group from 1 h ($p = 0.032$) to 4 h ($p = 0.049$) of resuscitation. Resuscitation with centhaquine resulted in a significantly greater number of patients with improved blood lactate (control 46.9%; centhaquine 69.3%; $p = 0.03$) and the base deficit (control 43.7%; centhaquine 69.8%; $p = 0.01$) than in the control group. ARDS and MODS improved with centhaquine, and an 8.8% absolute reduction in 28-day all-cause mortality was observed in the centhaquine group.

Conclusion Centhaquine is an efficacious resuscitative agent for treating hypovolemic shock. The efficacy of centhaquine in distributive shock is being explored.

Trial Registration Clinical Trials Registry, India; ctri.icmr.org.in, CTRI/2019/01/017196; clinicaltrials.gov, NCT04045327.

1 Introduction

Severe blood or fluid loss due to trauma, gastrointestinal bleeding, major surgery, postpartum hemorrhage, diarrhea, or vomiting can cause hypovolemic shock [1, 2]. About 1.9 million people worldwide die because of hemorrhagic shock every year [3], most dying within the first 6 h [4]. The main features of hypovolemic shock include hypotension, increased blood lactate levels, and base deficit. Hypovolemia decreases cardiac preload to a critical level, causing a dramatic drop in cardiac output that results in low tissue blood perfusion, ultimately leading to multiple organ dysfunction and death. Across the world, patients in intensive care units (ICUs) are resuscitated with fluid therapy to restore blood volume and tissue blood perfusion [5]. Although the goal is

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Key Points

A multicentric randomized controlled trial was conducted to evaluate the efficacy of centhaquine in 105 patients with hypovolemic shock.

Patients were randomized 2:1 to receive centhaquine or saline. Centhaquine was administered at a dose of 0.01 mg/kg in 100 mL saline and infused over 1 h. The control group received 100 mL of saline over a 1-h infusion.

Centhaquine increased cardiac preload and decreased cardiac afterload to augment cardiac output during resuscitation.

Centhaquine improved blood pressure and shock index, reduced blood lactate levels, and improved base deficit. Acute respiratory distress syndrome and multiple organ dysfunction syndrome improved with centhaquine.

An 8.8% absolute reduction in 28-day all-cause mortality was observed in the centhaquine group. There were no drug-related adverse events in the study.

to increase the intravascular circulating volume, fluid tends to move out into the extravascular space. An ideal resuscitation fluid should rapidly and effectively increase intravascular volume with sustained effect and minimal third space losses [2].

Numerous attempts have been made to develop an effective resuscitative agent, without success. Agents that could decrease metabolic activity to reduce oxygen demand have been studied. Histone deacetylase inhibitors [6, 7], hydrogen sulfide and its donor [8, 9], mitochondria-targeted hydrogen sulfide donor AP39 [10], formulations consisting of d-beta-hydroxybutyrate and melatonin [11], and other hibernation-based approaches have been tried [12], but none has shown any promise clinically. Hemoglobin-based blood substitutes (oxygen carriers) were developed as resuscitative agents. Diaspirin crosslinked hemoglobin was found to be effective in animal models of hemorrhagic shock [13, 14] but failed in phase III clinical trials [15, 16]. Polymerized hemoglobins effective in experimental models [17, 18] were not successful clinically [19–21]. Numerous other approaches to developing hemoglobin-based resuscitative agents [22] have been unsuccessful [23]. Efforts to develop a pharmacological resuscitative agent have met with failure, and much of the research and development interest in this area has diminished.

Advancement has been limited to damage-control resuscitation to restore intravascular volume, prevent dilutional coagulopathy, and preserve tissue oxygenation [24]. An ideal replacement for whole blood is the use of blood products in a balanced ratio of 1:1:1 for units of plasma to platelets to red blood cells [25, 26]. Vasopressors are the only pharmacological agents available for resuscitation [27, 28] and are associated with arrhythmias, fluid extravasation, and ischemia [29, 30]. The current standard of care (SOC) is inadequate and is based on resuscitative agents developed more than 5 decades ago; a need remains for novel resuscitative agents [31].

A substantial amount of blood pooled on the venous side can be returned to the heart and shifted towards the arterial side for better tissue perfusion and oxygenation. Stimulation of α_{2B} adrenergic receptors, located on the smooth muscle cells [32], produced dose-dependent constriction of human veins [33]. Centhaquine is a novel first-in-class resuscitative agent that acts on α_{2B} adrenergic receptors to produce venous constriction and increase venous return to the heart, resulting in increased cardiac output [34, 35]. It also has little action on α_{2A} adrenergic receptors to reduce sympathetic drive and decrease systemic vascular resistance [36], contributing to improved tissue blood perfusion. The mechanism of action of centhaquine makes it an ideal candidate for the treatment of patients with hypovolemic shock. Enhancing tissue blood perfusion is a significant advantage in reducing resuscitation volume and preventing fluid extravasation. Centhaquine has no action on beta-adrenergic receptors, which diminishes the possibility of arrhythmias. The safety and efficacy of centhaquine were evaluated extensively in preclinical models [37–41], healthy volunteers [42], and patients [34]. Centhaquine was safe and effective in a phase II study and significantly improved blood lactate levels, base deficit, and blood pressure [34, 42]. Based on these highly encouraging data, we undertook a phase III study, the results of which are described here.

2 Methods

2.1 Trial Design

This was a prospective, multicenter, randomized, placebo-controlled, double-blinded phase III clinical study of centhaquine in patients with hypovolemic shock receiving the best SOC. Centhaquine was found to be efficacious in a phase II study, with statistically significant improvements in blood lactate levels ($p = 0.0012$), base deficit ($p < 0.0001$), and blood pressure ($p < 0.0001$) and a trend towards reduced mortality [34]. Therefore, in consultation and agreement with regulatory authorities, patients were randomized in a 2:1 ratio either to receive centhaquine 0.01 mg/kg by intravenous infusion along with SOC or to receive SOC plus saline. The study duration for an individual patient was 28 days, including two study visits: visit 1 on day 1 included

screening, randomization, baseline measurements, and treatment, and visit 2 was at the end of the study (day 28 + 7).

2.2 Regulatory Oversight

The study was conducted in compliance with the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP), the Helsinki declaration, and local regulatory requirements. The study protocol (PMZ-2010/CT-3.1/2018) dated July 16, 2018, was approved by the Drugs Controller General of India (DCGI), Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India (DCGI CT NOC. No. CT/ND/66/2018). Furthermore, each institutional ethics committee reviewed and approved the study protocol before initiating patient enrolment. The trial was registered at the Clinical Trials Registry, India (CTRI/2019/01/017196), and the United States National Library of Medicine, ClinicalTrials.gov (NCT04045327). Each site's ethics committee was informed of any protocol deviation, amendment, subject exclusion or withdrawal, and serious adverse events (SAEs) (details of participating sites are provided in Table 1 in the electronic supplementary material [ESM]).

2.3 Patient Population

Patients were screened for study eligibility according to the following inclusion criteria: (1) aged ≥ 18 years, (2) systolic blood pressure (SBP) ≤ 90 mmHg, (3) blood lactate levels ≥ 2 mmol/L, and (4) receiving SOC in a hospital or ICU setting. SOC generally included airway maintenance, fluid resuscitation with crystalloids/colloids, blood products, and vasopressors according to the treatment guidelines in the local hospital setting. Exclusion criteria were as follows: (1) female patients with current pregnancy (patients with postpartum hemorrhage were included); (2) patients participating in other clinical trials; (3) patients with a life-threatening systemic disease, such as terminal stage cancer or AIDS, or needing organ support due to chronic kidney failure, liver failure, or decompensated heart failure.

2.4 Consent

The patients included in this study were in a state of life-threatening shock. For patients who were not fit to give consent themselves at the time of treatment initiation, informed consent was provided by their legally authorized representative (LAR). The investigator informed the patient or a LAR verbally and in writing of the details of the study relevant to a decision about whether to participate in the study. The informed consent form included all the elements required as per the ICH-GCP recommendations and schedule Y. The informed consent forms, in English and regional languages, were approved by the respective ethics committees and the DCGI. The entire consent process was recorded audiovisually, labeled, and stored securely at the study site. Per regulatory requirements, medical confidentiality and data protection were ensured, and the investigator stored the signed informed consent forms.

2.5 Randomization and Blinding

An interactive web response system (IWRS) containing randomization codes was used to randomize eligible patients to the treatment groups. The patient and all relevant personnel involved with the study's conduct and interpretation (including investigator, investigational site personnel, and the sponsor or designee's staff) were blinded to the study drug (centhaquine/normal saline) and the randomization codes. The dispensing activity was carried out by an unblinded pharmacist independent of the monitoring team. The pharmacist signed an undertaking to not disclose the study treatments to the study team. The biostatistician and the unblinded pharmacist were independent of the study team. The final randomization list was held in strict confidence and was accessible only to authorized people until study completion. Treatment unblinding was not necessary for any of the patients enrolled in this study, but emergency unblinding was possible through the IWRS. As per study protocol, the investigator or their designee was permitted to unblind the code if medically needed. The date, time, and reason for any emergency unblinding were to be recorded in that patient's medical record, and any adverse event (AE) or SAE that required unblinding of the treatment was to be recorded and reported as specified in the protocol. Each patient was monitored closely throughout their hospitalization and followed until discharge from randomization. The investigator assessed each patient for safety and efficacy parameters over 28 days from randomization.

2.6 Treatment

At baseline, various demographic data (age, sex, body weight, body mass index), chest X-ray, electrocardiogram (ECG), and vital signs were recorded. Baseline blood tests included hematology, blood lactate, base deficit, serum chemistry, and liver and kidney function tests. The patient's physical examination, medical history, concomitant illness, concomitant medications, initial shock index (SI), quick sequential organ failure assessment (qSOFA), Glasgow Coma Scale (GCS), and acute respiratory distress syndrome (ARDS) were noted. SI, defined as heart rate divided by SBP, has a normal range of 0.5–0.7 in healthy subjects. SI ≥

1.0 has been associated with significantly poorer outcomes [43, 44]. SI in conjunction with qSOFA provide a good prediction of likely outcomes [43, 45–47]. The study drug (centhaquine citrate 1.0 mg in a 10 mL vial) was manufactured by Pharmazz India Private Limited at Gufic Biosciences Limited and was supplied to the investigators at the participating sites. Patients who met the eligibility criteria were randomized 2:1 to the centhaquine group or the control group, respectively. All patients in both groups received the SOC (airway maintenance, fluid resuscitation with crystalloids/colloids, blood products, and/or vasopressors) for hypovolemic shock throughout the study according to local institutional standard practice. Centhaquine or normal saline was administered intravenously after randomization, and all patients continued receiving SOC for hypovolemic shock. Patients in the centhaquine group received centhaquine 0.01 mg/kg body weight as an intravenous infusion over 1 h in 100 mL normal saline. The next dose of centhaquine was administered if SBP fell below or remained below 90 mmHg but not within 4 h of the previous dose, and the total number of doses did not exceed three per day. If needed, centhaquine was continued for 2 days postrandomization. A minimum of one dose and a maximum of six doses of centhaquine were administered within the first 48 h postrandomization. An equal volume of normal saline (100 mL) was administered as an intravenous infusion over 1 h postrandomization in the control group. Specific intravenous treatments and dose selection were based on preclinical proof-of-concept studies conducted in our laboratory [37–41]. The maximum tolerated dose of centhaquine was 0.1 mg/kg, as established in the safety and tolerability phase I study [42].

2.7 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) was convened, and its responsibilities were determined before study initiation. The members included a senior practicing physician with extensive experience in critical care medicine, a biostatistician, and a clinical pharmacologist. The DSMB was independent of the study investigators and the sponsor. The DSMB had access to SAEs and any other AEs that the investigator or the medical monitor considered important. The DSMB reviewed the study data on safety and critical efficacy endpoints at predetermined intervals.

2.8 Safety Evaluation

All patients who received treatment were included in the safety analysis. The study investigator assessed safety during the treatment period and during the follow-up period post-treatment based on AEs, physical examination, vital signs [heart rate, SBP and diastolic blood pressure (DBP), body temperature, and respiratory rate], ECG, and clinical laboratory parameters as per protocol. A variety of biochemical tests, serum chemistry tests, hematological variables, coagulation variables, urine output, and organ function tests such as kidney and liver function tests were assessed. AEs that occurred or worsened during or after treatment were recorded. All AEs were coded by system organ class and preferred term using the latest version of the International Conference on Harmonisation Medical Dictionary for Regulatory Activities. All patients were followed-up for safety assessment to the end of the study on day 28.

2.9 Efficacy Assessments

This study's primary objectives were to determine (1) change in SBP and DBP, (2) change in blood lactate levels, and (3) change in the base deficit. For all these endpoints, changes were mean through 48 h. The study's key secondary objectives included the proportion of patients with 28-day all-cause mortality. The amount of fluids, blood products, and vasopressors administered in the first 48 h; the duration of hospital stay; time in ICU; time on ventilator support; and ARDS and multiple organ dysfunction syndrome (MODS) were recorded. An area under the curve from 0 to 48 h ($AUC_{0–48}$) was calculated for the mean differences in SBP, DBP, and pulse pressure from baseline as an integrated measurement to assess the cumulative effect of resuscitation. ARDS and MODS were determined using established methods [48–50].

2.10 Sample Size and Statistical Analysis

The sample size was calculated according to the results of our phase II trial (CTRI/2017/03/008184, NCT04056065) [34]. In the phase II study, SBP in the centhaquine group improved from 87.3 mmHg at baseline to 121.4 mmHg (39.5% increase) at 48 h of resuscitation, whereas, in the control group, SBP improved from 90.4 mmHg at baseline to 108.8 mmHg (25.4% increase) at 48 h of resuscitation. The statistical power of the phase II study was 80%. Centhaquine proved efficacious in a phase II study, with statistically significant improvements in blood lactate levels ($p = 0.0012$), base deficit ($p < 0.0001$), and blood pressure ($p < 0.0001$), and a trend towards reduced mortality. Therefore, in consultation and agreement with regulatory authorities, patients were randomized in a 2:1 ratio to the centhaquine group (SOC + centhaquine) or to the control group (SOC + saline) in the phase III study. Given that variable hospital practices resulted in some differences in the SOC, the power was set to 80% to minimize variability, the enrolment ratio was 2:1, and the significance level (alpha) used was 0.05. To achieve this, we estimated that a sample size of 69 patients (46 in the centhaquine group and 23 in the control group) was enough to achieve

a power of 80% when the level of significance alpha was 0.05. We increased the study power to 90% with the alpha at 0.05 because of the complex etiology of hypovolemic shock and the effort required to conduct this trial in the critical care setting with a novel investigational agent. We needed approximately 84 patients (56 in the centhaquine group and 28 in the control group) to keep the power of the study at > 90%, alpha, 0.05. Considering a discontinuation rate of 20%, we planned enrolment of 105 patients (70 in the centhaquine group and 35 in the control group) in this study. The results of the trial are presented as mean ± standard error of the mean (SEM). The unpaired *t* test (two-tailed) with Welch's correction was used to analyze two sets of data with unequal variances to compare the continuous and discrete variables at baseline and follow-ups. Parametric analysis was carried out using one-way analysis of variance without assuming equal variances with normal probabilistic distribution, and Tukey's multiple comparisons test estimated the significance of differences. Group comparison was carried out using a Chi-squared test. The Baptista–Pike method was used to calculate odds ratios (ORs). *p* values < 0.05 were considered significant at the 95% confidence level and < 0.10 at the 90% confidence level. Demographic variables and patient characteristics were summarized descriptively by treatment assignments. Demographic variables include age, sex, weight, and body mass index. Variables measured on a continuous scale, such as the patient's age at the time of enrolment, the number of nonmissing observations (*n*), mean, and SEM, were tabulated by treatment assignments. All available data were used in the analyses. Each group was summarized individually. Data not available were assessed as "missing values", and the observed population only were evaluated. The statistical analysis was processed with GraphPad Prism 9.0.2 (GraphPad, San Diego, CA, USA).

3 Results

3.1 Patient Enrolment and Demographics

This study was conducted in 14 emergency rooms/ICUs across India (Table 1 in the ESM). All the centers had emergency medical facilities and uniform SOC for the management of patients in hypovolemic shock. Patients in hypovolemic shock due to blood loss or fluid loss resulting in a drop in SBP ≤ 90 mmHg and an increase in lactate level ≥ 2 mmol/L were included. All patients continued to receive standard shock treatment. A total of 197 patients were assessed, and 105 patients met the eligibility criteria and were enrolled in the study: 71 to the centhaquine group and 34 to the control group. In the centhaquine group, one patient withdrew consent and two were excluded by the investigator (one patient each was diagnosed with fulminant tuberculosis and refractory septic shock). In total, 34 patients (22 male and 12 female) in the control group and 68 patients (41 male and 27 female) in the centhaquine group completed the study (Fig. 1). The average age of patients was 36.5 years in the control group and 42.8 years in the centhaquine group (Table 1). The difference in age (6.3 ± 3.6) between the two groups indicated that the average age was higher in the centhaquine group than in the control group.

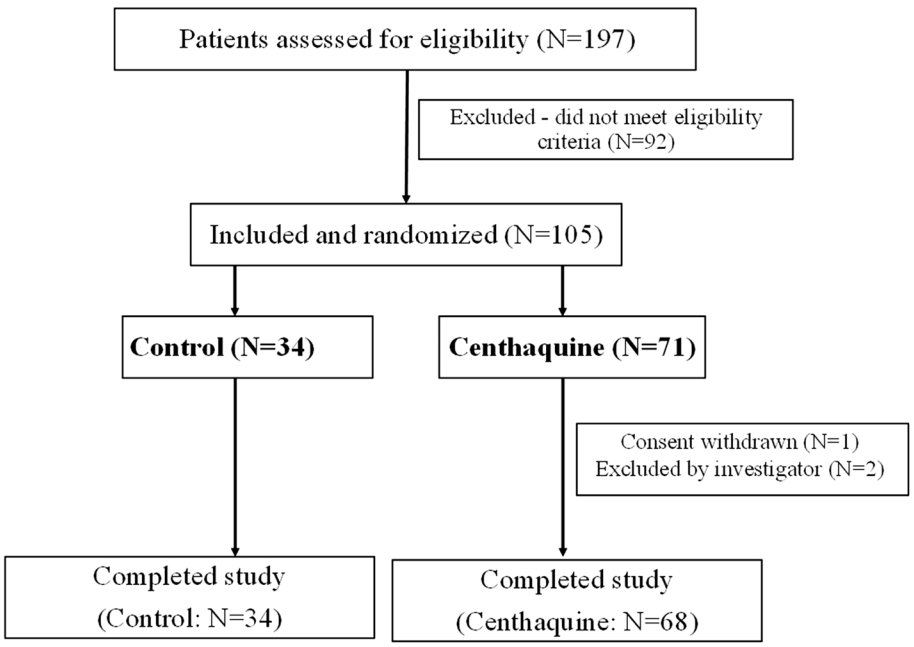


Fig. 1 Patient enrolment, randomization, and trial completion

Table 1 Baseline characteristics of patients

Characteristics	Control ($N=34$)	Centhaquine ($N=68$)
Age (years)	36.50 ± 2.81	42.81 ± 2.31
Body weight (kg)	56.74 ± 1.62	58.90 ± 1.37
Body mass index (kg/m^2)	21.56 ± 0.59	22.72 ± 0.51
Sex		
Men	22 (64.71)	41 (60.29)
Women	12 (35.29)	27 (39.71)
Medical history		
Hypertension	3 (8.82)	1 (1.47)
Diabetes	4 (11.76)	3 (4.41)
Renal disorders	1 (2.94)	3 (4.41)
Respiratory disease	1 (2.94)	2 (2.94)
Ischemic heart disease	–	1 (1.47)
Liver fibrosis	1 (2.94)	–
Hepatitis	1 (2.94)	–
Preeclampsia	–	1 (2.94)
Reason for hypovolemic shock		
Trauma	10 (29.41)	32 (47.06)
Postsurgery	5 (14.71)	3 (4.41)
Postpartum hemorrhage	2 (5.88)	6 (8.82)
Vaginal bleeding	2 (5.88)	7 (10.29)
Gastroenteritis	15 (44.12)	20 (29.41)
Clinical factors		
Systolic blood pressure (mmHg)	83.62 ± 1.48	83.52 ± 1.13
Diastolic blood pressure (mmHg)	53.00 ± 1.47	55.82 ± 1.21
Heart rate (beats/min)	115.15 ± 3.32	107.76 ± 2.61
Shock index	1.39 ± 0.05	1.32 ± 0.05
qSOFA	1.82 ± 0.12	1.91 ± 0.08
Respiratory rate (breaths/min)	24.88 ± 1.32	24.00 ± 0.86
Body temperature (°C)	36.76 ± 0.07	36.80 ± 0.06
Blood lactate (mmol/L)	4.13 ± 0.40	4.50 ± 0.29
Base deficit (mmol/L)	−7.36 ± 1.07	−7.58 ± 0.56
Hemoglobin (g/dL)	10.41 ± 0.47	9.64 ± 0.35
Hematocrit (%)	31.90 ± 1.56	29.48 ± 1.09
Creatinine (mg/dL)	1.28 ± 0.13	1.22 ± 0.08
Glomerular filtration rate (mL/min/1.73 m^2)	78.84 ± 5.42	77.41 ± 4.30
Glasgow Coma Scale	14.29 ± 0.31	13.40 ± 0.42
Acute respiratory distress syndrome	0.15 ± 0.05	0.18 ± 0.04
pH	7.32 ± 0.02	7.34 ± 0.01
pCO_2 (mmHg)	33.65 ± 1.36	31.98 ± 0.90
paO_2 (mmHg)	117.04 ± 9.39	113.48 ± 5.62

Data are presented as n (%) or mean ± standard error of the mean

paO_2 partial pressure of oxygen, *pCO_2* partial pressure of carbon dioxide, *pH* power of hydrogen, *qSOFA* quick sequential organ failure assessment

3.2 Patient Assessment at the Time of Inclusion

The history of hypertension, diabetes, renal and hepatic disorders, and other medical conditions was similar in both groups (Table 1). However, trauma was the predominant cause of hypovolemic shock in 47.1% of those in the centhaquine group but 29.4% of those in the control group ($p=0.08$). On the other hand, gastroenteritis was the leading cause of hypovolemic shock for 44.1% of those in the control group and 29.4% of those in the centhaquine group

($p = 0.14$). Other reasons for hypovolemic shock, such as postsurgical blood loss, postpartum hemorrhage, and vaginal bleeding, did not differ between the groups. The percentage of patients needing surgical intervention during hospitalization was 26.47% in the control group and 33.82% in the centhaquine group ($p = 0.45$). The baseline clinical parameters blood pressure, heart rate, respiratory rate, base deficit, and body temperature were similar in both groups (Table 1). Blood lactate level was 4.1 ± 0.4 mmol/L in the control group and 4.5 ± 0.2 mmol/L in the centhaquine group. Hemoglobin level was slightly lower in the centhaquine group (9.6 ± 0.3 g/dL) than in the control group (10.4 ± 0.4 g/dL); similarly, hematocrit was a little lower in the centhaquine group (29.5 ± 1.1%) than in the control group (31.9 ± 1.6%) (Table 1). The difference between the mean hemoglobin (− 0.76 ± 0.59) and hematocrit levels (− 2.41 ± 1.89) between the groups suggested that blood loss was slightly higher in the centhaquine group than in the control group. SI and qSOFA at baseline were similar in the two groups: The SI was 1.39 ± 0.05 in the control group and 1.32 ± 0.05 in the centhaquine group ($p = 0.292$), and the qSOFA score was 1.82 ± 0.12 in the control group and 1.91 ± 0.08 in the centhaquine group ($p = 0.541$). Creatinine levels and glomerular filtration rates were similar in the two groups. GCS at baseline was 14.29 ± 0.31 in the control group and 13.40 ± 0.42 in the centhaquine group. ARDS at baseline was similar between the two groups. The total volume of fluids (crystalloids, colloids) administered before randomization was comparable between the groups. The total blood and blood products administered before randomization was 0.05 ± 0.04 L in the control group and 0.12 ± 0.04 L in the centhaquine group. The amount of vasopressors administered before randomization was similar in both groups (Table 2). Tables 2 and 3 in the ESM provide details on the cause of hypovolemic shock for individual patients in the control and centhaquine groups, respectively.

3.3 Total Fluids, Blood and Blood Products, and Vasopressors

After randomization, the number of doses of study drug administered averaged 1.47 ± 0.19 per patient in the control group and 1.27 ± 0.03 per patient in the centhaquine group ($p = 0.36$) during 48 h of resuscitation (Table 2). Following randomization, the total amount of fluids administered in 48 h was 4.61 ± 0.30 L in the centhaquine group and 4.65 ± 0.37 L in the control group (Fig. 2 and Table 2). The amount of blood and blood products infused during the first 24 and 48 h was similar in both groups (Table 2 and Fig. 2). A total cumulative dose of vasopressors administered in 48 h in the control group (4.40 ± 2.41 mg) appeared to be higher than in the centhaquine group (2.76 ± 1.28 mg); this

Table 2 Standard treatment administered to patients before randomization and during the first 24 and 48 h of resuscitation

Group	Fluids (L)			Blood products (L)					Vasopressors (mg)
	Crystalloids	Colloids	Total volume	Blood	Packed RBC	FFP	Platelets	Cryoprecipitate	Total volume	Total dose
Predose (before randomization)										
Control	0.76 ± 0.15	0.044 ± 0.02	0.81 ± 0.17	–	0.033 ± 0.02	0.021 ± 0.021	–	–	0.051 ± 0.04	0.23 ± −0.12
Centhaquine	0.75 ± 0.09	0.057 ± 0.02	0.80 ± 0.11	0.031 ± 0.021	0.072 ± 0.02	0.008 ± 0.008	–	0.011 ± 0.011	0.120 ± 0.04	0.37 ± 0.17
Postdose (first 24 h of resuscitation)										
Control	2.86 ± 0.27	0.079 ± 0.04	2.94 ± 0.31	0.061 ± 0.033	0.113 ± 0.04	0.079 ± 0.056	–	–	0.254 ± 0.09	3.83 ± 2.31
Centhaquine	2.77 ± 0.20	0.032 ± 0.02	2.79 ± 0.23	0.005 ± 0.005	0.181 ± 0.04	0.054 ± 0.027	0.0093 ± 0.006	–	0.249 ± 0.07	2.26 ± 1.20
Postdose (first 48 h of resuscitation)										
Control	4.58 ± 0.37	0.079 ± 0.04	4.65 ± 0.37	0.074 ± 0.043	0.162 ± 0.05	0.136 ± 0.078	0.010 ± 0.010	–	0.382 ± 0.14	4.40 ± 2.41
Centhaquine	4.57 ± 0.29	0.038 ± 0.02	4.61 ± 0.30	0.005 ± 0.005	0.259 ± 0.05	0.054 ± 0.027	0.0093 ± 0.006	–	0.328 ± 0.08	2.76 ± 1.28

The fluids administered to the patients were crystalloids (normal saline, dextrose, sodium bicarbonate, PlasmaLyte, and lactated ringer) and colloids (albumin, Haemaccel, and Gelofusine). The vasopressors used were adrenaline (epinephrine), noradrenaline (norepinephrine), and vasopressin

FFP fresh frozen plasma, *RBC* red blood cells

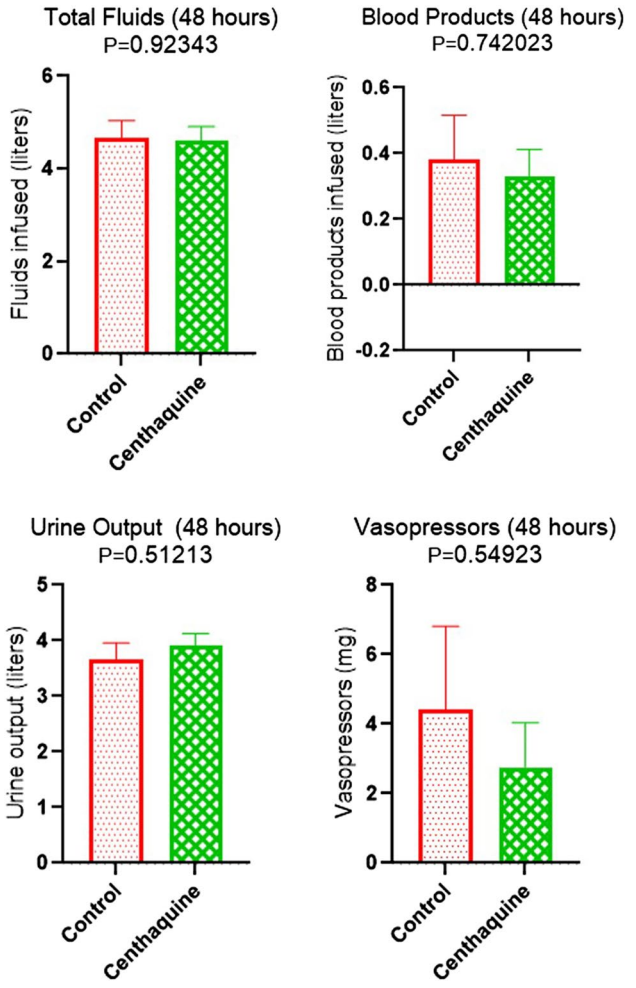


Fig. 2 Total volume of fluid, blood products, and vasopressors administered during the first 48 h in the control and centhaquine groups. Total urine output in the first 48 h in the control and centhaquine groups. Data are presented as mean ± standard error

difference was not statistically significant ($p = 0.55$; Fig. 2 and Table 2). Table 2 shows the types of vasopressors used, although mostly norepinephrine was used. During the first 48 h of resuscitation, urine output was similar in both groups (Fig. 2). Table 4 in the ESM details the pharmacological treatment provided to patients in the control and centhaquine groups, with both groups receiving comparatively similar pharmacological agents.

3.4 Time in Hospital, in the Intensive Care Unit, and on the Ventilator

The duration of hospital stay was 6.9 ± 1.4 and 8.7 ± 1.2 days for the control and centhaquine groups, respectively. Patients in the centhaquine group stayed in the hospital for 1.7 ± 1.8 days longer than the patients in the control group. Duration of stay in the ICU was 2.2 ± 0.4 days and 2.9 ± 0.7 days for the control and centhaquine groups, respectively. Patients in the centhaquine group stayed 0.7 ± 0.8 ($p = 0.38$) days longer in the ICU than those in the control group. Although hospital stays for patients in the centhaquine group were longer than for those in the control group, the duration of time in the ICU was no longer than that for the control group. The percentage of time patients spent in the ICU was similar: 46.6 ± 7.9% in the control group and 46.0 ± 5.7% in the centhaquine group ($p = 0.95$). Time on the ventilator was 0.08 ± 0.05 days in the control group and 0.86 ± 0.5 days in the centhaquine group.

3.5 Systemic Hemodynamics

In the initial hours of resuscitation, SBP increased more significantly in the centhaquine group than in the control group (Fig. 3). The mean difference in SBP from baseline was 3.6 mmHg ($p = 0.95$) in the control group and 5.6 mmHg ($p = 0.02$) in the centhaquine group at 15 minutes of resuscitation and 6.3 mmHg ($p = 0.09$) and 8.6 mmHg ($p < 0.0001$), respectively, at 30 minutes of resuscitation. The increase in SBP from baseline was greater in the centhaquine group than in the control group at 1, 12, 24, and 48 h of resuscitation. The mean difference in SBP from baseline was 11.0 mmHg in the control group and 15.2 mmHg in the centhaquine group at 1 h of resuscitation, 23.9 and 26.4 mmHg, respectively, at 12 h, and 27.6 and 32.0 mmHg, respectively, at 24 h. The SBP at 48 h after resuscitation was 116.6 ± 1.6 and 119.8 ± 1.8 mmHg in the control and centhaquine groups, respectively (Fig. 3 and Table 3). The number of patients with SBP > 90 mmHg at 12 h of resuscitation was higher in the centhaquine (96.9%) group than in the control (87.5%) group. At 24 h of resuscitation, the number of patients with SBP ≥ 110 mmHg was significantly higher in the centhaquine (79.7%) group than in the control group (60.6%; Chi-squared test, OR 2.55; 95% confidence interval [CI] 1.03–6.39; $p = 0.04$). An SBP ≥ 120 mmHg at 48 h of resuscitation was recorded for 46.9 and 56.2% of patients in the control and centhaquine groups, respectively (Fig. 3).

The increase in DBP was similar in both groups (Fig. 4). The mean difference in DBP from baseline was 4.6 mmHg in the control group and 3.9 mmHg in the centhaquine group at 15 minutes and 5.6 and 5.7 mmHg, respectively, at 30 minutes. The increase in DBP from baseline was similar in both groups at 1, 12, 24, and 48 h of resuscitation. The mean difference in DBP from baseline was 8.8 and 7.8 mmHg in the control and centhaquine groups, respectively, at 1 h of resuscitation, 15.6 and 15.1 mmHg, respectively, at 12 h, 16.7 and 16.5 mmHg, respectively, at 24 h, and 74.6 ± 1.3 and 76.5 ± 0.9 mmHg, respectively, at 48 h (Fig. 4). The percentage of patients with DBP > 65 mmHg at 12 h of resuscitation was 72.3% in the centhaquine group and

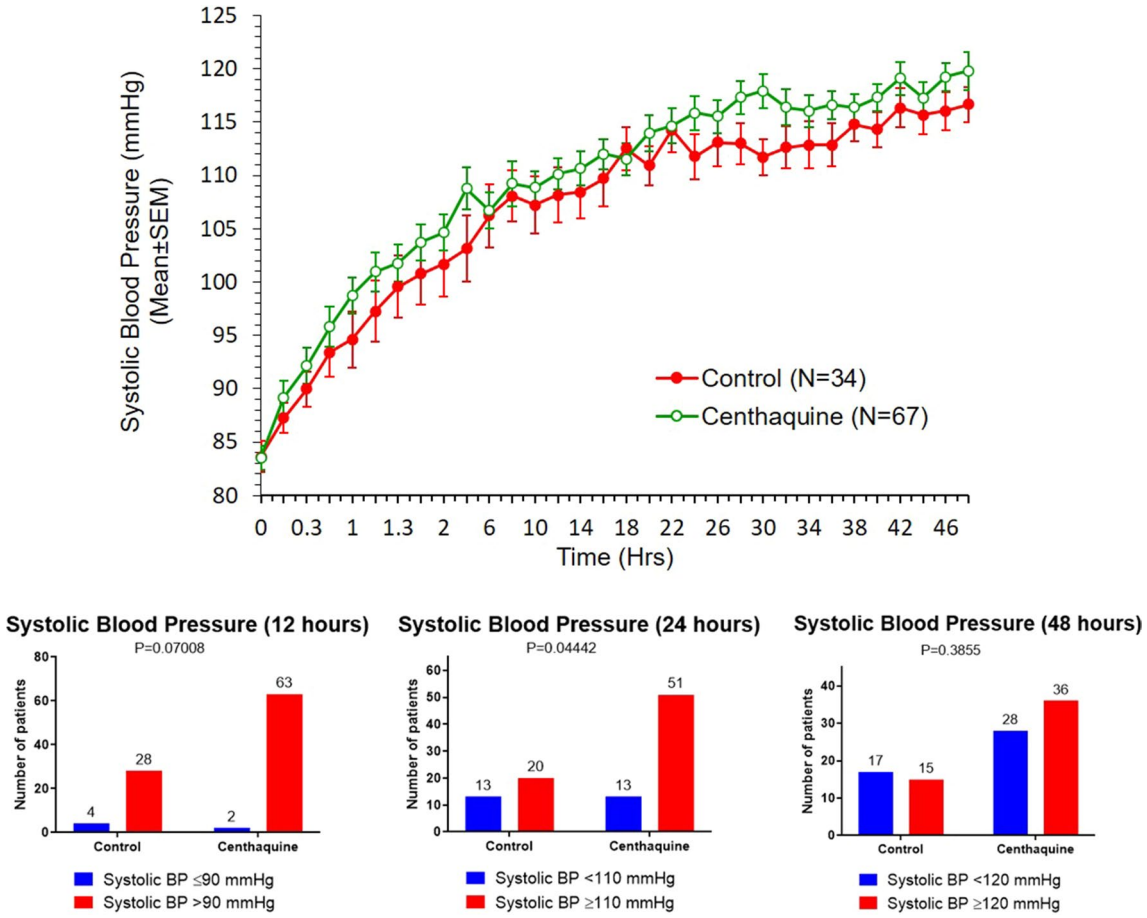


Fig. 3 Systolic BP during the first 48 h in the control and centhaquine groups. The upper panel shows data as the mean ± SEM. The lower panel indicates the number of patients with improved systolic BP at 12, 24, and 48 h of resuscitation. *BP* blood pressure, *SEM* standard error of the mean

60.6% in the control group. At 24 h of resuscitation, the percentage of patients with DBP ≥ 70 mmHg was significantly higher in the centhaquine (76.6%) group than in the control (51.5%) group (Chi-squared test, OR 3.07; 95% CI 1.21–7.27; $p=0.01$). A DBP ≥ 80 mmHg at 48 h of resuscitation was recorded in 31.2 and 50.0% of patients in the control and centhaquine groups, respectively (Fig. 4).

Pulse pressure in the initial hours of resuscitation was more significantly increased with centhaquine than in the control group. The mean difference in pulse pressure from baseline was −0.7 and 1.9 mmHg in the control and centhaquine groups, respectively, at 15 minutes of resuscitation, 0.8 and 2.9 mmHg, respectively, at 30 minutes, 2.6 mmHg ($p=0.98$) and 5.8 mmHg ($p=0.001$), respectively, at 45 minutes, 2.2 mmHg ($p=0.99$) and 7.5 mmHg ($p<0.0001$), respectively, at 60 minutes, and 5.5 mmHg ($p=0.07$) and 8.6 mmHg ($p<0.0001$), respectively, at 90 min. An increase in pulse pressure from a baseline of 30.6 ± 1.2 to 42.1 ± 1.1 mmHg (an increase of 11.0 mmHg) at 48 h of resuscitation was observed in the control group, whereas it increased from a baseline of 28.4 ± 1.0 to 43.3 ± 1.4 mmHg (increase of 14.7 mmHg) in the centhaquine group.

The $AUC_{0–48}$ of the mean difference in SBP, DBP, and pulse pressure from baseline to various time intervals from baseline to 48 h was determined (Fig. 5). The $AUC_{0–48}$ for SBP was 709.6 in the control group and 801.8 in the centhaquine group, indicating a 12.9% increase for centhaquine over that in the control group. The $AUC_{0–48}$ for DBP was 464.9 in the control group and 430.3 in the centhaquine group, indicating a decrease of 7.4% for centhaquine over the control group. The $AUC_{0–48}$ for pulse pressure was 245.1 in the control group and 363.1 in the centhaquine group, an increase of 48.1% for centhaquine over the control group (Fig. 5).

A decrease in heart rate was observed in both groups. Heart rate decreased from a baseline of 114.6 ± 3.1 to 88.4 ± 3.9 beats/minute on day 2 of resuscitation in the control group and from a baseline of 106.5 ± 2.3 to 83.1 ± 1.8 beats/

Table 3 Patients' vitals recorded from day 1 (baseline) through day 28

Vitals	Group	Baseline	After administration of study drug						
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 28
SBP (mmHg)	Control	83.18 ± 1.36	111.31 ± 2.43	115.10 ± 1.67	117.95 ± 2.75	119.33 ± 2.75	120.75 ± 3.12	123.20 ± 4.41	117.04 ± 1.48
	Centhaquine	83.42 ± 1.14	115.69 ± 1.58	119.02 ± 1.41	121.10 ± 1.52	121.56 ± 2.19	123.04 ± 1.80	122.50 ± 1.82	119.98 ± 1.27
DBP (mmHg)	Control	52.76 ± 1.43	70.69 ± 1.93	74.10 ± 1.80	79.15 ± 1.92	79.56 ± 1.76	77.69 ± 2.04	82.07 ± 2.87	77.31 ± 0.97
	Centhaquine	55.76 ± 1.16	72.59 ± 1.17	74.24 ± 1.06	76.00 ± 1.27	79.15 ± 1.71	79.96 ± 1.49	79.73 ± 1.21	77.84 ± 0.90
Heart rate (beats/min)	Control	114.58 ± 3.17	88.38 ± 3.99	84.68 ± 3.41	89.20 ± 2.63	86.84 ± 6.96	82.82 ± 6.97	83.75 ± 6.98	79.65 ± 2.14
	Centhaquine	106.48 ± 2.34	83.08 ± 1.79	83.24 ± 1.72	85.44 ± 2.13	85.35 ± 2.07	84.48 ± 1.93	83.69 ± 1.78	80.21 ± 1.42
Respiratory rate (breaths/min)	Control	24.91 ± 1.27	20.59 ± 0.88	20.65 ± 1.15	20.90 ± 0.92	20.22 ± 0.62	20.44 ± 0.86	19.53 ± 0.70	19.65 ± 0.53
	Centhaquine	23.76 ± 0.84	19.94 ± 0.47	19.03 ± 0.32	20.74 ± 0.41	20.03 ± 0.60	20.41 ± 0.53	20.04 ± 0.41	19.14 ± 0.34
Body temperature (ºC)	Control	36.70 ± 0.06	36.82 ± 0.04	36.85 ± 0.05	37.00 ± 0.11	36.92 ± 0.04	36.94 ± 0.04	36.84 ± 0.06	36.72 ± 0.04
	Centhaquine	36.73 ± 0.06	36.81 ± 0.03	37.80 ± 0.98	36.90 ± 0.04	36.85 ± 0.06	36.85 ± 0.04	36.84 ± 0.06	36.74 ± 0.03

Data are presented as mean ± standard error of the mean

DBP diastolic blood pressure, *SBP* Systolic blood pressure

min in the centhaquine group (Table 3). SBP, DBP, heart rate, respiratory rate, and body temperature records up to 28 days are provided in Table 3.

3.6 Shock Index

The mean SI at the time of inclusion (0 h) was 1.39 and 1.32 in the control and centhaquine groups, respectively ($p=0.29$), indicating that the degree of shock was moderate to severe and similar in both groups. At 1 h of resuscitation, the mean SI decreased to 1.17 and 1.02 in the control and centhaquine groups, respectively, significantly lower in the centhaquine group (difference between means 0.15 ± 0.07; 95% CI − 0.29 to − 0.01; $p=0.03$). The mean SI was significantly lower in the centhaquine group at 4 h of resuscitation (difference between means 0.14 ± 0.07; 95% CI − 0.27 to − 0.0003; $p=0.049$). The SI significantly improved in the centhaquine group in the first 4 h of resuscitation (Fig. 6).

3.7 Blood Lactate Levels

Blood lactate levels in patients with hypovolemic shock were high on day 1, ranging from 2.04 to 11.0 mmol/L (mean ± SEM 4.44 ± 0.29) in the centhaquine group and from 2.04 to 14.1 mmol/L (mean ± SEM 4.14 ± 0.42) in the control group. Treatment with centhaquine decreased blood lactate levels, as evidenced by blood lactate levels on day 3 that ranged from 0.6 to 4.82 mmol/L (mean ± SEM 1.43 ± 0.09). Except for one (of 68 patients), every patient treated with centhaquine had lower blood lactate levels on day 3 than on day 1. In that one patient, blood lactate levels were 2.69 and 4.82 mmol/L on day 1 and day 3, respectively. In the centhaquine group, this patient was the only outlier, with no decrease in blood lactate levels. In the control group, blood lactate levels on day 3 ranged from 0.32 to 7.52 mmol/L (mean ± SEM 1.91 ± 0.26). In this group, two (of 34) patients had higher blood lactate levels on day 3 than on day 1. One patient had blood lactate levels of 4.80 and 5.30 mmol/L on days 1 and 3, respectively, and the other patient had blood lactate levels of 2.12 and 2.48 mmol/L on days 1 and 3, respectively. The percentage of patients with blood lactate levels ≤ 1.5 mmol was 46.9% in the control group and 69.3% in the centhaquine group (OR 2.56; 95% CI 1.04–5.87; $p=0.03$) (Fig. 7).

3.8 Base Deficit

The base deficit on day 1 ranged from 0.10 to − 29.4 mmol/L (mean ± SEM − 7.36 ± 1.07) and from − 1.60 to − 21.8 mmol/L (mean ± SEM − 7.58 ± 0.56) in the control and centhaquine groups, respectively. An improvement in the base deficit was observed on day 3 of resuscitation, and only four of 68 patients (5.9%) treated with centhaquine had a lower base deficit on day 3 than on day 1, whereas, in the control group, seven of 34 patients (20.6%) had a lower base deficit on day 3 than on day 1. The mean ± SEM base deficit on day 3 was − 1.84 ± 0.50 mmol/L and − 3.3 ± 0.9 mmol/L

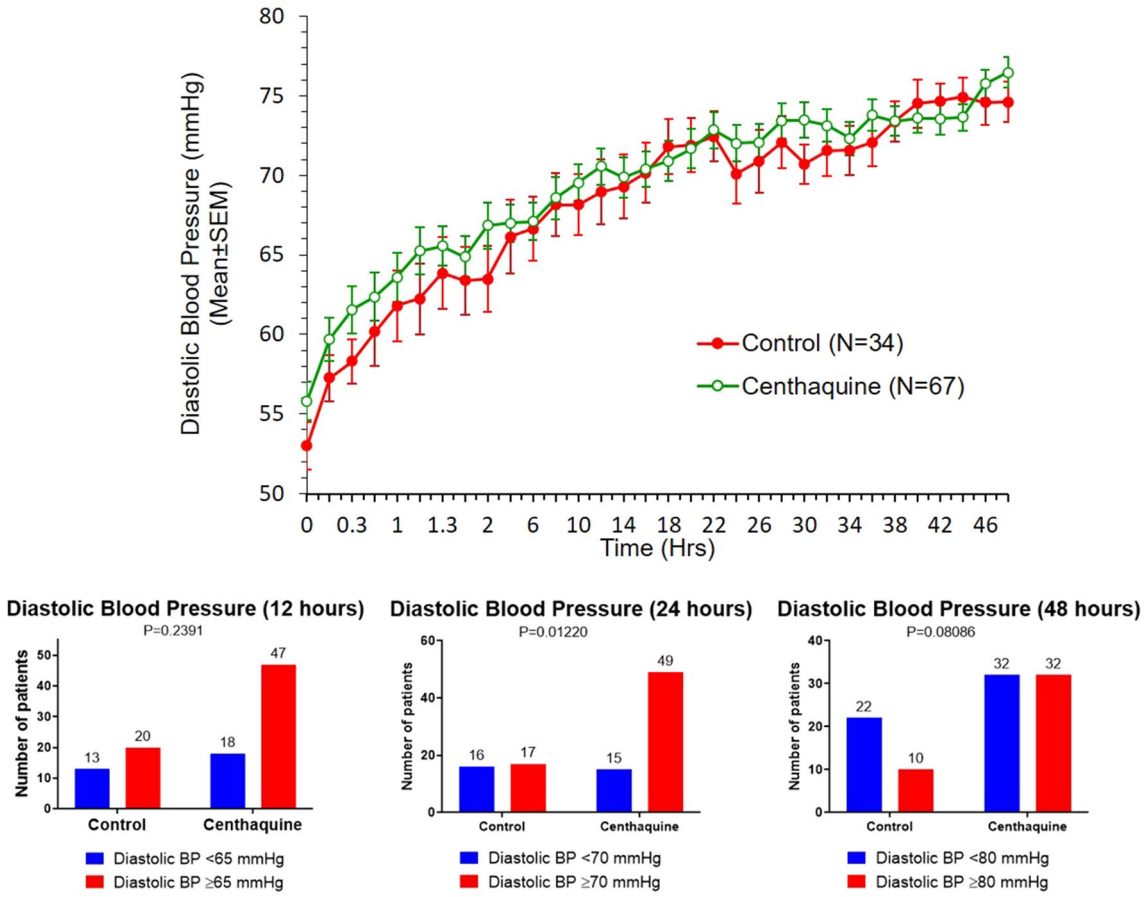


Fig. 4 Diastolic BP during the first 48 h in the control and centhaquine groups. The upper panel shows data as the mean ± SEM. The lower panel indicates the number of patients with improved diastolic BP at 12, 24, and 48 h of resuscitation. *BP* blood pressure, *SEM* standard error of the mean

in the centhaquine and control groups, respectively. On day 3 of resuscitation, the base deficit improved by 1.49 ± 1.04 mmol/L more in patients treated with centhaquine than in those in the control group. On day 3 of resuscitation, the number of patients with a base deficit of less than − 2 was 43.7% in the control group and 69.8% in the centhaquine group (OR 2.98; 95% CI 1.22–6.91; $p = 0.014$) (Fig. 8).

3.9 Acute Respiratory Distress Syndrome and Multiple Organ Dysfunction Syndrome

ARDS was compared between day 1 (before resuscitation) and day 3 of resuscitation. In patients receiving the SOC in the control group, the difference between means from day 1 to day 3 was − 0.06 ± 0.05 (95% CI − 0.16 to − 0.04; $p = 0.22$). Conversely, in the centhaquine group, the ARDS difference between means from day 1 to day 3 was − 0.09 ± 0.05 (95% CI − 0.19 to − 0.002; $p = 0.04$). These results indicate that centhaquine treatment significantly improved ARDS following resuscitation, whereas the improvement in the control group was minor (Fig. 9 and Table 4).

MODS was compared between day 3 and day 7 of resuscitation. There was no improvement in MODS in the control group, and the difference between means was 0.59 ± 0.9 (95% CI − 1.43 to 2.61; $p = 0.54$), whereas, in the centhaquine group, the difference between means was − 0.55 ± 0.3 (95% CI − 1.23 to 0.13; $p = 0.11$). The change trended towards worsening in the control group (MODS from 1.14 to 1.73) and towards improvement in the centhaquine group (MODS from 1.37 to 0.82). Centhaquine treatment decreased MODS, whereas MODS increased and worsened in the control group (Fig. 9 and Table 4). The percentage of patients with two or more MODS scores on day 7 was significantly lower in the centhaquine group (13.6%) than in the control group (45.4%) (OR 5.28; 95% CI 0.85–23.32; $p = 0.04$).

3.10 All-Cause Mortality

Within 48 h of resuscitation, mortality was 1/34 in the control group and 1/68 in the centhaquine group. In the control arm, 28-day all-cause mortality was 11.8% compared with

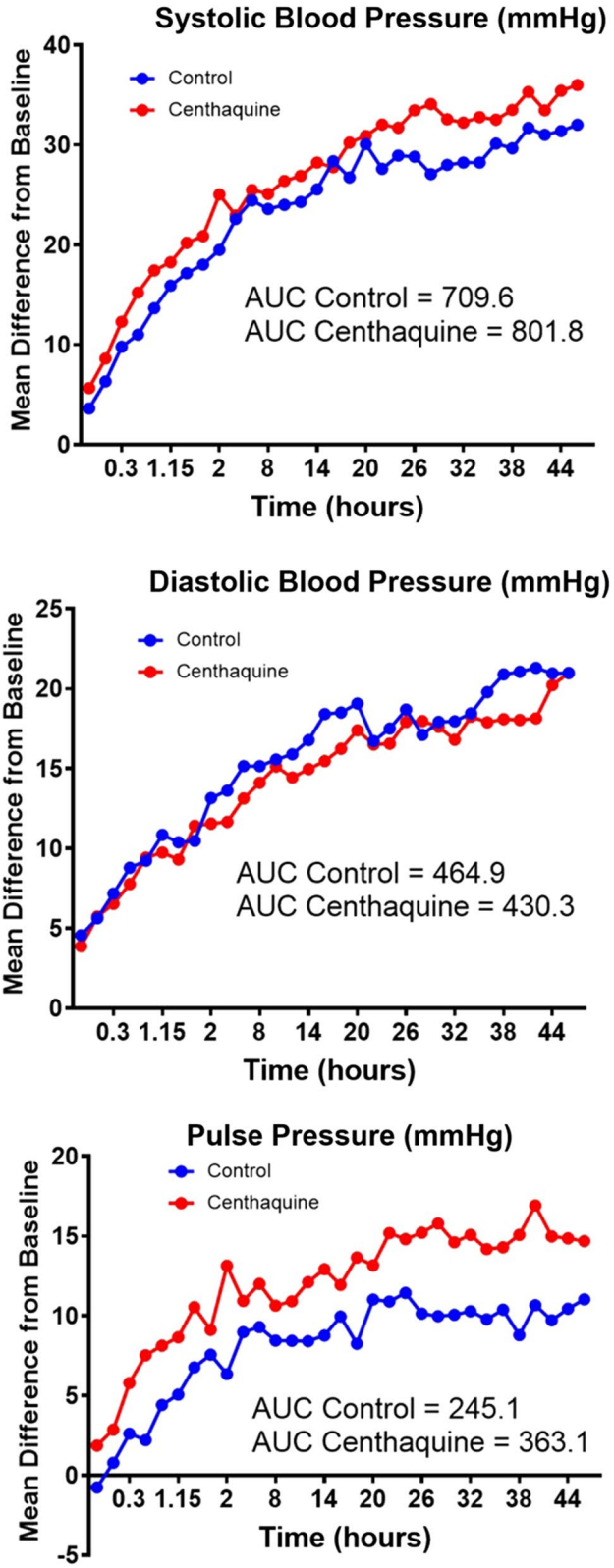


Fig. 5 Mean difference from baseline to 48 h at various time intervals plotted to determine the AUC for systolic blood pressure, diastolic blood pressure, and pulse pressure. Compared with the control group, the AUC_{0-48} for systolic blood pressure was higher by 12.99%, diastolic blood pressure was lower by 7.44%, and pulse pressure was higher by 48.14% in the centhaquine group. A significant increase in pulse pressure in the centhaquine group strongly suggests increased stroke volume. *AUC* area under the curve

2.9% in the centhaquine arm (OR 4.40; 95% CI 0.96–23.74; $p = 0.07$), with an 8.8% absolute reduction in 28-day all-cause mortality.

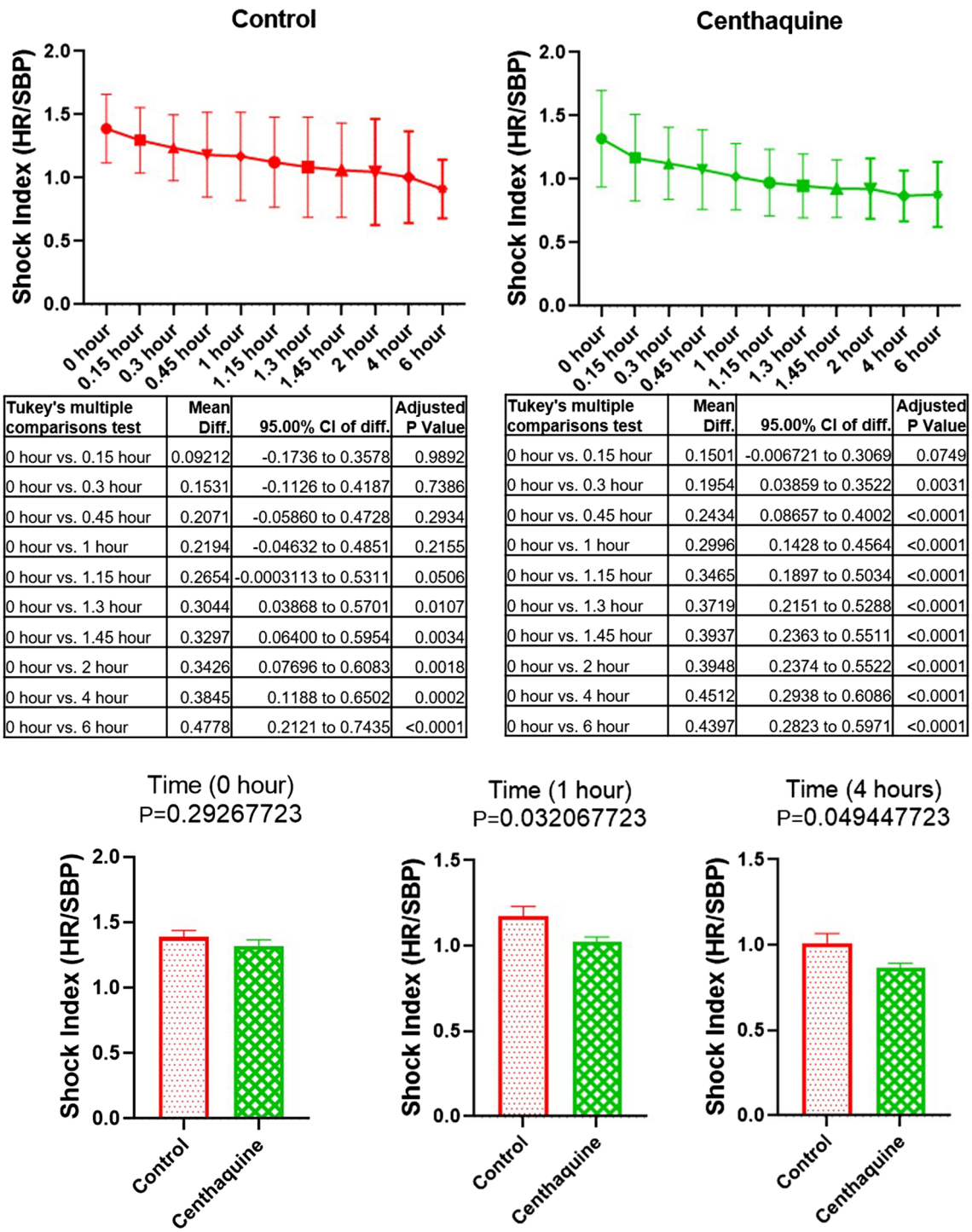
3.11 Safety and Tolerability

Centhaquine was well-tolerated, and a repeat dose, if needed, was administered to patients without any sequelae. No clinically significant effect of the study drug was observed on biochemical or hematological parameters (Table 5). Nine AEs were reported in nine of 105 patients included in the study. Four deaths were reported in the control group ($N = 34$). Five AEs were reported in five patients in the centhaquine group ($N = 71$): two were deaths, two were elevated serum creatinine levels (moderate severity), and one was vomiting (mild severity). These latter three AEs resolved with medical intervention without any sequelae. None of these AEs were related to the drug treatment (Table 6).

4 Discussion

Efforts to develop an effective resuscitative agent have not been successful. Although the use of blood products in ratios that epitomize blood transfusion has been observed to improve outcomes [24, 51], fluids and vasopressors are the main elements of resuscitation, and they have undesired effects [2, 29, 30]. The results from this randomized multicenter trial suggest that centhaquine is an effective resuscitative agent for hypovolemic shock. Its resuscitative action is based upon stimulation of venous α_{2B} adrenergic receptors to produce constriction and increase venous return to the heart, cardiac preload, cardiac output, and tissue perfusion [34, 37, 42]. It has no beta-adrenergic activity, mitigating the risk of arrhythmias.

In this trial, the reasons for hypovolemic shock and the extent of blood loss were similar in the control and centhaquine groups. Blood pressure and lactate levels at the time of enrolment were similar in both groups. The severity of shock was also similar in the two groups, with a qSOFA $\geq$ 2 (associated with a greater risk of worse outcome) of 67.6% in the control group and 73.1% in the centhaquine group. Baseline GCS scores were similar in both groups, indicating a similar neurological status between the two groups. In India and neighboring countries, the SOC for critically ill patients involves fluid therapy, keeping in mind cumulative fluid balance, blood products, airway maintenance,



Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Adjusted P Value
0 hour vs. 0.15 hour	0.09212	-0.1736 to 0.3578	0.9892
0 hour vs. 0.3 hour	0.1531	-0.1126 to 0.4187	0.7386
0 hour vs. 0.45 hour	0.2071	-0.05860 to 0.4728	0.2934
0 hour vs. 1 hour	0.2194	-0.04632 to 0.4851	0.2155
0 hour vs. 1.15 hour	0.2654	-0.0003113 to 0.5311	0.0506
0 hour vs. 1.3 hour	0.3044	0.03868 to 0.5701	0.0107
0 hour vs. 1.45 hour	0.3297	0.06400 to 0.5954	0.0034
0 hour vs. 2 hour	0.3426	0.07696 to 0.6083	0.0018
0 hour vs. 4 hour	0.3845	0.1188 to 0.6502	0.0002
0 hour vs. 6 hour	0.4778	0.2121 to 0.7435	<0.0001

Tukey's multiple comparisons test	Mean Diff.	95.00% CI of diff.	Adjusted P Value
0 hour vs. 0.15 hour	0.1501	-0.006721 to 0.3069	0.0749
0 hour vs. 0.3 hour	0.1954	0.03859 to 0.3522	0.0031
0 hour vs. 0.45 hour	0.2434	0.08657 to 0.4002	<0.0001
0 hour vs. 1 hour	0.2996	0.1428 to 0.4564	<0.0001
0 hour vs. 1.15 hour	0.3465	0.1897 to 0.5034	<0.0001
0 hour vs. 1.3 hour	0.3719	0.2151 to 0.5288	<0.0001
0 hour vs. 1.45 hour	0.3937	0.2363 to 0.5511	<0.0001
0 hour vs. 2 hour	0.3948	0.2374 to 0.5522	<0.0001
0 hour vs. 4 hour	0.4512	0.2938 to 0.6086	<0.0001
0 hour vs. 6 hour	0.4397	0.2823 to 0.5971	<0.0001

Fig. 6 Shock index (HR/SBP), an important indicator of cardiac performance (left ventricular stroke work) in early hemorrhage, was significantly improved by centhaquine in the first 4 h of resuscitation. *CI* confidence interval, *Diff.* difference, *HR* heart rate, *SBP* systolic blood pressure

and the use of vasopressors [52]. Such an approach is common across the globe and was followed in the present study. During the first 48 h of resuscitation, fluids, blood, blood products, vasopressors, and urine output was similar in both groups. Significantly more patients had improved SBP and DBP in the centhaquine group than in the control group. A

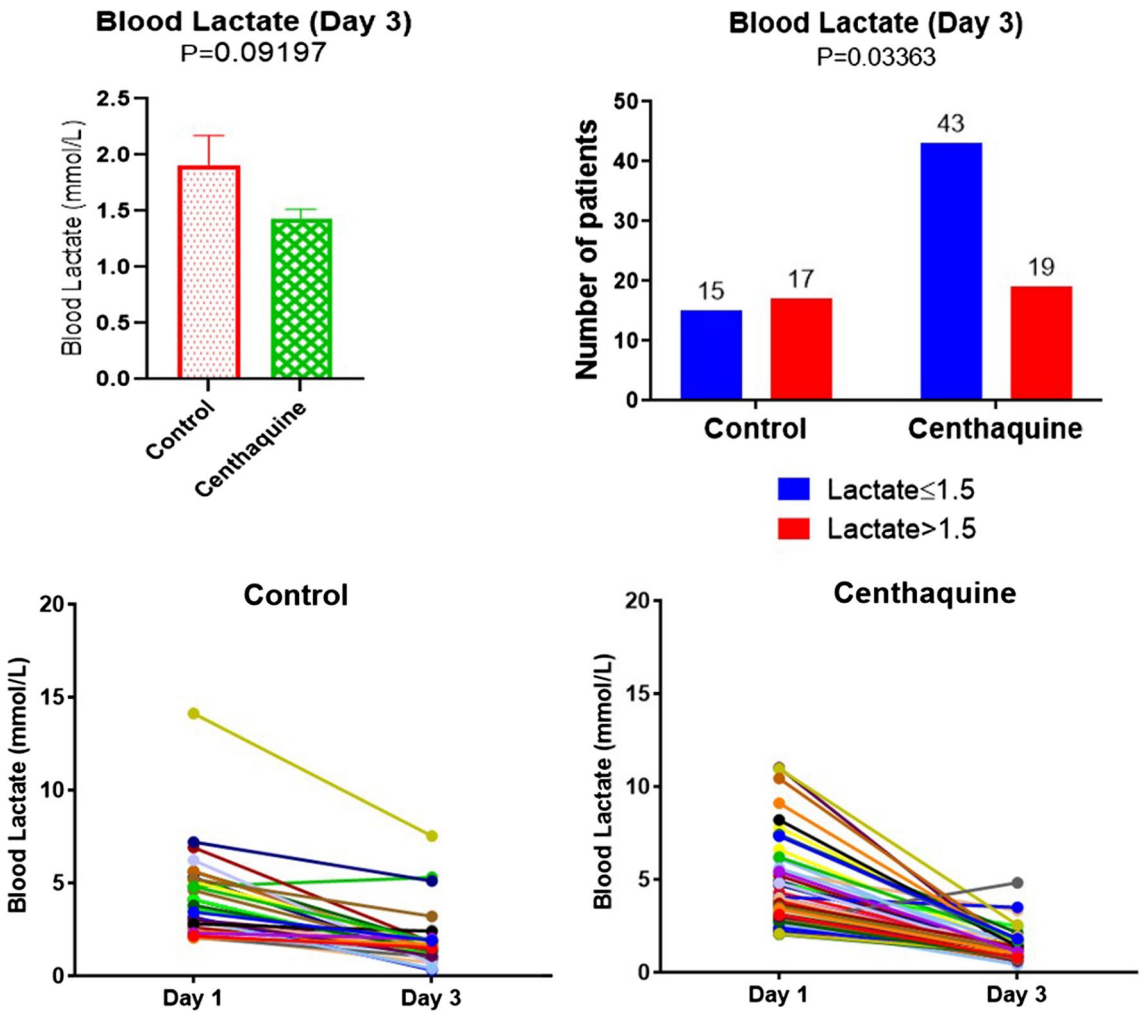


Fig. 7 Blood lactate levels in the control and centhaquine groups on day 3 of resuscitation (upper panel). Changes in blood lactate levels following resuscitation of patients with hypovolemic shock in control and centhaquine groups (lower panel)

7.4% decrease in $AUC_{0–48}$ of the mean difference in DBP from baseline in the centhaquine group compared with the control group allowed more ventricular filling, increasing cardiac output. An increase in $AUC_{0–48}$ of 12.9% in SBP in the centhaquine group compared with the control group indicated that the rate of venous return to the heart was higher in the centhaquine group than in the control group. The primary determinant of pulse pressure is the stroke volume, and a 48.1% increase in $AUC_{0–48}$ of the mean difference in pulse pressure from baseline in the centhaquine group compared with the control group indicated a significant increase in stroke volume due to centhaquine.

Hypovolemic shock results in a drop in cardiac output, lowering tissue and organ blood perfusion, leading to multiple organ failure and death. Vasopressors increase blood pressure by arterial constriction and increasing the heart rate. Cardiac output can increase because of an increase in heart rate, but it does not account for the total increase in cardiac output [53]. In total, 60–70% of the total blood volume pooled in the venous system is adjustable [54]. The venous system is critically important following hemorrhage because it can be used to mobilize pooled (unstressed) blood volume towards systemic (stressed) circulation [35, 55]. In a patient with hypovolemic shock, centhaquine converts the venous unstressed blood volume to stressed blood volume and improves cardiac output and blood circulation, making it an ideal candidate for the resuscitation of patients.

SI, an important prognostic indicator, is linearly inversely related to physiologic parameters, such as cardiac index, stroke volume, left ventricular stroke work, and mean arterial pressure [43, 56, 57]. SI significantly improved ($p < 0.0001$) in the centhaquine group in the first 4 h of resuscitation. A difference between the centhaquine and control groups was observed within the first hour of resuscitation, where a decrease in SI was significant (0.15 ± 0.07; $p = 0.03$) with centhaquine compared with the control group. The initial

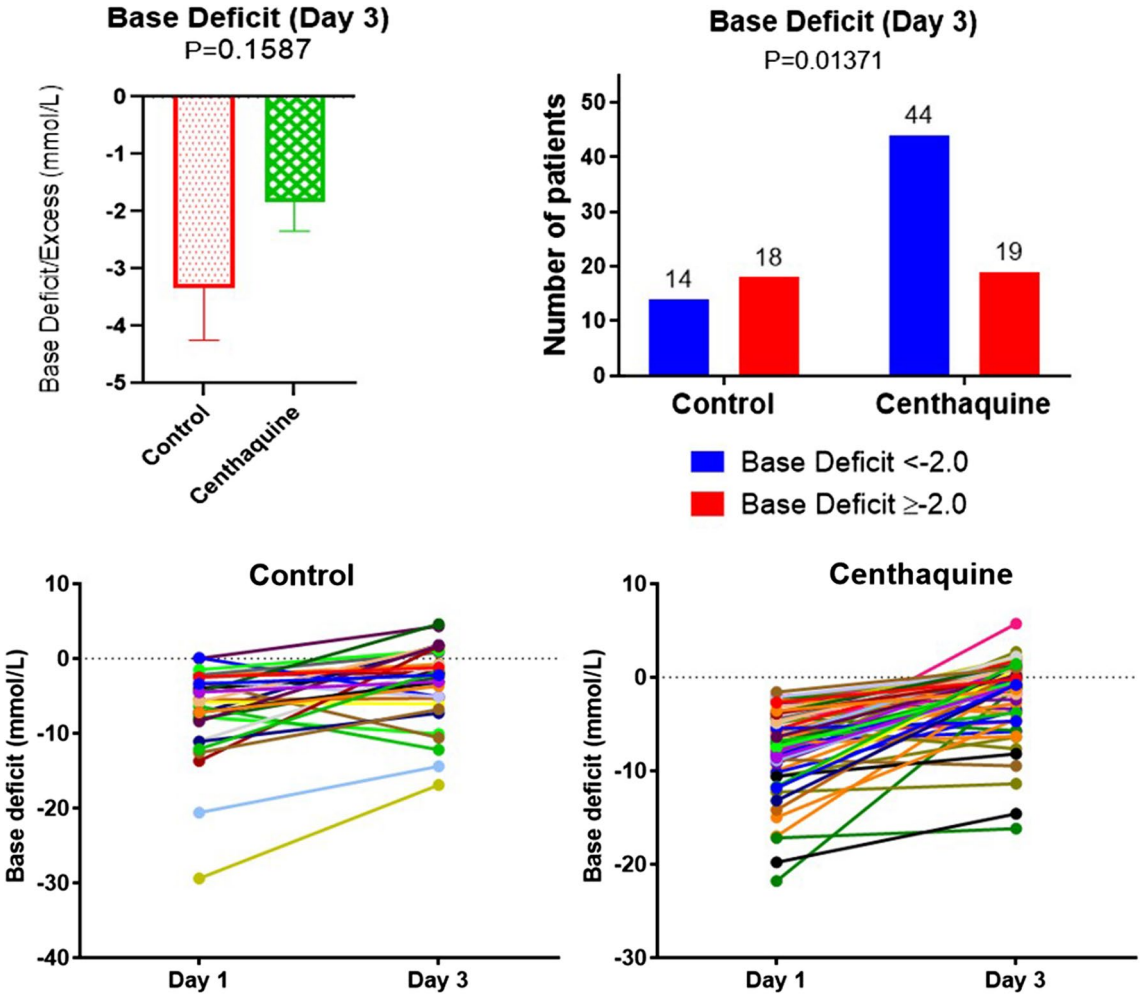


Fig. 8 Base deficit in control and centhaquine groups on day 3 of resuscitation (upper panel). Changes in base deficit following resuscitation of patients with hypovolemic shock in control and centhaquine groups of individual patients (lower panel)

hours of resuscitation are the most critical in improving outcomes for these patients.

Under conditions of shock, inadequate blood flow to the tissues results in increased blood lactate levels. High blood lactate levels and an increase in the base deficit are suggestive of poor outcomes and high mortality rates [58]. Early lactate clearance is associated with decreased mortality, ICU length of stay, and duration of mechanical ventilation [59]. In the present study, the number of patients with a blood lactate level of ≤ 1.5 mmol/L at day 3 of resuscitation was 46.9% in the control group and 69.3% in the centhaquine group ($p = 0.03$). Similarly, the base deficit of less than − 2 mmol/L on day 3 of resuscitation was significantly ($p = 0.01$) higher in the centhaquine group (69.8%) than in the control group (43.7%).

Centhaquine significantly improved ARDS and MODS. Studies in a porcine model of hemorrhagic shock showed that centhaquine significantly improved Horowitz index (327 ± 10 and 392 ± 16 in the control and centhaquine groups, respectively) and reduced pulmonary edema [41, 42]. This study indicated an improvement in ARDS in patients with hypovolemic shock. In the control group, there was an improvement in ARDS on day 3 compared with day 1, but it was not statistically significant. Conversely, in the

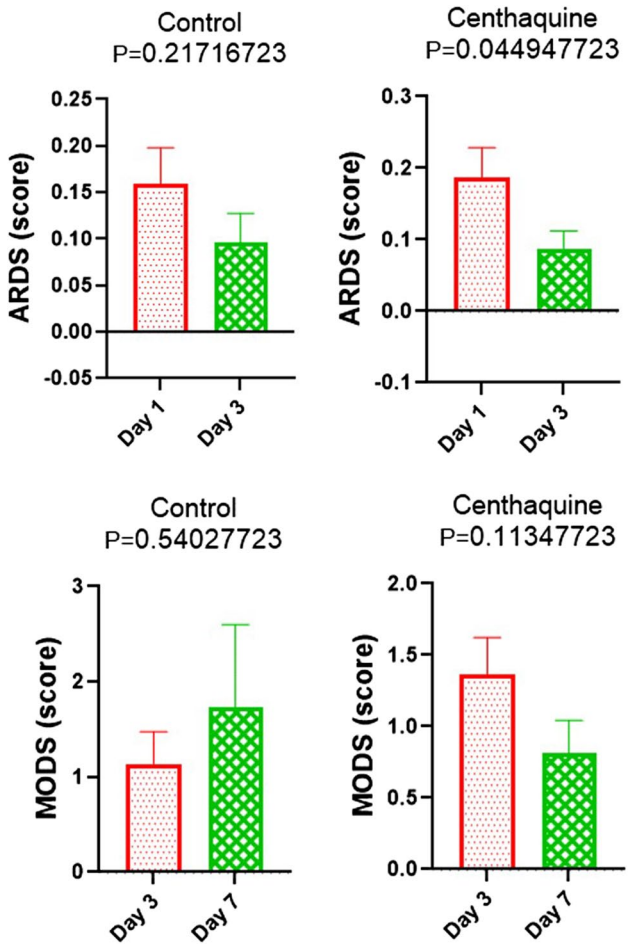


Fig. 9 ARDS was compared between day 1 (before resuscitation) and day 3 of resuscitation. Centhaquine treatment significantly improved ARDS following resuscitation, whereas improvement was minor in the control group. MODS was compared between day 3 and day 7 of resuscitation. In the control group, MODS worsened from 1.138 to 1.727, whereas it improved from 1.367 to 0.8182 in the centhaquine group. *ARDS* acute respiratory distress syndrome, *MODS* multiple organ dysfunction syndrome

centhaquine group, a significant ($p = 0.04$) improvement in ARDS was observed on day 3 of resuscitation compared with day1. MODS increased on day 7 compared with day 3 in the control group and decreased on day 7 compared with day 1 in the centhaquine group. A direct comparison of MODS on day 7 between the control and centhaquine groups revealed a MODS of < 2 in 86.3% of those in the centhaquine group compared with 54.5% of patients in the control group ($p = 0.04$).

In total, 55% of all trauma patients have hypocalcemia [60], which worsens with infusion of blood and blood products because citrate is used for storage and chelates calcium when infused. A drop in calcium can aggravate coagulopathy, leading to continued hemorrhage [61]. Calcium levels in the present study were similarly improved, from 1.78 ± 0.09 to 2.05 ± 0.10 mmol/L in the control group and from 1.80 ± 0.07 to 2.06 ± 0.06 mmol/L in the centhaquine group, indicating that centhaquine did not affect serum calcium. Centhaquine also did not affect serum sodium and potassium levels and other biochemical parameters (Table 5).

Improvements in all the discussed clinical and biological markers appeared to contribute to improved outcomes and reduced deaths in the centhaquine group. Mortality is the primary outcome for most clinical trials in critical care medicine; however, many factors can influence this outcome [62]. A meta-analysis of trials with a study intervention reported reduced mortality in 27 randomized controlled trials of 15,612 patients and increased mortality in 16 randomized controlled trials of 10,462 patients [62]. These trials were carried out in the general ICU population or in patients with sepsis, and no specific study investigated patients in hypovolemic shock. Upon further analysis, only 13 randomized controlled trials demonstrated reduced mortality rates, and these were attributed to disease conditions rather than to the new therapy [62].

In summary, none of the new therapies has demonstrated any reduction in mortality. We carefully included a more homogeneous patient population to avoid heterogeneous factors influencing the outcome so we could determine the effect of the intervention (centhaquine) on clinical outcomes. To our knowledge, this is the only late-stage clinical study that has demonstrated a significant survival advantage, with

Table 4 Patients GCS, MODS, and ARDS, recorded through day 28

Score	Group	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 28
GCS	Control	14.29 ± 0.31	14.66 ± 0.20	14.97 ± 0.03	15.00 ± 0.00	15.00 ± 0.00	15.00 ± 0.00	15.00 ± 0.00	15.00 ± 0.00
	Centhaquine	13.40 ± 0.42	14.34 ± 0.22	14.21 ± 0.29	14.23 ± 0.35	14.29 ± 0.39	14.26 ± 0.46	14.23 ± 0.46	14.91 ± 0.09
MODS	Control			1.14 ± 0.34	1.65 ± 0.50	1.20 ± 0.34	1.54 ± 0.69	1.73 ± 0.87	0.25 ± 0.12
	Centhaquine			1.37 ± 0.26	1.82 ± 0.41	1.34 ± 0.26	1.09 ± 0.29	0.82 ± 0.22	0.33 ± 0.10
ARDS	Control	0.15 ± 0.05	0.02 ± 0.01	0.08 ± 0.04	0.05 ± 0.04	0.01 ± 0.01	0.06 ± 0.05	0.06 ± 0.06	0.03 ± 0.03
	Centhaquine	0.18 ± 0.04	0.13 ± 0.03	0.08 ± 0.02	0.13 ± 0.04	0.05 ± 0.02	0.03 ± 0.02	0.08 ± 0.04	0.03 ± 0.02

Data are presented as mean ± standard error of the mean

ARDS acute respiratory distresss syndrome, *GCS* Glasgow Coma Scale, *MODS* multiple organ dysfunction syndrome

Table 5 Patients' hematological, biochemical, and serum electrolyte levels

	Control group ($N = 34$)			Centhaquine group ($N = 68$)		
	Day 1 (baseline)	Day 3	Day 28	Day 1 (baseline)	Day 3	Day 28
Hematology						
Hemoglobin (g/dL)	10.41 ± 0.47	10.29 ± 0.42	12.37 ± 0.23	9.64 ± 0.35	9.96 ± 0.30	11.56 ± 0.29
Hematocrit (%)	31.90 ± 1.56	31.15 ± 1.16	37.72 ± 0.85	29.48 ± 1.09	30.57 ± 0.79	36.27 ± 0.74
Red blood cells (10^6/mm^3)	3.66 ± 0.17	–	4.32 ± 0.10	3.43 ± 0.12	–	4.23 ± 0.09
White blood cells (/mm^3)	12,429.12 ± 960.93	–	7322.40 ± 320.40	12,166.04 ± 693.06	–	7896.55 ± 290.31
Neutrophils (%)	77.83 ± 2.23	–	59.81 ± 1.30	77.07 ± 1.47	–	62.81 ± 1.18
Lymphocytes (%)	17.32 ± 1.88	–	32.29 ± 1.24	17.28 ± 1.16	–	30.65 ± 1.05
Monocytes (%)	2.77 ± 0.45	–	3.56 ± 0.67	2.74 ± 0.27	–	2.93 ± 0.29
Eosinophils (%)	1.97 ± 0.29	–	3.20 ± 0.38	2.76 ± 0.39	–	3.65 ± 0.33
Basophils (%)	0.08 ± 0.04	–	0.22 ± 0.08	0.10 ± 0.03	–	0.20 ± 0.05
Reticulocytes (%)	1.92 ± 0.21	–	1.28 ± 0.11	1.50 ± 0.10	–	1.29 ± 0.07
Mean corpuscular volume (fL)	87.97 ± 1.20	–	87.17 ± 0.95	85.75 ± 0.88	–	86.50 ± 0.63
Mean corpuscular hemoglobin (Pg)	28.83 ± 0.52	–	28.79 ± 0.44	28.06 ± 0.43	–	28.67 ± 0.27
Platelets (/mm^3)	192,294.12 ± 16,816.75	228,160.00 ± 14,019.59		188,776.12 ± 9260.97		230,645.45 ± 9755.28
Lipid profile						
Triglyceride (mg/dL)	112.98 ± 6.04	–	128.87 ± 7.61	129.63 ± 6.94	–	136.51 ± 7.55
Total cholesterol (mg/dL)	134.78 ± 7.43	–	149.33 ± 4.98	143.43 ± 4.72	–	157.05 ± 4.43
High-density lipoprotein (mg/dL)	39.19 ± 1.79	–	44.43 ± 1.49	41.52 ± 1.18	–	43.28 ± 1.06
Low-density lipoprotein (mg/dL)	73.35 ± 5.75	–	80.59 ± 5.35	77.41 ± 4.02	–	89.87 ± 3.72
Very-low-density lipoprotein (mg/dL)	24.48 ± 1.56	–	28.69 ± 1.86	28.18 ± 1.49	–	29.24 ± 1.53
Kidney function						
Serum creatinine (mg/dL)	1.28 ± 0.13	1.05 ± 0.10	0.86 ± 0.04	1.22 ± 0.08	1.18 ± 0.12	0.88 ± 0.03
Blood urea nitrogen (mg/dL)	19.32 ± 3.19	–	12.08 ± 0.51	16.28 ± 1.03	–	11.91 ± 0.47
Glomerular filtration rate (ml/min/1.73 m^2)	78.84 ± 5.42	93.68 ± 6.60	106.22 ± 6.41	77.41 ± 4.30	84.18 ± 4.04	96.55 ± 3.51
Liver function						
Alanine aminotransferase (U/L)	60.14 ± 26.58	–	23.05 ± 1.60	58.73 ± 12.96	–	25.06 ± 2.18
Aspartate aminotransferase (U/L)	121.29 ± 73.15	–	26.66 ± 2.26	67.19 ± 10.50	–	24.97 ± 1.92
Serum bilirubin (mg/dL)	0.99 ± 0.07	–	0.72 ± 0.03	1.07 ± 0.13	–	0.72 ± 0.03
Alkaline phosphatase (IU/L)	108.45 ± 11.13	–	112.78 ± 12.39	121.63 ± 13.35	–	108.41 ± 8.68
Serum albumin (g/dL)	3.54 ± 0.10	–	3.98 ± 0.08	3.55 ± 0.07	–	3.87 ± 0.06

Table 5 (continued)

	Control group ($N = 34$)			Centhaquine group ($N = 68$)		
	Day 1 (baseline)	Day 3	Day 28	Day 1 (baseline)	Day 3	Day 28
Blood glucose (mg/dL)	140.23 ± 9.43	–	95.90 ± 4.32	139.06 ± 10.54	–	104.26 ± 4.21
Serum electrolyte						
Sodium (mmol/L)	136.38 ± 0.96	–	137.23 ± 1.17	136.49 ± 0.65	–	137.37 ± 0.63
Potassium (mmol/L)	4.13 ± 0.16	–	3.96 ± 0.05	4.16 ± 0.12	–	3.89 ± 0.05
Calcium (mmol/L)	1.78 ± 0.09	–	2.05 ± 0.10	1.80 ± 0.07	–	2.06 ± 0.06
Arterial blood gases						
pH	7.32 ± 0.02	7.40 ± 0.01	–	7.34 ± 0.01	7.40 ± 0.01	–
pCO_2 (mmHg)	33.65 ± 1.36	36.00 ± 1.50	–	31.98 ± 0.90	35.49 ± 0.71	–
paO_2 (mmHg)	117.04 ± 9.39	96.01 ± 5.42	–	113.48 ± 5.62	99.12 ± 3.70	–
FiO_2	0.26 ± 0.02	0.22 ± 0.01	–	0.27 ± 0.02	0.22 ± 0.01	–

Data are presented as mean ± standard error of the mean

pH power of hydrogen, paO_2 partial pressure of oxygen, pCO_2 partial pressure of carbon dioxide, FiO_2 fraction of inspired oxygen

Table 6 Safety of centhaquine and incidence of adverse events

Event	Control group ($N=34$)	Centhaquine group ($N=68$)
Adverse events of any grade		
Increase in blood creatinine	0 (0)	2 (2.94)
Vomiting	0 (0)	1 (1.47)
Serious adverse events		
Deaths	4 (11.76)	2 (2.94)

Data are presented as *n* (%)

an 8.8% absolute reduction in mortality. Centhaquine was safe and well-tolerated, with no drug-related AEs (Table 6). Centhaquine obtained marketing authorization from the regulatory authorities in India for the treatment of patients in hypovolemic shock in 2020. We conducted a meta-analysis of mortality data obtained from phase II and III studies because the inclusion criteria were similar and found that mortality was 10.71% in the control group ($N=56$) and 2.20% in the centhaquine group ($N=91$) (OR 5.34; 95% CI 1.27–26.50; $p=0.03$), which is statistically significant at the 95% CI.

The mortality observed in our study in the control group was a little lower than in previous studies. A study analyzing 4038 patients from 120 ICUs in India reported a mortality rate of 20.8% in well-equipped ICUs [63]. Further analysis showed that mortality in trauma patients was 14.1% (26 of 185) [63], which is slightly higher than the 11.8% observed in our control group. Similarly, data for 9354 patients from the Australia India Trauma Systems Collaboration registry showed 30-day mortality of 12.4% [64]. Treatment with centhaquine produced an absolute reduction in 28-day all-cause mortality of 8.8%.

The effect of centhaquine on the systemic hemodynamics of patients in hypovolemic shock depends on the fluid status. A limitation of this study is that we did not examine the effect of centhaquine on the volume status of patients in hypovolemic shock. Centhaquine was administered in a total volume of 100 mL over 60 min; this is a small volume and not likely to cause any volume overload. Moreover, in the first 48 h of resuscitation, the total volume of fluids administered, blood products administered, and urine output were similar in both groups. More frequent determination of blood lactate levels could have provided the time taken by centhaquine to reduce blood lactate. Another limitation of this study was that, although this was a multicenter study, it was conducted exclusively in patients from India. We recognize that the demographics and SOC may vary in other countries. In this study, many patients were not treated within the golden hour, resulting in a greater possibility of developing secondary complications. Delayed intervention is likely to result in the release of inflammatory and apoptotic substances, producing additional organ damage and failure of multiple organs, resulting in greater mortality. In countries where patients are likely to be resuscitated within the golden hour, secondary complications are less likely, and we expect centhaquine to have greater effectiveness.

Future studies may explore the therapeutic potential of centhaquine in the treatment of other forms of shock associated with hemodynamic instability or refractory hypotension and resulting in multiorgan failure and ultimately death. Some of these conditions may include distributive shock. Septic shock is a type of distributive shock where a significant shift occurs within the vascular compartment and out

of the vascular system, resulting in a state of hypovolemia managed by administration of fluids and vasopressors [65]. A few drug candidates are under development for sepsis to reduce organ dysfunction [66]. Centhaquine increases cardiac preload and reduces cardiac afterload. An increase in cardiac preload can benefit patients with distributive shock. Centhaquine can be helpful in septic shock management, like in hypovolemic shock, as it augments cardiac output and improves tissue blood perfusion. Both we and other investigators are likely to initiate studies to determine the efficacy of centhaquine in patients with septic shock.

Where does centhaquine fit in a typical resuscitation protocol? Patients with uncontrolled bleeding undergo damage-control resuscitation to stop blood loss and initiate resuscitation, keeping in mind permissive hypotension targeting a mean arterial pressure of 65 mmHg [67, 68]. Resuscitation with centhaquine is likely to limit the use of vasopressors and may help achieve resuscitation free of arterial constriction [35]. If required, a balanced resuscitation may be followed by blood or blood product transfusion in a ratio similar to that of whole blood [67].

5 Conclusion

Centhaquine (Lyfaquin®) is a highly effective resuscitative agent for treating hypovolemic shock as an adjuvant to SOC.

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Declarations

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Conflicts of interest/Competeing interest Anil Gulati has issued and pending patents and is an employee and stockholder of Pharmazz, Inc. Rajat Choudhuri, Ajay Gupta, Saurabh Singh, S.K. Noushad Ali, Gursaran Kaur Sidhu, Parvez David Haque, Prashant Rahate, Aditya R. Bothra, Gyan P. Singh, Sanjiv Maheshwari, Deepak Jeswani, Sameer Haveri, Apurva Agarwal, and Nilesh Radheshyam Agrawal have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study protocol (PMZ-2010/CT-3.1/2018) dated July 16, 2018, was approved by the Drugs Controller General of India (DCGI), Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India (DCGI CT NOC. No.: CT/ND/66/2018). Furthermore, each institutional ethics committee reviewed and approved the study protocol before initiating patient enrolment.

Consent Written informed consent was obtained from all patients or their legally authorized representatives.

Availability of data and material The anonymized patient datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request from a bona fide researcher/research group.

Author contributions Study concept and design: AG; investigation: RC, AG, SS, SKNA, GKS, PDH, PR, ARB, GPS, SM, DJ, SH, AA, and NRA; acquisition of data: RC, AG, SS, SKNA, GKS, PDH, PR, ARB, GPS, SM, DJ, SH, AA, and NRA; analysis and interpretation of data: AG; drafting of the manuscript: AG; review of the manuscript: RC, AG, SS, SKNA, GKS, PDH, PR, ARB, GPS, SM, DJ, SH, AA, and NRA; funding acquisition: AG.

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