

Comparison between Terlipressin and Catecholamine Infusion in the Management of Vasodilatory Shock: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Vasodilatory shock is a grave sign of cardiovascular failure. The use of vasoactive infusions is indicated when fluid resuscitation fails to restore adequate arterial pressure and tissue perfusion. Therefore, the proper management of clinically diverse shock states necessitates thorough knowledge of the mechanisms of action of vasoconstrictor drugs. The aim of this study was to compare between Terlipressin and catecholamine infusion in the management of vasodilatory shock. Study design: Meta-analysis Methods: Online databases (PubMed, Embase, BioMed, and the Cochrane Central Register of Controlled trials) were utilized for randomized studies ever performed in humans with Terlipressin in any clinical setting. Results: Twelve trials were included, involving a total of 1063 patients. The risk of bias was low. The meta-analysis found that there was no significant reduction in mortality. There was a significant reduction in heart rate, a significant increase in cardiac index, SVRI and UOP. There was no significant change in the rest of the hemodynamic variables among the included studies (MAP, SVI, PAOP, MPAP, PVRI, LVSWI, RVSWI and RAP). There was a significant decrease in IDO₂, a significant increase in pH and a significant decrease in BE. There was no significant change in PO₂ and PCO₂ among the studies. There was a significant reduction in serum lactate and hemoglobin, while no significant change was observed in INR. This meta-analysis showed no significance of Terlipressin over catecholamines in reducing mortality rates, however, terlipressin is associated with reduction of HR, increase in SVRI, reduction of serum lactate level and increase in UOP.

Keywords: Terlipressin; catecholamines; meta-analysis; randomized trials; vasodilatory shock.

Introduction

Vasodilatory shock is a critical sign of cardiovascular failure. The end result is the loss of physiologic vasoregulatory mechanisms following the lack of vascular responsiveness to endogenous vasoconstrictors, hence, the uncontrolled vasodilation despite receiving standard therapy. Management of patients with refractory shock continues to prove problematic due to the limited number of randomized trials that are currently in existence ^[1].

Of all critically ill patients, about 7% will advance into refractory shock with short-term mortality over 50% ^[2]. Thus, in-depth understanding of the various mechanisms of action of vasoconstrictors is necessary to optimize their clinical application ^[3].

The cornerstone of initial shock management is aggressive fluid resuscitation followed by continuous infusion of vasoactive drugs when fluids fail to restore sufficient mean arterial pressure and tissue perfusion ^[4]. At present, catecholamines are the vasopressors of choice, but the development of refractory shock states as a result of adrenergic hyposensitivity compel the provision of alternative options ^[5].

Other drugs being studied as alternatives to catecholamines are vasopressin and its analogue terlipressin. Vasopressin is a hormone released from the posterior pituitary gland and has a myriad of actions mediated via tissue-specific receptors. The vasopressor action of both vasopressin and terlipressin has been of interest due to the relative deficiency of vasopressin in patients with vasodilatory shock and the observation that, when exogenously administered, vasopressin reduces the use

of catecholamines through restoring the vascular tone, enhancing catecholamines responsiveness and raising the blood pressure ^[6].

Methods

This study adheres to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) ^[7]. No patient consent was required as all analyzed data were collected from previously published literature. Research Ethics Committee (REC) code and number is {M.S. 5.12.2021}. This study was conducted over a period of 6 months from June 2022 to December 2022.

Search Strategy:

Pertinent studies have been independently searched in MEDLINE, PubMed, EMBASE, BioMed and the Cochrane Central Register of Clinical Trials (CENTRAL). Our search strategy targeted any randomized controlled trials (RCTs) ever performed in human beings with Terlipressin in any clinical setting with no language restrictions. The search was conducted by using Boolean operators (AND/OR) to link the following keywords: terlipressin, catecholamine, norepinephrine, vasodilatory shock, septic shock and randomized trial. Additionally, we employed backward snowballing (i.e., scanning of references of retrieved articles and relevant reviews) to obtain further studies. The search process steps are described in Figure 1.

Eligibility criteria

With the aid of predetermined selection criteria, two reviewers independently identified all the studies. Disagreements

that arose during the selection of the primary study were arbitrated by a third reviewer. The following criteria should be met by studies to be included in this meta-analysis:

- (1) Subjects: Adult patients who suffer from vasodilatory shock.
- (2) Interventions: studies which analyze the effect of terlipressin compared with catecholamine infusion in patients with vasodilatory shock.
- (3) Comparisons: Control group received catecholamine infusion.
- (4) Outcomes: survival, hemodynamic data and biochemical data. The included study must have reported at least one of the results.
- (5) Type of literature: Clinically randomized controlled trials (RCTs) all published journals.

Selection of studies:

After database search, the three reviewers checked the abstracts of the collected studies independently. After that, the reviewers checked the full text of the articles included in meta-analysis which matched the inclusion criteria. Any conflicts about the studies to include were resolved by the most senior author. When duplicate reports of the same study were found in preliminary abstracts and articles, data was analyzed from the most complete dataset.

Exclusion criteria:

Studies were excluded if:

- a) They were case studies, observational studies, and letters to editors, systematic reviews or meta-analyses.

- b) They involved pediatric patients.
- c) Their outcomes are not of interest.
- d) They contained absent or deficient data.
- e) The study authors were inaccessible or did not reply if extra data from their trials were requested.

Data extraction:

Data were independently extracted from each report by authors, using a data-recording form developed for this purpose. After extraction, data were reviewed and compared. Disagreements between the two extractors were solved by consensus among the investigators. Whenever needed, additional information concerning a specific study was obtained by directly questioning the principal investigator.

Definition of endpoints:

The study endpoints included overall survival, change in hemodynamic variables, change in blood gases and oxygenation variables; and change in biochemical variables. The survival time was defined as the time from randomization until death from any cause or was censored on the date of the last follow-up assessment.

Quality assessment and risk of bias:

The quality of trials was assessed using the risk of bias tools recommended by the Cochrane collaboration. We appointed an estimation of high, unclear, or low to the following items: Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Any disparities have been identified through discussion.

Statistical analysis:

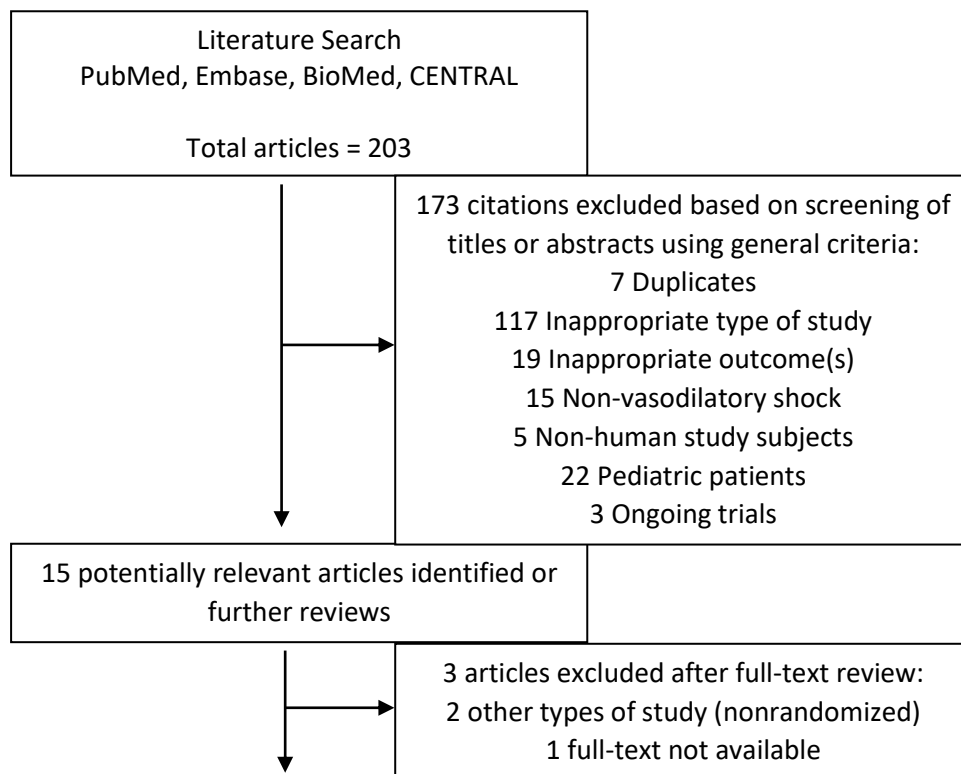
We conducted this analysis to pool the results of trials comparing the effect of terlipressin and catecholamine infusion in the treatment of vasodilatory shock using Review Manager (RevMan), Version 5.4.1 Copenhagen (The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

For heterogeneity measurement, chi-square test was used to calculate P and I square values. No significant heterogeneity was identified if ($P > 0.10$) and ($I^2 < 50\%$), so a fixed-effect model for analysis of data was applied. When the heterogeneity was significant, a random-effects model is applied. For studies that only provide the interquartile range (IQR) for outcomes based on continuous measures, by dividing the IQR by 1.35, we were able to determine the standard deviation (S.D.)

from the data [8]. For dichotomous outcomes, we estimated risk ratios (R.R.s) and their accompanying 95% confidence intervals (CIs). The definition of statistical significance used a two-sided alpha of 0.05, and clinical significance interpretations focused on CIs.

Results**Literature Search**

Our search identified 203 studies through database searching and other sources. 188 articles were screened. Of these articles, 173 were excluded after screening, and 15 were assessed for eligibility. Ultimately, 12 randomized trials were included for analysis, with the remainder excluded as outlined in the PRISMA flow diagram (Fig. 1).



12 articles included in meta-analysis
(1063 study participants)

Figure 1: Literature search strategy**Characteristics and quality of studies included in the meta-analysis**

The studies included in the analysis are detailed in Table 1. Twelve randomized studies were identified for inclusion in this study involving a total of 1063 patients. Bias risk in the twelve trials was assessed to be generally low. (Fig. 2)

Table 1 Characteristics of included studies.

Study ID	Study design	Disease	Intervention	Dose	No. of patients	Age (yrs.)
Albanèse et al, 2005 [9]	Prospective, randomized, open-label study	Septic Shock	N	$1.7 \pm 0.9 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	10	65 (24-76)
			TP	8 patients received one bolus of 1 mg of terlipressin and 2 patients received two boluses of 1 mg of terlipressin	10	66 (23-79)
Morelli et al, 2008 [10]	Prospective, randomized, controlled study	Septic Shock	N	$\geq 0.9 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	20	67 ± 40
			N + TP	1 mg single dose	19	66 ± 41.48
			N + TP + Db	1 mg single dose of terlipressin followed by $\geq 3.0 \mu\text{g.kg}^{-1}.\text{min}^{-1}$ dobutamine	20	66 ± 33.33
Morelli et al, 2009 [11]	Prospective, randomized, controlled, pilot	Septic Shock	N	$15 \mu\text{g.min}^{-1}$ plus open label NE	15	64 (59-72)
			N + TP	$1.3 \mu\text{g.kg}^{-1}.\text{h}^{-1}$ plus open label NE	15	67 (60-71)
			N + AVP	0.04 U.min^{-1} plus open label NE	15	66 (60-74)
Morelli et al, 2011 [12]	Randomized, controlled, double-blind, clinical trial	Septic Shock	N	Titrated to maintain MAP between 65 and 75 mmHg	20	66 (58-74)
			N + TP	$1 \mu\text{g.kg}^{-1}.\text{h}^{-1}$	20	65 (51-71)
			N + AVP	0.04 U.min^{-1}	20	71 (48-78)
Hua et al, 2013 [13]	Prospective, randomized study	ARDS + Septic Shock	D	Up to $20 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	16	52.2 ± 14.0
			TP	$1.3 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	16	56.6 ± 16.4
Xiao et al, 2015 [14]	Prospective, randomized, blind	Septic Shock	N	$>0.5 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	17	62 ± 12
			N + TP	$1.3 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	15	63 ± 11
Labib et al, 2016 [15]	Prospective, randomized, double-blinded	Septic Shock	N + A	$0.2 \mu\text{g.kg}^{-1}.\text{min}^{-1}$	37	42.6 ± 11.3
			N + TP	$1.3 \mu\text{g.kg}^{-1}.\text{h}^{-1}$	39	44.5 ± 12
Zhi et al, 2017 [16]	Prospective, single-blind, randomized controlled trial	ARDS + Septic Shock	N	$>1 \mu\text{g.min}^{-1}$	26	55.7 ± 16.1
			TP	$0.01-0.04 \text{ U.min}^{-1}$	31	58.5 ± 17.8
Choudhury et al, 2017 [17]	Prospective, randomized	Liver Cirrhosis + Septic Shock	N	$7.5-60 \mu\text{g.min}^{-1}$	42	48.29 ± 12.53
			TP	$1.3-5.2 \mu\text{g.min}^{-1}$	42	46.76 ± 12.11
Liu et al, 2018 [18]	Multicenter, randomized, double-blinded trial	Septic Shock	N	$4-30 \mu\text{g.min}^{-1}$	266	61.09 ± 16.20
			TP	$20-160 \mu\text{g.h}^{-1}$	260	60.93 ± 15.86
Wang et al, 2022 [19]	Parallel randomized controlled trial	Septic shock	N	Titrated to maintain MAP greater than 65 mmHg	12	66.3 ± 15.2
			N+TP	$1.3 \mu\text{g.kg.h}^{-1}$	10	61.7 ± 16.2
Sahoo et al, 2022 [20]	Prospective, open-label, randomized	Septic shock	N	$0.01-3 \mu\text{g.kg.min}^{-1}$ titrated to achieve target blood pressure 65-70 mmHg	25	48.84 ± 19.08



Figure 2: A. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. **B.** Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Mortality

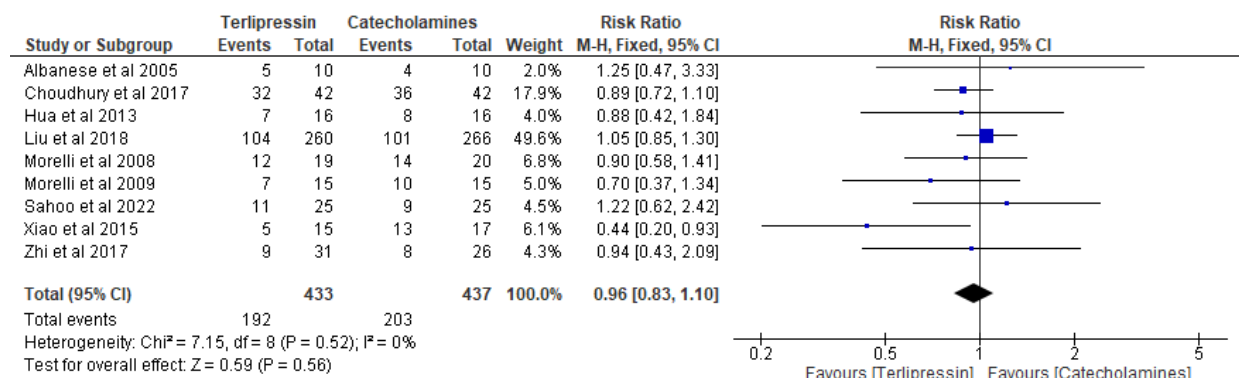
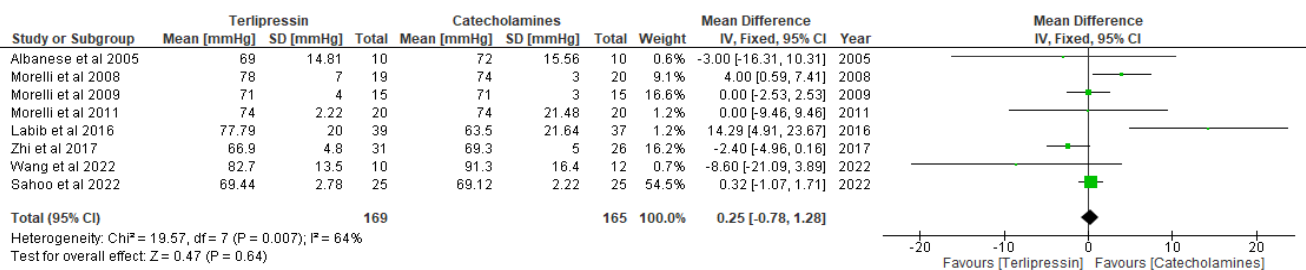
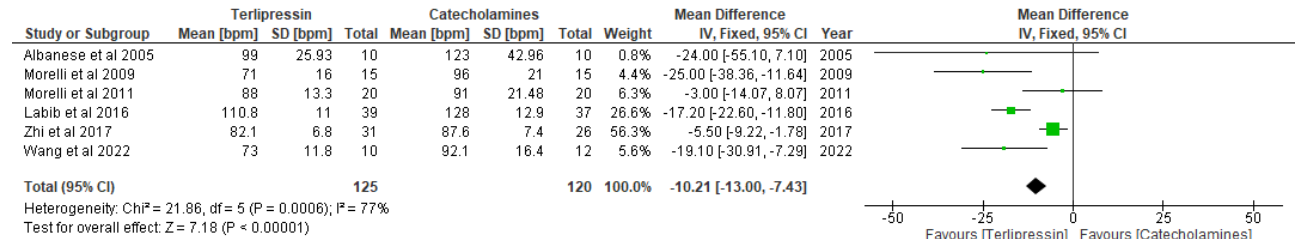


Figure 3: Incidence of Mortality. The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in mortality, with a RR of 0.96 and low heterogeneity (95% CI, RR = 0.96 [0.83, 1.10]; $I^2 = 0\%$; $P = 0.56$). CI, confidence interval; M-H, Mantel and Haenszel; TP, terlipressin; RR, risk ratio.

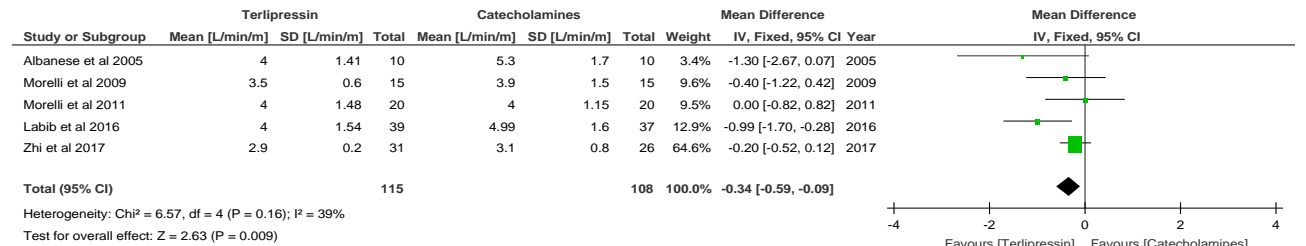
Hemodynamic variables



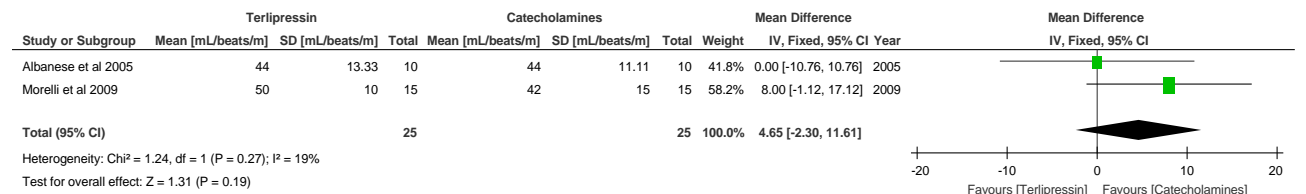
A: MAP (mmHg)



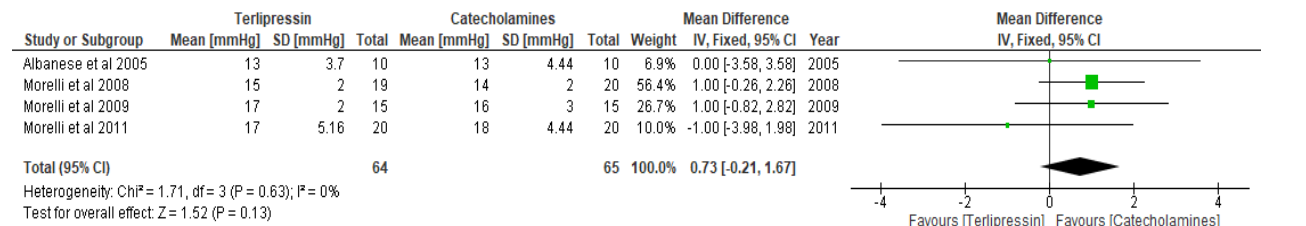
B: HR (bpm)



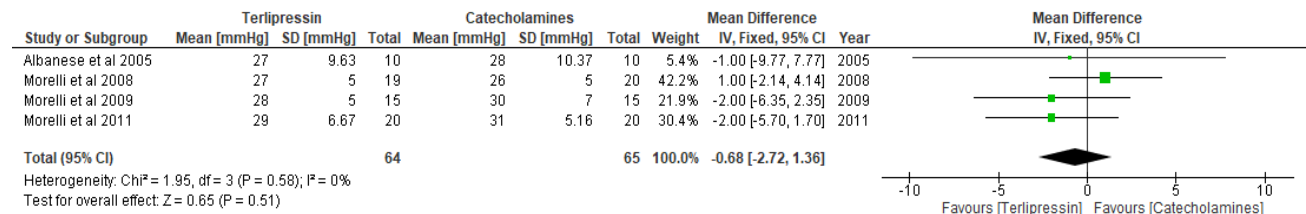
C: Cardiac Index [L/min/m]



D: SVI (mL/beat/m)



E: PAOP (mmHg)



F: MPAP (mmHg)

Figure 4A : Hemodynamic Variables: All data were obtained within the first 48h.

A. The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in MAP, with a MD of 0.25 and high heterogeneity (95% CI, MD = 0.25 [-0.78, 1.28]; $I^2 = 64\%$; $P = 0.64$). MAP, mean arterial pressure; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **B.** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant decrease in HR, with a MD of -10.21 and high heterogeneity (95% CI, MD = -10.21 [-13.00, -7.43]; $I^2 = 77\%$; $P < 0.00001$). HR, heart rate; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **C.** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant increase in cardiac index, with a MD of -0.34 and low heterogeneity (95% CI, MD = -0.34 [-0.59, -0.09]; $I^2 = 39\%$; $P = 0.009$). CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean

difference. **D:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in SVI, with a MD of 4.65 and low heterogeneity (95% CI, MD = 4.65 [-2.30, 11.61]; $I^2 = 19\%$; $P = 0.19$). SVI, stroke volume index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **E:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in PAOP, with a MD of 0.73 and low heterogeneity (95% CI, MD = 0.73 [-0.21, -1.67]; $I^2 = 0\%$; $P = 0.13$). PAOP, pulmonary artery occlusion pressure; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **F:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in MPAP, with a MD of -0.68 and low heterogeneity (95% CI, MD = -0.68 [-2.72, 1.36]; $I^2 = 0\%$; $P = 0.51$). MPAP, mean pulmonary artery pressure; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference.

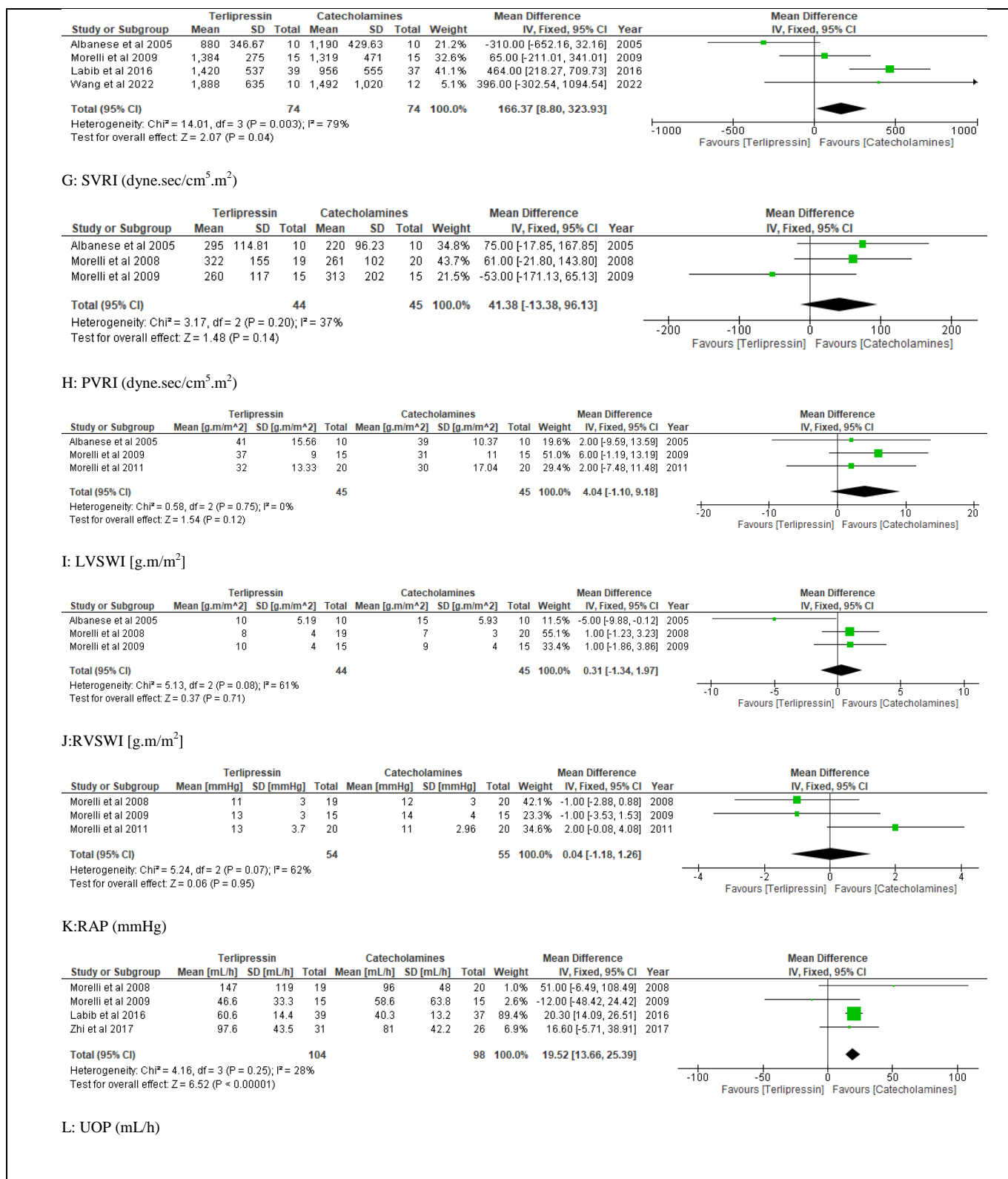


Figure 4 B: Hemodynamic Variables: All data were obtained within the first 48h.

G: The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant increase in SVRI, with a MD of 166.37 and high heterogeneity (95% CI, MD = 166.37 [8.80, 323.93]; $I^2 = 79\%$; $P = 0.04$). SVRI, systemic vascular resistance index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **H:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in PVRI, with a MD of 41.38 and low heterogeneity (95% CI, MD = 41.38 [-13.38, 96.13]; $I^2 = 37\%$; $P = 0.14$). PVRI, pulmonary vascular resistance index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **I:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in LVSWI, with a MD of 4.04 and low heterogeneity (95% CI, MD = 4.04 [-1.10, 9.18]; $I^2 = 0\%$, $P = 0.12$). LVSWI, left ventricular stroke work index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **J:**

The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in RVSWI, with a MD of 0.31 and high heterogeneity (95% CI, MD = 0.31 [-1.34; 1.97]; $I^2 = 61\%$; $P = 0.71$). RVSWI, right ventricular stroke work index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **K:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in RAP, with a MD of 0.04 and high heterogeneity (95% CI, MD = 0.04 [-1.18, 1.26]; $I^2 = 62\%$; $P = 0.95$). RAP, right atrial pressure; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **L:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant increase in UOP, with a MD of 19.52 and low heterogeneity (95% CI, MD = 19.52 [13.66, 25.39]; $I^2 = 28\%$; $P < 0.00001$). UOP, urine output; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference.

Oxygenation variables and blood gases

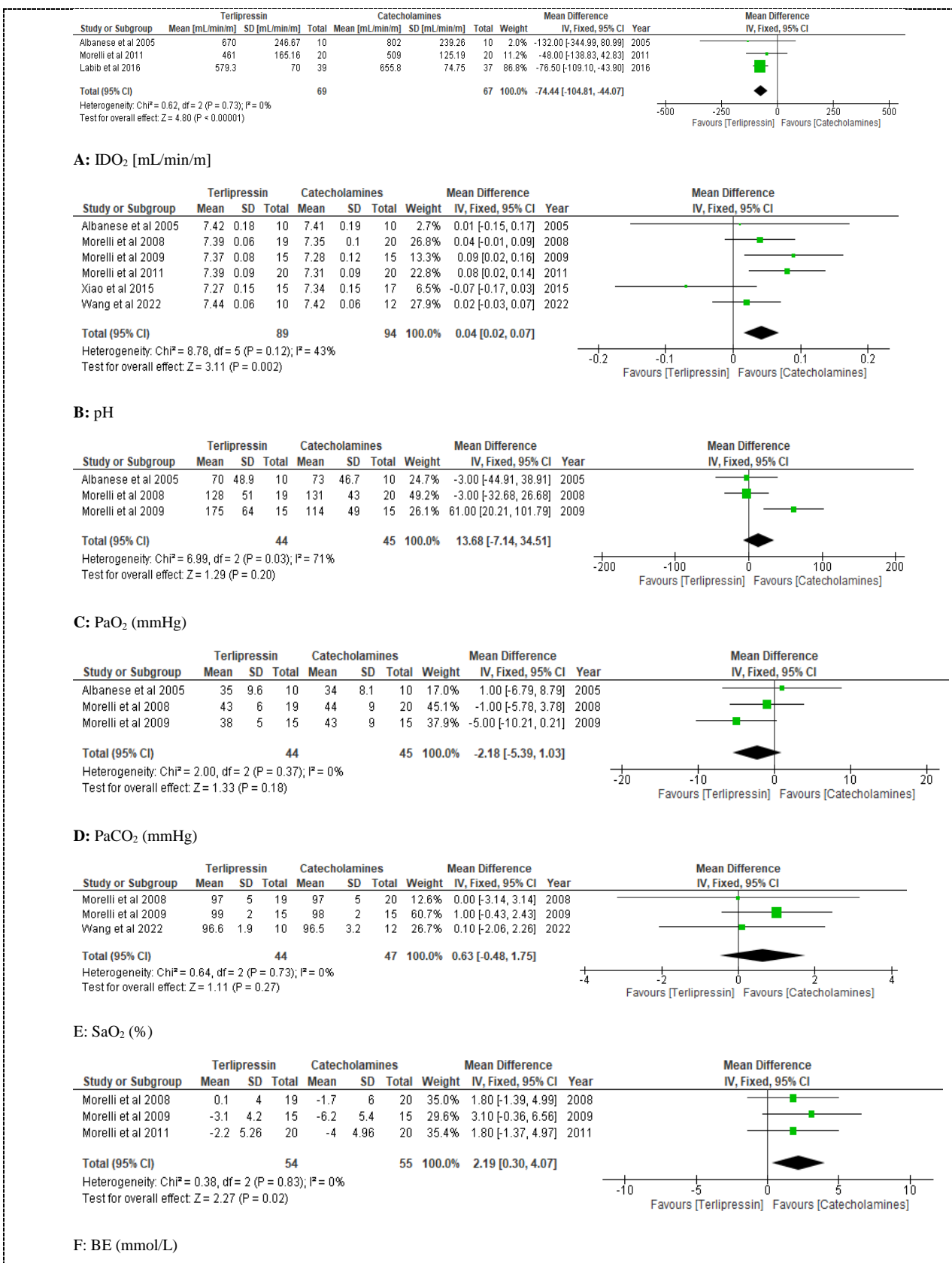
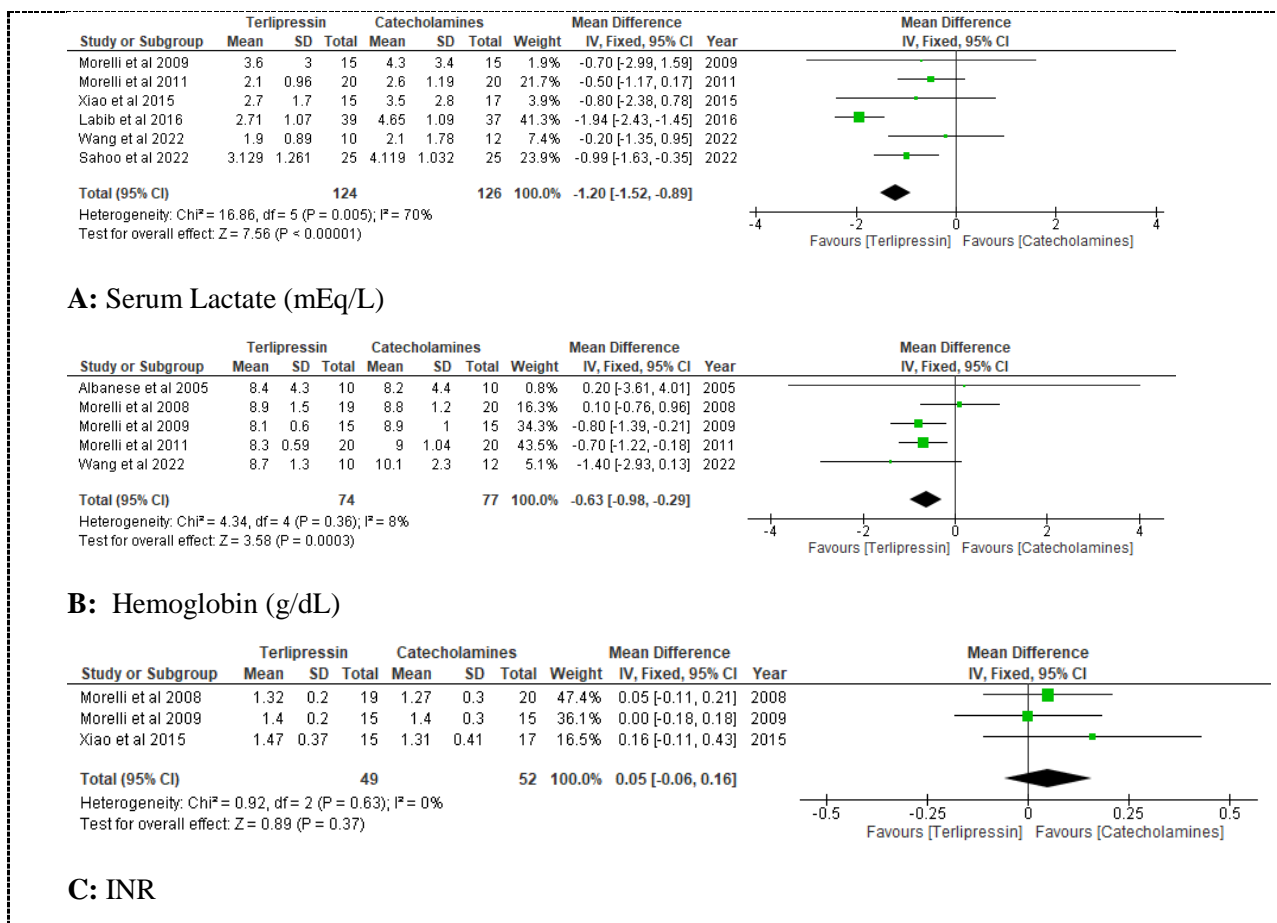


Figure 5: Oxygenation variables and blood gases: All data were obtained within the first 48h.

A: The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant decrease in IDO₂, with a MD of -74.44 and low heterogeneity (95% CI, MD = -74.44 [-104.81, -44.07]; $I^2=0\%$; $P < 0.00001$). IDO₂, oxygen delivery index; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **B:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant increase in pH, with a MD of 0.05 and low heterogeneity (95% CI, MD = 0.04 [0.02, 0.07]; $I^2=43\%$; $P = 0.002$). CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **C:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in PaO₂, with a MD of 13.68 and high heterogeneity (95% CI, MD = 13.68 [-7.14, 34.51]; $I^2=71\%$; $P = 0.20$). PaO₂, arterial partial pressure of oxygen; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **D:**

The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change PaCO₂, with a MD of -2.81 and low heterogeneity (95% CI, MD = -2.81 [-5.39, 1.03]; $I^2=0\%$, $P = 0.18$). PaCO₂, arterial partial pressure of carbon dioxide; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **E:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change SaO₂, with a MD of 0.63 and low heterogeneity (95% CI, MD = 0.63 [-0.48, 1.75]; $I^2=0\%$, $P = 0.27$). SaO₂, arterial oxygen saturation; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **F:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant decrease in BE, with a MD of 2.19 and low heterogeneity (95% CI, MD = 2.19 [0.30, 4.07]; $I^2=0\%$; $P = 0.02$). BE, arterial base excess; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference.

Biochemical variables:



3.1. Figure 6: Biochemical variables: All data were obtained within the first 48h.

A

: The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant decrease in serum lactate, with a MD of -1.20 and high heterogeneity (95% CI, -1.20 [-1.52, -0.89]; I² = 70%; P < 0.00001). CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **B:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a significant decrease in hemoglobin, with a MD of -0.63 and low heterogeneity (95% CI, MD = -0.63 [-0.98,

-0.29]; I² = 8%; P = 0.0003). CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference. **C:** The forest plot diagram shows that the addition of TP in vasodilatory shock resulted in a non-significant change in INR, with a MD of 0.05 and low heterogeneity (95% CI, MD = 0.05 [-0.06, -0.16]; I² = 0%; P = 0.37). INR, international normalized ratio; CI, confidence interval; IV, inverse variance; TP, terlipressin; MD, mean difference.

Discussion

Vasodilatory shock, also known as distributive shock, is a medical emergency, being one of the four main classifications of shock together with cardiogenic, hypovolemic and obstructive shock. As proposed by the name, systemic vasodilation occurs, limiting the blood flow to vital organs and consequently resulting in their damage. [21, 22] If failed to be promptly treated, organ damage may be permanent ending in death from multi organ failure. [23, 24, 25]

The pathogenesis of vasodilatation is multimodal, the major contributor being excessive nitric oxide (NO) production brought about by up regulation of inducible NO synthase (iNOS) and increased activity of the neuronal NOS isoform (nNOS), being mediated via the cyclic guanosine monophosphate (cGMP) pathway. [26] It has also been found that adenosine triphosphate (ATP)-sensitive potassium (K^+ ATP) channels play a critical role in the regulation of arterial vascular smooth muscle tone, as well as in the pathophysiology of catecholamine tachyphylaxis during systemic inflammation and shock states. [27] Other mechanisms include adrenoceptor desensitization and down regulation in response to high circulating levels of catecholamines. [28, 29] Not least of all, the relative vasopressin deficiency observed in septic shock has been recognized as a contributive factor to vasodilation in septic shock and serves as the basis of the emergence of vasopressin and its analogues in the management of septic shock. [6, 30]

The most common cause of vasodilatory shock is sepsis. In the United States, the

incidence of sepsis is around 750,000 cases per year with high mortality rates up to 70%, rendering it the 10th leading cause of death. [31, 32, 33]. The management of a patient with septic shock consists of antimicrobial/anti-inflammatory agents as well as early goal directed therapy. Early goal directed therapy includes fluid resuscitation, transfusion of blood and blood components and infusion of vasopressors and/or inotropes as appropriate. [34, 35].

Currently, norepinephrine as a continuous intravenous infusion is the vasopressor of choice for patients who remain hypotensive despite fluid resuscitation. Norepinephrine is a catecholamine with predominantly adrenergic properties acting to raise peripheral vascular resistance and maintain organ perfusion. On the other hand, Terlipressin was found to possess an excellent dose/response relationship in patients with septic shock. [36] The first to report Terlipressin's pressor effect were O'Brien and colleagues. They found out that bolus administration of terlipressin was followed by a marked pressor response in patients with septic shock. [37]

Terlipressin, a synthetic analog of vasopressin, has emerged as a potential therapeutic option for the management of vasodilatory shock. It exerts its effects by stimulating vasopressin V1 receptors, resulting in vasoconstriction and subsequent improvement in hemodynamic stability. Terlipressin offers several advantages over catecholamines, including a more selective vasoconstrictive action, longer duration of effect, and potentially fewer adverse effects. [38]

The comparison between terlipressin and catecholamine infusion in the management of vasodilatory shock has been the subject of increasing interest. While individual studies have provided insights into their relative efficacy, the heterogeneity of findings necessitates a comprehensive synthesis of the available evidence.^[39] A meta-analysis of randomized controlled trials (RCTs) can offer a robust evaluation of the comparative effectiveness of these interventions, helping to inform clinical decision-making.

In this meta-analysis, we included only RCTs (Randomized Controlled Trials) which compared the use of terlipressin with catecholamines in the clinical setting of septic shock. We concluded that, overall, terlipressin administration failed to decrease mortality.

Our findings concurred with a meta-analysis conducted which evaluated the efficacy and safety of terlipressin in comparison with norepinephrine for patients in septic shock and concluded that terlipressin showed no added survival benefit for septic shock patients, although it could decrease heart rate in the late phase of septic shock compared with norepinephrine without further liver and kidney injury.^[40]

Another study showed the impact of terlipressin on norepinephrine requirements in patients with late advanced septic shock refractory to catecholamines to be ineffective in reducing the mortality of patients.^[41]

On the contrary, a systematic review compared the effect of terlipressin versus norepinephrine in hepatorenal syndrome and found that norepinephrine leads to less adverse events and low mortality rates.^[42]

Our study also found out that terlipressin in vasodilatory shock resulted in a significant decrease in heart rate. This is a very valuable finding because it could mean that the development and/or progression of myocardial dysfunction associated with septic shock and tachycardia-induced cardiomyopathy could be prevented.

A systematic review, meta-analysis, and trial sequential analysis (TSA) was conducted to compare AVP and TP to conventional therapy. Systematic review included all reports of AVP/TP use in the pediatric population. They reported that the addition of AVP/TP in refractory shock resulted in a significant decrease in the HR, with a pooled MD of -12.25 beats per minute and intermediate heterogeneity (95% CI, -18.96 to -5.55 ; $I^2 = 67\%$)^[43]

We concluded that the addition of TP in vasodilatory shock resulted in a significant increase in SVRI, with a MD of 166.37 and high heterogeneity (95% CI, MD = 166.37 [$8.80, 323.93$]; $I^2 = 79\%$; $P = 0.04$). The addition of TP in vasodilatory shock resulted in a non-significant change in PVRI, with a MD of 41.38 and low heterogeneity (95% CI, MD = 41.38 [$-13.38, 96.13$]; $I^2 = 37\%$; $P = 0.14$). The addition of TP in vasodilatory shock resulted in a non-significant change in LVSWI, with a MD of 4.04 and low heterogeneity (95% CI, MD = 4.04 [$-1.10, 9.18$]; $I^2 = 0\%$, $P = 0.12$). The addition of TP in vasodilatory shock resulted in a non-significant change in RVSWI, with a MD of 0.31 and high heterogeneity (95% CI, MD = 0.31 [$-1.34; 1.97$]; $I^2 = 61\%$; $P = 0.71$).

Nevertheless, proven that after the introduction of terlipressin, significant

increases in SVRI, PVRI, LVSWI, and RVSWI were observed.^[44]

Comparable to our study, who performed a systematic review and meta-analysis of publications between 1966 and 2011 was performed. Nine trials covering 998 participants. The terlipressin group showed a significant reduction in oxygen delivery index ($-16.0 \pm 2.64\%$ vs. $-2.0 \pm 6.28\%$; $P=0.036$)^[45]

Studies which used bolus infusion of terlipressin in adults with septic shock has been consistently followed by a marked increase in urine output and creatinine clearance accompanied by reductions in heart rate and cardiac output, mainly due to a marked increase in left ventricular afterload. However, in some patients, terlipressin bolus infusion was associated with a reduction in global VO_2 .^[44, 46, 47] We also found that arterial lactate concentrations decreased following terlipressin injection in the following studies^[9, 11, 12, 14, 15, and 46].

Conversely, the results of a comparative study between terlipressin alone and dobutamine and terlipressin in septic shock patients carried showed no statistically significant changes in UOP and serum lactate levels remained constant.^[48]

This meta-analysis has a number of limitations such as differences in the terlipressin dosing regimen adopted among the included trials, types of open-label catecholamines used, timing and duration of terlipressin or control drugs, and other conventional therapies during septic shock which might lead to the observed heterogeneity and further impair the validity of our findings. Additionally, the underlying diseases and causes of septic

shock were not the same across the included studies.

Conclusion:

This meta-analysis showed no significance of terlipressin over catecholamines in reducing mortality rates, however, terlipressin is associated with reduction of HR, increase in SVRI, reduction of serum lactate level and increase in UOP.

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