ORIGINAL ARTICLE

Combined Sildenafil and Dapoxetine versus Sildenafil Alone in the Treatment of Dapoxetine Non-Responding Mono-symptomatic Premature Ejaculation: A Randomized Comparative Study

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Abstract

Background: ***Septic shock, a critical condition marked by circulatory failure and organ dysfunction from an abnormal response to infection, requires immediate hemodynamic resuscitation to restore tissue perfusion and improve outcomes. This study assessed changes in hemodynamic parameters in septic shock patients before and after fluid resuscitation.***

Aim: ***To evaluate the hemodynamic changes before and after resuscitation by either colloids or crystalloids .***

Patient and Methods: ***60 patients with septic shock in the emergency and critical care departments of Al-Azhar University Hospitals were divided into two groups, A and B, with 30 patients in each group. Hemodynamic parameters such as blood pressure were measured at baseline and three hours after administering 30 mL/kg fluid resuscitation according to standard guidelines. The effects of saline versus albumin were also compared.***

Conclusion: Marked hemodynamic improvements occurred following protocolized resuscitation, with crystalloids achieving the best corrections.

Keywords: Dapoxetine; Premature ejaculation; Sildenafil; Combination therapy

1. Introduction

Sepsis is a major global health threat, with mortality reaching 50% for shock. The septic shock features cardiovascular dysfunction and metabolic derangements, substantially increasing mortality risk .[1] Complex pathophysiology triggers profound hemodynamic instability, oxygen debt, and risk of multi-organ failure. Management prioritizes early recognition and swift protocolized resuscitation focused on restoring systemic pressures, cellular perfusion, and metabolism to prevent irreversible tissue injury .[2]

Sepsis is defined as infection with acute organ injury per SOFA score criteria. Septic shock is defined as sepsis with persisting hypotension needing vasopressors to maintain MAP ≥65mmHg and serum lactate exceeding two mmol/L despite fluid resuscitation .[3,4] Warning tools enable earlier detection to lower subsequent organ failure and mortality. Bacterial infection often leads to the release of inflammatory mediators, endothelial activation, loss of circulating volume, and pathological vasodilation, causing shock .[5] Uncontrolled complement activation, immunothrombosis, and direct cytopathic effects inflict endothelial injury .[6] Imbalanced inflammation, along with dysregulated microvascular flow, causes cytopathic hypoxia, anaerobic metabolism, and bioenergetic failure. Heterogeneous perfusion deficits, metabolic shutdown, and cellular injury beget non-uniform multi-organ failure .[7]

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The Berlin guidelines (Sepsis-3, 2016) define septic shock as a severe form of sepsis, diagnosed when a patient has persistent hypotension requiring vasopressors to maintain a MAP of 65 mm Hg or higher, along with elevated lactate levels over two mmol/L despite adequate fluid resuscitation. These criteria reflect significant circulatory and metabolic dysfunction. Score≥2, and the need for vasopressor therapy to maintain a mean arterial pressure (MAP) ≥65 mmHg. Exclusion criteria included pregnancy, shock due to etiologies other than sepsis, and inability to provide informed consent.

Microcirculatory shunting prevents oxygen utilization despite macrocirculatory resuscitation.[8] Inflammation increases adhesion molecule expression and microvascular plugging. Near infrared spectroscopy reveals regional tissue oxygen saturation variability despite optimization .[9]. Cellular hibernation from bioenergetic crisis allows vital oxidative processes to become disabled. Accumulated mitochondrial damage can prompt cellular necrosis .[10] Microvascular dysfunction prevents oxygen from reaching tissue beds, worsening cellular dysfunction .[11]

Individual anti-inflammatory strategies have failed to reduce mortality thus far .[12] Management remains centered on early recognition, enabling prompt fluid resuscitation and vasopressors to stabilize tissue perfusion before irreparable cellular necrosis. Screening tools identify likely septic patients. Initial treatment includes prompt antibiotics, source control, and organ support like lung-protective ventilation .[13] Salvage therapies can be considered for refractory shock, but the degree of early hemodynamic optimization best correlates with outcomes .[14]

Shock features low systemic and microvascular resistance, cardiac output and oxygen delivery alongside tissue hypoxia. Inflammation provokes cytokine release causing vascular and myocardial dysfunction yielding collapse .[15] Nitric oxide inhibits vasoconstriction causing pathological shunting and hypotension. Cytokines undermine myocardial contractility and compliance, decreasing stroke volume alongside structural right heart strain from lung injury .[16]

Resuscitation goals are to urgently restore adequate perfusion and cellular oxygenation to prevent irreparable bioenergetic crisis and necrosis .[17] Initial priorities are stabilizing blood pressure and cardiac output to re-establish systemic perfusion, with MAP ≥65 mmHg targeted to balance risks .[18] However, microcirculatory and metabolic indicators like serum lactate, mixed venous oxygen saturation, and urine output determine outcomes by reflecting cellular recovery .[19] Failing to reverse metabolic dysfunction from cytopathic hypoxia risks ongoing organ failure regardless of macrocirculation .[20]. The aim of this study was to evaluate the hemodynamic changes before and after resuscitation in a comparative study of septic shock patients.

The primary aim of this study is to evaluate the effect of fluid resuscitation on hemodynamic parameters (SBP-DAP-MAP-HR-ScvO2-SvO2-SaO2-CO)

The secondary outcome is to determine whether resuscitation with crystalloids is better than or the same as colloids on hemodynamic parameters.

2. Patients and methods

This is a comparative clinical study conducted on 60 adult patients with septic shock according to Berlin guidelines admitted to the Emergency and Critical care departments of Al-Azhar University Hospitals from May 2021 to June 2022.

Patients were divided into two equal groups, each of 30 randomly using computer-generated numbers and sealed opaque envelopes, with one group receiving saline (S group) and the other group receiving 20% albumin solution (A group) for initial fluid resuscitation. Baseline demographic data, suspected source of infection, hemodynamic parameters, and biomarker levels were recorded. These parameters were reassessed 3 hours after initiating protocol-driven resuscitation with 30 ml/kg intravenous crystalloid fluid, and vasopressors titrated to achieve the target MAP.

The cardiac index is measured using transthoracic echocardiography through the following equation (CI = COP[SV X HR]/BSA). ScvO2 was measured through a blood sample withdrawn from CVC and measured by an ABG analyzer device.

Sample size calculation

The sample size calculation for the study was based on assumptions from Guarracino et al. (2019), using a 95% two-sided confidence level, 80% power, and a 5% alpha error. The calculation employed the following equation:

Although specific effect size and standard deviation values were not provided, the calculation using Epi Info STATCALC software determined a sample size of 52 per group. This was increased to 60 to account for potential dropouts during follow-up, ensuring the study's robustness and reliability.

Statistical Analysis

Statistical analysis was performed using SPSS version 22. Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean and standard deviation and compared between groups using the student's t-test or Mann-Whitney U test as appropriate.

Categorical variables were compared using the chi-square test. P-values <0.05 were considered statistically significant.

3. Results

The study included 268 patients who were evenly randomized into S/D combination and S-only groups. Sixteen patients (14 in the S/D combination group and 2 in the S-only group) discontinued the study owing to noncompliance or loss to follow-up, leaving 252 patients (S/D combination, 120; S-only, 132) for the final analysis (Figure 1).

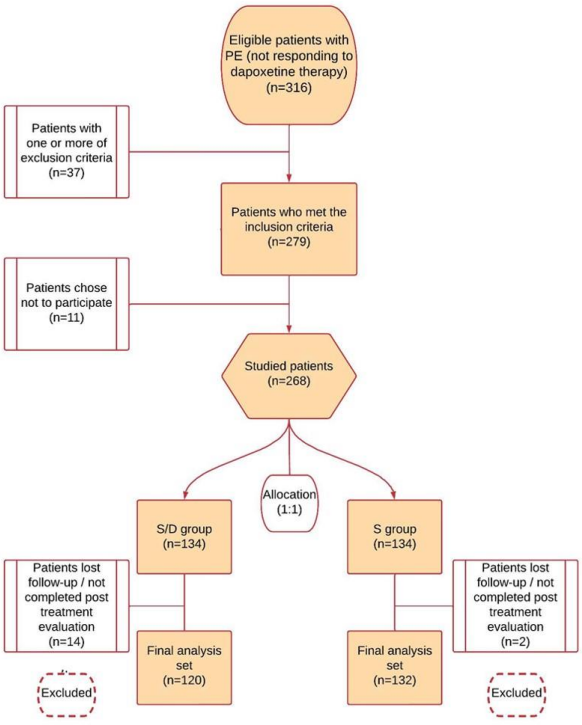


Figure 1. CONSORT flow diagram of patient disposition.

The median age of participants was 45.0 years (IQR: 16.8), and the median body mass index (BMI) was 25.0 kg/m² (IQR: 3.0), with 61.9% categorized as overweight or obese. A total of 34.5% of participants were smokers, and nearly half (49.6%) had a university-level education. Medical comorbidities were reported in 28.6% of patients, including diabetes mellitus (21.0%), hypertension (19.8%), and ischemic heart disease (5.2%). Baseline demographic and clinical characteristics were comparable between groups, except for a significantly longer median duration of prior dapoxetine use in the S/D group compared to the S-only group (p = 0.010) (Table 1).

Table 1. Demographics, and baseline clinical characteristics.

	S/D COMBINATION (N=120)	S-ONLY (N=132)	P VALUE
AGE, YEARS MEDIAN (IQR) MIN. TO MAX.	44.0 (16.8) 22.0 to 65.0	46.0 (18.8) 24.0 to 68.0	0.259
BMI (KG/M²) MEDIAN (IQR) MIN. TO MAX.	25.0 (3.0) 22.0 to 30.0	25.0 (4.0) 20.0 to 33.0	0.453
PARITY MEDIAN (IQR) MIN. TO MAX.	2.0 (1.0) 0 to 5	3.0 (2.0) 0 to 7	0.362
EDUCATION LEVEL, *N* (%) HIGH SCHOOL OR LESS UNIVERSITY	54 (45.0) 66 (55.0)	73 (55.3) 59 (44.7)	0.102
SMOKING, *N* (%)	40 (33.3)	47 (35.6)	0.705
PRE-ENROLMENT DAPOXETINE, WEEKS MEDIAN (IQR) MIN. TO MAX.	11.0 (2.0) 8.0 to 16.0	10.0 (4.0) 8.0 to 19.0	0.010
COMORBIDITIES, *N* (%)	32 (26.7)	40 (30.3)	0.523
YES *TYPE* DIABETES MELLITUS HYPERTENSION ISCHEMIC HEART DISEASE MULTIPLE COMORBIDITIES	22 (18.3) 24 (20.0) 5 (4.2) 14 (11.7)	31 (23.5) 26 (19.7) 8 (6.1) 17 (12.9)	0.316 0.952 0.803 0.915

IQR, Interquartile range; S/D, Combined sildenafil/dapoxetine; S-only, Sildenafil-only.

Before treatment, none of the patients were satisfied with their sexual activity. Of these, 54.0% ejaculated within one minute of vaginal penetration, and 42.9% had an IELT of less than two minutes. Post-treatment, both groups demonstrated significant improvements in all assessed sexual parameters. In the S/D combination group, the average IELT increased from 2.0 minutes to 3.78 minutes (p < 0.001), while in the S-only group, IELT increased from 1.0 minute to 3.52 minutes (p < 0.001). Similar improvements were observed in PEDT, IIEF-5, satisfaction scores, and frequency of sexual intercourse in both groups (all p < 0.001). Post-treatment IELT, PEDT, sexual satisfaction scores, and frequency of sexual intercourse were comparable between groups. The S-only group exhibited slightly higher post-treatment IIEF-5 scores than the S/D combination group (p = 0.032). However, a comparison of pre- and post-treatment mean changes showed no significant differences between groups for any sexual parameter (Table 2).

Table 2. Patient-reported sexual parameters in both groups.

	S/D COMBINATION (N=120)	S-ONLY (N=132)	THE DIFFERENCE IN MEAN CHANGE ± SE (95% CI)	PB-VALUE
IELT, MINUTE				
PRE-TREATMENT	1.54± 0.56	1.45± 0.56		0.158
POST-TREATMENT	3.78± 2.91	3.52± 2.67	0.17±0.351 (-0.52, 0.87)	0.564
MEAN CHANGE (95% CI)	2.24 ± 2.87 (1.74, 2.78)	2.07 ± 2.71 (1.61, 2.53)		0.551
PA-VALUE	<0.001	<0.001		
PEDT SCORE				
PRE-TREATMENT	13.54± 1.68	13.16± 1.61		0.072
POST-TREATMENT	10.13± 4.60	10.11± 3.94	-0.36±0.530 (-1.41,0.68)	0.672
MEAN CHANGE (95% CI)	-3.41 ± 4.67(-4.16, -2..49)	-3.05 ± 3.73(-3.74 to -2.38		0.721
PA-VALUE	<0.001	<0.001)		
IIEF-5 SCORE				
PRE-TREATMENT	22.47± 0.71	22.56± 0.58		0.052
POST-TREATMENT	23.73± 0.88	23.98± 0.82	-0.15±0.129 (-0.41,0.11)	0.032
MEAN CHANGE (95% CI)	1.27 ± 1.15(1.06–1.48)	1.42 ± 0.91 (1.26–1.57)		0.501
PA-VALUE	<0.001	<0.001		
FREQUENCY OF SEXUAL INTERCOURSE/WEEK	2.42± 0.96	2.30± 1.02		0.304
PRE-TREATMENT	2.96± 0.76	2.85± 0.75	-0.01±0.143 (-0.29,0.27)	0.206
POST-TREATMENT	0.54 ± 1.09(0.37–0.73)	0.55 ± 1.17(0.35–0.76)		0.693
MEAN CHANGE (95% CI)	<0.001	<0.001		
PA-VALUE				
SEXUAL SATISFACTION SCORE	1.18± 0.71	1.34±0.76		0.128
PRE-TREATMENT	2.52± 1.60	2.51±1.71	0.18±0.209 (-0.24,0.59)	0.942
POST-TREATMENT	1.34 ± 1.59(1.05–1.61)	1.17 ± 1.72(0.86–1.48)		0.397
MEAN CHANGE (95% CI)	<0.001	<0.001		
PA-VALUE				

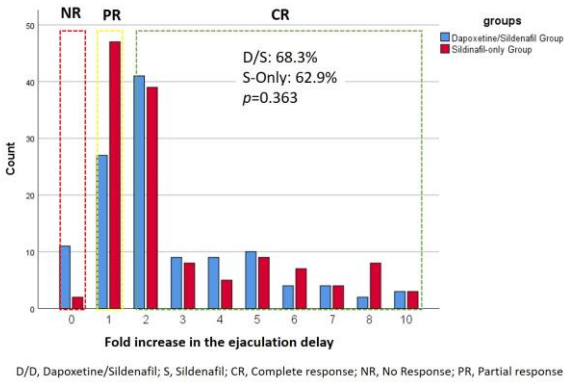
Data are expressed as the mean ± SD.

pa Significant difference compared with the baseline.

Pb Significant difference between both groups.

CI, Confidence interval; IIEF-5, International Index of erectile function; IELT, Intravaginal ejaculatory latency time; PEDT, Premature ejaculation diagnostic tool; S/D, Combined sildenafil/dapoxetine; S-only, Sildenafil-only; SD, Standard deviation.

The drug-induced ejaculation delay, measured as FIs in geometric mean IELT, showed a response (≥2-FI) in 65.5% of patients. Among responders, 78.8% had a FI of 2–5, and 21.2% had a FI of 5–10. In the S/D group, 68.3% responded, with 73.5% showing a FI of 2–5 and 15.9% a FI of 5–10, compared to 62.9% in the S-only group, with 84.1% showing a FI of 2–5 and 26.5% a FI of 5–10. Response rates did not differ significantly between groups (p = 0.363) (Figure 2).



D/D, Dapoxetine/Sildenafil; S, Sildenafil; CR, Complete response; NR, No Response; PR, Partial response

Figure 2. Drug-induced delay in ejaculation, represented as fold increases in the geometric mean intravaginal ejaculation latency time (IELT).

Adverse events were mild and similar between groups. The most commonly reported side effects included headache, flushing, nausea, and palpitations, with no statistically significant intergroup differences. However, dyspepsia was reported more frequently in the S/D combination group (11.7%) than in the S-only group (1.5%; p = 0.005) (Table 3).

Table 3: Side effects in both groups.

	S/D COMBINATION (N=120)	S-ONLY (N=132)	P VALUE
HEADACHE	20 (16.7)	18 (13.6)	0.688
FLUSHING	26 (21.7)	23 (17.4)	0.588
NAUSEA	5 (4.2)	3 (2.3	0.638
PALPITATION	6 (5.0)	7 (5.3)	0.856
DYSPEPSIA	14 (11.7)	2 (1.5)	0.005
DIARRHEA	1 (0.8)	0 (0.0)	>0.999
FATIGUE	7 (5.8)	6 (4.5)	0.878

S/D, Combined sildenafil/dapoxetine; S-only, Sildenafil-only.

4. Discussion

This was an comparative clinical study on 60 septic shock patients divided into a saline group and an albumin group at Al-Azhar University Hospitals. The two groups had similar baseline demographic characteristics like age, gender, height, weight and temperature. The most common source of sepsis was pulmonary, followed by abdominal, bloodstream and other sources.

At baseline prior to fluid resuscitation, the two groups had similar hemodynamic compromise, with mean arterial pressure (MAP) around 60-65 mmHg, elevated heart rate around 120-125 bpm, and reduced central venous oxygen saturation (ScvO2) around 60-65% (Table 2). The mean cardiac index (CI) was also reduced at 1.67-1.94 L/min/m2. These parameters are indicative of distributive shock due to systemic vasodilation and hypoperfusion seen in septic shock.[20]

After 6 hours of protocol fluid resuscitation, both groups demonstrated significant improvements in hemodynamics (Table 5). MAP increased to 75-80 mmHg, heart rate decreased to 105-110 bpm, and

ScvO2 increased to 68-72%. There were no statistically significant differences between the two fluid types in any of the hemodynamic parameters after resuscitation.

A meta-analysis by Xu JY et al[21], including 14 randomized controlled trials (n=1,652 patients), similarly found no clinically significant difference in hemodynamic endpoints when comparing albumin to Saline solutions for initial resuscitation in sepsis. Multiple other studies have also shown equivalence between albumin and saline for hemodynamic resuscitation goals.[22]

The primary outcomes showed similar improvements in both groups after fluid resuscitation (Table 6A). MAP increased by approximately 20 mmHg, cardiac index increased by 1 L/min/m2, and ScvO2 increased by 10% in both arms. There were no statistically significant differences between the two fluid types for any of the primary outcome measures.

These findings align with the results of the ALBIOS trial, a multicenter randomized controlled trial (n=1,818 patients) comparing 20% albumin vs saline for fluid resuscitation in severe sepsis and septic shock, which found no difference in hemodynamic improvement at 6, 12, and 24 hours between the two fluid strategies.[23] A patient-level meta-analysis of 17 randomized trials (n=3,033 patients) also concluded that albumin versus saline did not impact the overall hemodynamic response in sepsis.[24]

Several biomarkers were assessed at baseline and after fluid resuscitation, including lactate, C-reactive protein (CRP), procalcitonin (PCT), and B-type natriuretic peptide (BNP) (Table 7).

At baseline, non-survivors had significantly higher lactate and BNP levels compared to survivors in both groups. Elevated lactate is a known indicator of tissue hypoperfusion in sepsis and predicts higher mortality.[4] BNP level also correlates with sepsis severity and prognosis.[5] After resuscitation, the lactate and BNP levels among non-survivors remained significantly higher than survivors in both groups.

The more rapid normalization of lactate following protocolized EGDT fluid resuscitation has been associated with improved survival in septic shock in a number of studies.[6] The persistence of elevated lactate after resuscitation may signify ongoing global tissue hypoxia or impaired clearance and portends worse outcomes.

There were no significant differences between the two fluid types in biomarker response. This corroborates findings from the CRISTAL trial, a multicenter randomized trial (n=2,857 patients), which found no difference in lactate clearance when comparing colloids (including albumin) to saline in critically ill patients.[7]

Non-survivors had significantly longer ICU and hospital length of stay compared to survivors in both groups. All non-survivors required mechanical ventilation. Overall ICU mortality was 37% in the saline group and 27% in the albumin group (p=0.46).

Prior meta-analyses have found no significant difference in mortality when comparing albumin to saline for septic shock resuscitation.[8] The ALBIOS trial similarly found no difference in 28 or 90 day mortality between albumin and saline.[9]

4. Conclusion

In this observational study of 60 septic shock patients divided into saline and albumin groups, Initial hemodynamic compromise improved significantly after 6 hours of fluid resuscitation in both groups, with no significant differences between them. Both groups showed similar improvements in blood pressure, cardiac output, and oxygen saturation. Biomarkers like lactate and BNP were higher in non-survivors, who also had longer ICU and hospital stays. Overall, in-hospital mortality was 25%, with no significant difference between groups.

Disclosure

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Authorship

All authors have a substantial contribution to the article

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There are no conflicts of interest.

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