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REVIEW

Vasopressin and Terlipressin in the Treatment of Vasodilatory Septic Shock: A Systematic Review *

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ABSTRACT

Background: Vasodilatory septic shock unresponsive to fluid resuscitation requires the addition of vasopressors. Catecholamines remain the first line vasopressor therapy, but treatment failure is a potential problem. Vasopressin and its analogue, terlipressin, have been used for this indication.

Objective: This systematic review aims to evaluate the effects of vasopressin and terlipressin on mortality and morbidity outcomes in patients with vasodilatory shock. Secondary outcomes include the effects of vasopressin and terlipressin on haemodynamic stability and organ function.

Method: A computerised search of MEDLINE from January 1966 till June 2010 and screening of references of relevant articles were conducted. Only prospective, randomised controlled trials comparing vasopressin or terlipressin versus standard vasopressors or placebo were included.

Results: Seven studies using vasopressin, three using terlipressin and one using both were identified. Four vasopressin trials assessing mortality and morbidity outcomes showed a trend towards benefit for mortality in adults but possibly adverse outcomes in a small paediatric study. No data was available on the long-term mortality and morbidity outcomes of terlipressin. Vasopressin and terlipressin were similar to standard vasopressors in maintaining haemodynamic parameters, while allowing a beneficial catecholamine-sparing effect. These agents also had a neutral to positive effect on organ function.

Conclusion: Vasopressin and terlipressin was comparable to conventional agents in the maintenance of haemodynamic stability and organ function in vasodilatory shock. Since morbidity and mortality data do not differentiate vasopressin and terlipressin from catecholamines, their role remains unclear. More large studies evaluating the long-term outcomes in this group of patients are required.

Keywords: distributive, sepsis, shock, terlipressin, vasodilatory, vasopressin

INTRODUCTION

Septic shock is the most common type of vasodilatory shock and is associated with high mortality rates of 28 to 50% in the intensive care unit (ICU)[1]. Aggressive fluid resuscitation is the first-line therapy for vasodilatory septic shock[1,2]. Septic shock not responding to fluid resuscitation often requires vasoactive agents to maintain haemodynamic stability. The Surviving Sepsis Campaign 2008 guidelines recommend the use of dopamine or norepinephrine as first-line vasopressors for septic shock not responding to fluid resuscitation[2]. However, treatment failure with catecholamines is not uncommon. In addition, high doses of catecholamines lead to unwanted adverse effects such as tachyarrhythmias, myocardial ischaemia, renal dysfunction, digital ischaemia and many others. Hence, alternatives for haemodynamic support have to be considered, including the use of corticosteroids and vasopressin.

There are various reasons why vasopressin has been investigated in the treatment of septic shock.

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Studies have shown that the majority of patients with septic shock present with relative vasopressin deficiency[3,4] and hence, it has been suggested that administration of exogenous vasopressin to maintain sufficient levels of serum vasopressin may have a role in maintaining haemodynamic stability in septic shock.

Vasopressin maintains blood pressure through a variety of mechanisms[5,6]. Firstly, it induces constriction of vascular smooth muscle cells through action on the V1 receptors and decreases the nitric-oxide-mediated vasodilation of septic shock. Stimulation of V2 receptors in the kidney facilitates water retention, which in turn maintains intravascular volume. Vasopressin also stimulates V3 receptors in the pituitary gland to release the adrenocorticotropic hormone, prompting cortisol release to regulate inflammation associated with sepsis.

The non-selective vasoconstriction produced by catecholamines is associated with the undesired reduction of blood flow to certain tissues[6], resulting in renal dysfunction, ileus and digital ischaemia. Unlike catecholamines, vasopressin causes organ-specific vasodilation to increase perfusion in the cerebral, pulmonary, coronary and selected renal vascular beds. This reduces pulmonary artery pressure and may preserve cardiac and renal functions. Furthermore, tolerance to vasoconstrictive effects of catecholamines may result from sepsis-induced adrenergic receptor hyposensitivity. This leads to higher doses of catecholamines required to maintain blood pressure, which in turn augments their undesirable side effects. As the increase in systemic vascular resistance (SVR) and blood pressure induced by vasopressin is independent of adrenergic receptor stimulation, resistance to vasopressin therapy has yet to be demonstrated.

Terlipressin (tricyl-lysine vasopressin) is a synthetic analogue of vasopressin which is metabolised by endopeptidases to lysine vasopressin (LVP)[7], the form of vasopressin found in pigs. The main difference is the longer duration of activity of LVP, between 4 and 6 hours, compared with the shorter-acting vasopressin, with a half-life of 6 minutes 8. Ryckwaert *et al* demonstrated an intrinsic vasoconstrictive activity with terlipressin, which is separate from its vasopressin prodrug action[9]. Since vasopressin is not available in some countries[7], terlipressin has been studied as an alternative in septic shock.

Despite the postulated advantages of vasopressin and terlipressin in treating septic shock, the clinical effects of vasopressin and terlipressin remain unclear. Pilot studies in animals and case series provided initial data for the use of vasopressin and terlipressin for this indication. This systematic review aims to evaluate the effects of vasopressin and terlipressin on mortality and morbidity outcomes in adults and children with vasodilatory septic shock. Secondary outcomes include the effects of vasopressin or terlipressin on haemodynamic stability, organ function and adverse events.

METHODS

Data Sources and Searches

A computerised search of MEDLINE from January 1966 till June 2010 was conducted using the search terms "vasopressin", "terlipressin", "septic shock", "sepsis", "vasodilatory shock" and "distributive shock". References of all peer-reviewed original articles, guidelines, consensus statements and review articles were also examined.

Study Selection

Only prospective, randomised controlled trials comparing the use of vasopressin or terlipressin versus placebo or standard vasopressors in adults and children with vasodilatory septic shock were included.

The primary outcome measures of this review were mortality rates and morbidity measures such as length of ICU and hospital stay, and days free of organ dysfunction, vasopressors and mechanical ventilation. Secondary outcomes included effects of vasopressin and terlipressin on surrogate markers of septic shock, such as haemodynamic parameters, catecholamine requirements and organ function.

Data Extraction and Analysis

Two investigators independently screened titles and abstracts and identified articles that met the inclusion criteria. After a discussion to finalise studies eligible for the review, the two investigators independently extracted data from the studies using a standard data extraction form.

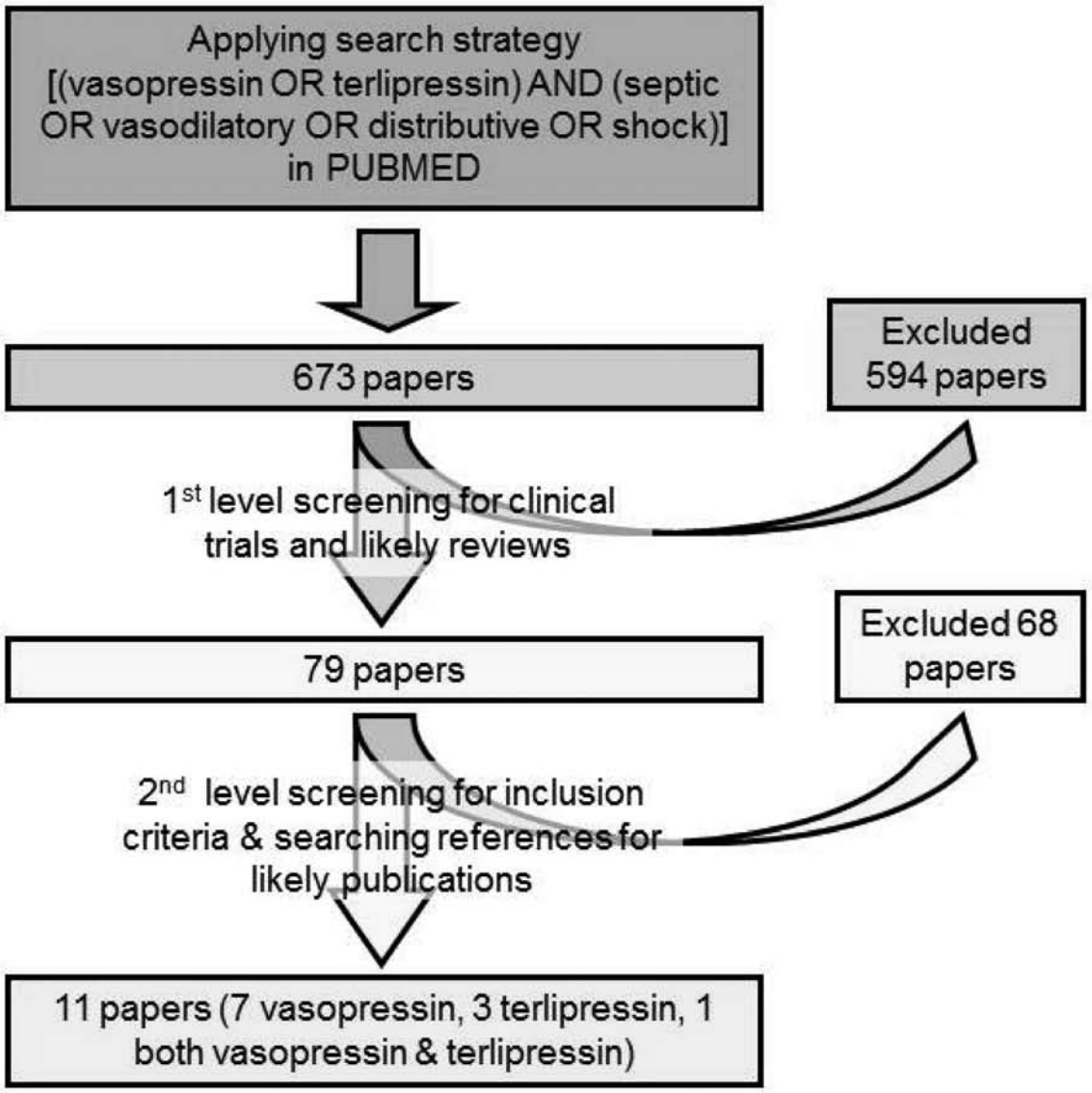


Fig. 1. Screening of papers to be included in review.

RESULTS

The search strategy yielded a total of 673 papers, of which 79 papers were either clinical trials or reviews (Fig. 1). Only 11 papers fulfilled the inclusion criteria, of which 7 of them investigated the use of vasopressin[10–16], 3 involved terlipressin[17–19] and 1 used both[20]. Most studies included patients with vasodilatory septic shock requiring vasopressors and compared the effect of adding vasopressin[10–16] or terlipressin[18,19] versus either placebo with open-label vasopressors[10,11,16] or continuing with standard vasopressors[12–15,18,19]. This is with the exception of 2 studies[17,20], which involved catecholamine-naïve patients and compared vasopressin or terlipressin with standard vasopressors such as norepinephrine. The characteristics of the studies are summarised in Table 1.

Table 1. Characteristics of studies included in review.

Author, Year	Study Design	Subjects	Treatment groups
Argenziano, 1997[10]	Single centre, prospective, randomised, controlled, double-blind trial	Adults with vasodilatory shock after cardio-pulmonary bypass requiring norepinephrine of at least 8 µg/min	Vasopressin 0.1U/min vs placebo
Malay, 1999[11]	Single centre, prospective, randomised, controlled, double-blind trial	Adults with septic shock resistant to fluids and requiring vasopressors (dopamine >3µg/kg/min and any dose of norepinephrine and/or phenylephrine)	Vasopressin 0.04U/min vs placebo
Patel, 2002[12]	Multicentre, prospective randomised, controlled, double-blind trial	Adults with severe septic shock resistant to fluids and requiring high dose vasopressors High dose vasopressors was defined as norepinephrine dose (µg/min) plus epinephrine dose (µg/min) plus dopamine dose divided by 4 (µg/kg/min) >5 for at least 1 hour	Vasopressin 0.01–0.08U/min vs norepinephrine 2–16µg/min
Dünser, 2003[13]	Single centre, prospective, randomised, controlled, open-label trial	Adults with vasodilatory shock secondary to cardiovascular surgery or systemic inflammatory response with and without sepsis, resistant to fluids and requiring norepinephrine of at least 0.5µg/kg/min	Vasopressin 4U/h and norepinephrine vs norepinephrine alone Norepinephrine was titrated to keep MAP >70mmHg to a maximum of 2.26µg/kg/min
Lauzier, 2006[14]	Multicentre, prospective, randomised, controlled, open-label trial	Adults with septic shock and receiving vasopressors for <12 hours	Vasopressin 0.04–0.20U/min vs norepinephrine 0.1–2.8µg/kg/min
Russel , 2008[15]	Multicentre, prospective, randomised, controlled, double-blind trial	Adults with septic shock resistant to fluids and requiring norepinephrine dose of at least 5µg/min	Vasopressin 0.01-0.03 U/min vs norepinephrine 5-15 µg/min
Choong, 2009[16]	Multicentre, prospective, randomised, controlled, double-blind trial	Children aged 1 month to 17 years with vasodilatory shock despite 40ml/kg of fluids and requiring vasopressors (dopamine of at least 10µg/kg/min or any dose of epinephrine/norepinephrine/ phenylephrine)	Vasopressin 0.0005–0.002U/kg/min vs placebo
Albanese, 2005[17]	Single centre, prospective, randomised, controlled, open-label trial	Catecholamine-naïve adults with severe septic shock (MAP <60mm Hg) and multiorgan dysfunction (≥2 organs affected) failing fluid expansion (no corticosteroids)	Terlipressin (1mg at baseline, +/- 1mg after 20 minutes) vs norepinephrine (0.3mcg/kg/ min – no maximum)
Morelli, 2008[18]	Single centre, prospective, randomised, controlled, open-label trial	Adults with septic shock and catecholamine-dependence (norepinephrine requirements >/=0.9mcg/kg/min to maintain a MAP of 65–75 mm Hg)	Terlipressin 1mg (1 dose) [n = 20] vs terlipressin 1mg (1 dose) + dobutamine (3–20 mcg/kg/min) [n = 19] vs norepinephrine (dose not defined) [n = 20]
Yildizdas, 2008[19]	Single centre, prospective, randomised, controlled, open-label trial	Children aged 1 month to 13 years with septic shock (sepsis with organ hypoperfusion or dysfunction) refractory to fluids and to high doses of catecholamines ("high" not defined)	Terlipressin (20mcg/kg/min Q6H up to 96 hours) vs standard treatment
Morelli, 2009[20]	Single centre, prospective, randomised, controlled, open-label trial	Catecholamine-naïve adults with septic shock (MAP <65mm Hg) failing volume resuscitation	Vasopressin (0.03 units/min) vs terlipressin (1.3mcg/kg/ min) vs norepinephrine (15 mcg/min)

Because of the heterogeneity of the patient populations, treatment strategies, study designs and types of outcome measures, pooled estimates of outcome measures could not be done. Instead, a qualitative assessment of the data was performed.

Primary Outcomes

Mortality and morbidity outcomes were assessed in 5 trials (Table 2). Four trials compared the use of vasopressin against norepinephrine[14,15] or placebo[11,16], of which 3 were in the adult population[11,14,15] and 1 in paediatrics[16]. A solitary study compared terlipressin versus no terlipressin in children with catecholamine-resistant septic shock[19].

Malay *et al* randomly assigned patients with septic shock requiring catecholamine vasopressors to receive either vasopressin 0.04 units/min (n=5) or placebo (n=5) for 24 hours[11]. Haemodynamic parameters and catecholamine requirements were evaluated at the end of 24 hours. Two patients in the placebo group died, while all patients in the vasopressin group survived the 24-hour study period. Since mortality and morbidity was not a primary objective of this study, statistical analysis was not performed.

Another study was conducted in a similar patient population by Lauzier *et al*, who randomly allocated patients to receive either open-label vasopressin (n=13) or norepinephrine (n=10) for 48 hours[14]. Outcomes measured included haemodynamic parameters, catecholamine requirements and organ function at specific time points throughout the study period. The ICU mortality rate was 23.1% and 30% in the vasopressin and norepinephrine group respectively (p=1.00).

In the paediatric population, Choong *et al* conducted a multicentre, randomised double-blind trial where children with vasodilatory shock received either low dose vasopressin at 0.0005 to 0.002 unit/kg/min (n=33) or placebo (n=32) in addition to open-label vasopressors[16]. In contrast to the studies in adult populations, there was a trend towards increased 30-day mortality in the vasopressin group when compared to placebo (30.3% and 15.6% respectively, P=0.24). There were no significant differences in morbidity outcomes such as days free of organ failure, vasopressors and ventilator, and length of ICU stay between both groups (Table 2).

Yildizdas *et al* randomised 58 paediatric intensive care patients with septic shock refractory to fluids and high-dose catecholamines to either the open-label terlipressin (n = 30) or control arms (n = 28)[19]. In this study, boluses of terlipressin 20mcg/kg were given every 6 hours up to a total of 96 hours. Length of ICU stay and ICU mortality rates were recorded. Mean days in ICU was 13.4 days in the terlipressin group, versus 20.2 days in the control group ($p \leq 0.01$). However, mortality was not significantly different between the groups, with 20 patients each from both groups not surviving. Interestingly, when the patients were stratified for survival, the non-survivors on terlipressin had a mean ICU stay of 10.4 days, compared with the non-survivors in the control arm with only 6.2 days; i.e. terlipressin seemed to prolong the lives, albeit temporarily, of these non-survivors.

However, there are drawbacks with the previous studies, including small sample sizes, short duration of follow-up and insufficient power to evaluate mortality rates with vasopressin or terlipressin use. The VASST study was a multicentre, randomised, controlled, double-blind trial designed to assess morbidity and mortality outcomes in the adult population[15]. Patients with septic shock and receiving norepinephrine ≥5μg/min were randomised to receive either low dose vasopressin at 0.01 to 0.03 units/min (n=396) or norepinephrine at 5 to 15 μg/min (n=382) in addition to open-label vasopressors. There was no significant difference between vasopressin and norepinephrine groups in the 28-day mortality rates (35.4% and 39.3% respectively, p=0.26) and 90-day mortality (43.9% and 49.6% respectively, p=0.11).

However, an *a priori* subgroup analysis showed a statistically significant lower mortality rate at 28 days (26.5% versus 35.7%, p=0.05) and 90 days (35.8% versus 46.1%, p=0.04) in the vasopressin group compared to the norepinephrine group in patients with less severe septic shock (patients with initial norepinephrine requirements of 5–14mcg/kg/min). Morbidity outcomes measured in the VASST trial included days alive and free of organ dysfunction during the first 28 days, days alive and free of vasopressor use, mechanical ventilation or renal replacement therapy, length of ICU and hospital stay. These morbidity outcomes were generally comparable between both vasopressin and norepinephrine group as presented in Table 2.

Table 2. Primary outcomes evaluated.

Author, Year	Mortality Outcomes	Results	Morbidity Outcomes	Results
Russell, 2008[15]	28-day mortality	35.4% vs 39.3% (P = 0.26) Odds Ratio 0.88	Days alive and free of any organ failure during the first 28 days	0 in both groups (P = 0.14)
	90-day mortality	43.9% vs 49.6% (P = 0.11) Odds Ratio 0.81	Days alive and free of vasopressor use, mechanical ventilation or renal replacement therapy	19 vs 17 (P = 0.61) 8.5 vs 6 (P = 0.24) 25 vs 23 (P = 0.64)
			Length of ICU stay Length of hospital stay	15 vs 16 (P = 0.14) 27 vs 26 (P = 0.23)
			Overall rates of serious adverse events Rate of cardiac arrest Rate of digital ischaemia	10.3% vs 10.5% (P = 1.00) 0.8% vs 2.1% (P = 0.14) 2.0% vs 0.5% (P = 0.11)
Lauzier, 2006[14]	ICU Mortality	23.1% vs 30% (P = 1)	Nil	Nil
Malay, 1999[11]	Death at 24 hours	0% vs 40% (P value not reported)	Nil	Nil
Choong, 2009[16]	30-day mortality	30.3% vs 15.6% (P = 0.24)	Organ failure–free days	22.0 vs 25.5 days (P = 0.11)
			Vasoactive-free days	25.2 vs 27.5 (P = 0.13)
			Ventilator-free days	16.5 vs 23.0 (P = 0.15)
			Length of PCCU stay	8.0 vs 8.5 days (P = 0.93)
Yildizdas, 2008[19]	PICU mortality	67.5% vs 71.4% (P = 0.1)	Ventilator requirements	73.3% vs 82% (P = 0.2)
			Duration of mechanical ventilation	4.4 vs 4.8 days (P = 0.2)
			Length of PICU stay	13.4 vs 20.2 days (P = 0.01)
			Length of PICU stay (non-survivors)	10.4 vs 6.2 days (P = 0.04)

Secondary Outcomes

Secondary outcomes included surrogate indicators of septic shock such as haemodynamic outcomes, organ function and adverse events. These outcomes were reported in 10 papers, which comprised of all the short-term randomised trials for vasopressin and terlipressin[10–14,16–20].

Haemodynamic Parameters

Among the 7 adult trials involving vasopressin[10–14,16,20] and 2 using terlipressin with and without dobutamine[17,18], haemodynamic outcomes were measured at 15 minutes[10], 1 hour[11,13,14,16], 2 hours[18], 4 hours[12,13,17], 6 hours[14,17], 8 hours[11], 12 hours[13,14,20], 24 hours[11,13,14,20], 36 hours[20], and 48 hours[13,14,20] after initiating the study drug. These haemodynamic outcomes included mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), SVR and catecholamine requirements. Both vasopressin continuous infusion and terlipressin boluses significantly improved MAP and SVR, but decreases HR and CI compared to baseline. These effects were similar to that of standard vasopressors, except that the increase in SVR observed with terlipressin was above and beyond that with norepinephrine[17,18]. Concurrent dobutamine administration, albeit at fairly high doses exceeding 20mcg/kg/min, was efficacious in overcoming this effect[18].

In the paediatric population, Yildizdas *et al* measured MAP and HR for up to 48 hours after terlipressin or standard therapy, and found improvements in both parameters when compared to baseline[19]. This was despite there being no measurements of cardiac output which could have helped to guide appropriateness of terlipressin use in these patients. Choong *et al* only reported

improvement of MAP 1 hour post initiation of vasopressin, which was again comparable between vasopressin and placebo[16].

The TERLIVAP trial, which compared continuous infusions of vasopressin, terlipressin or norepinephrine in catecholamine-naïve septic patients, found essentially no difference between all three drugs in elevating MAP and maintaining the CI[20]. The only significantly different haemodynamic parameter between the 3 groups was the reduced HR with terlipressin infusion, compared to the other 2 drugs and to the baseline.

Catecholamine Requirements

Use of vasopressin was associated with significantly reduced catecholamine requirements in adults[12–14]. Patel *et al* reported a reduction in the dose of norepinephrine infusion from 25.0mcg/min prior to the start of the study to 5.3mcg/min ($P<0.001$) at 4 hours in the vasopressin group while maintaining mean arterial pressure[12]. Dünser *et al* and Lauzier *et al* both showed that patients receiving vasopressin had significantly lower norepinephrine requirements compared to baseline, as well as compared to patients receiving norepinephrine[13,14].

Morelli *et al* reported a reduction in norepinephrine requirements in the terlipressin with and without dobutamine groups compared to baseline and also to the comparator group of norepinephrine[18]. The TERLIVAP trialists reported increased open-label norepinephrine requirements in the vasopressin and norepinephrine groups[20]; which was the converse of the terlipressin group which saw a significantly lower ($p\leq0.02$) norepinephrine requirements throughout the study period of 48 hours and beyond. This was, however, countered by the need for more dobutamine during the first 6 hours of terlipressin treatment ($p<0.05$).

Catecholamine requirements were reported in the paediatric terlipressin study as being no different between the treatment and control groups[19]. However, this effect may not be significant as this trial had 2 drawbacks, i.e. doses of catecholamines had already been maximised in this group of patients with refractory septic shock; and the catecholamines used in this trial were dopamine, dobutamine and epinephrine, norepinephrine being unavailable in Turkey.

Organ Function

Renal function was assessed using urine output[12,14,16,17,20], serum creatinine[11,13,16,19,20], blood urea nitrogen (BUN)[19] or creatinine clearance[12,14,18]. Vasopressin appeared to improve renal function by increasing urine output[12,14,16] and creatinine clearance[12,14] compared to norepinephrine. However, these benefits were not observed in other studies. Terlipressin had a variable neutral to positive effect on urine output, BUN and serum creatinine[17–19] when compared to norepinephrine or control. Although the increase in urine output was comparable between the terlipressin, vasopressin and norepinephrine groups in the TERLIVAP trial[20], serum creatinine levels were significantly higher with norepinephrine compared to terlipressin and vasopressin.

Effects on gastric and hepatic function were measured using gastric perfusion[13,14,20], and bilirubin concentration[13,14,16,18,20] and transaminases levels[13,14,18–20]. Most of the studies reported no significant differences, with the exception of 2 studies. Dünser *et al* reported a significantly higher serum bilirubin levels in the vasopressin group compared to the norepinephrine group[13]. The TERLIVAP trial showed that patients given terlipressin maintained a low bilirubin level throughout the study, in contrast to significant rises of 1.7 and 2.4 times the baseline bilirubin in the vasopressin and norepinephrine group respectively.

Respiratory indices such as arterial lactate concentration[13,14,16,19,20], PaO_2/FiO_2 ratio[13,14,19,20], oxygen delivery index (DO_2I) and oxygen consumption index (VO_2I)[13,14,17,18,20], were also reported. Vasopressin generally improved arterial lactate concentration and PaO_2/FiO_2 ratio compared to baseline[13,14], similar to standard vasopressors; but had variable effects on DO_2I. The use of intravenous terlipressin boluses of 1mg (or 20mcg/kg/min in paediatrics) was associated with a drop in DO_2I and VO_2I, but which did not correspond with clinical conditions. Interestingly, when terlipressin was given as a continuous infusion of 1.3mcg/kg/hour, this effect was not observed [20].

Adverse Effects

The reduced catecholamine requirement seen with vasopressin was associated with lower incidence of adverse effects such as new onset tachycardia[15,20] and cardiac arrest[15] with norepinephrine use.

On the other hand, Dünser *et al* and Russell *et al* reported a higher incidence of new ischaemic skin lesions and digital ischaemia respectively with the addition of vasopressin compared to norepinephrine alone, though both did not reach statistical significance[13,15].

DISCUSSION

Most of the clinical trials evaluating vasopressin and terlipressin were small and short-term in nature, investigating mainly the surrogate markers of septic shock such as haemodynamic stability, organ function and adverse events. The addition of vasopressin or terlipressin appeared to maintain haemodynamic parameters similar to standard vasopressors. This led to significantly reduced catecholamine requirements and lower incidence of adverse effects such as new onset tachycardia with norepinephrine use. Some studies[12,14,16] suggested an improvement in renal function (including urine output and creatinine clearance) with vasopressin use, while effects on other organ functions were comparable among vasopressin, terlipressin and standard vasopressors.

As these trials were not designed to assess long-term outcomes such as morbidity and mortality, conclusions regarding mortality and morbidity benefits of vasopressin in adult patients with vasodilatory septic shock largely depended on the results of the VASST trial[15]. A meta-analysis, which is usually useful in extrapolating data from studies involving small sample sizes, could not be performed due to the heterogeneity of subject populations, severity of sepsis in the subject populations, methods including the dose, administration and duration of vasopressin or terlipressin used, concurrent vasopressor treatment, and outcome measures reported in the studies, as it would not have yielded meaningful results and possibly lead to misleading conclusions. The heterogeneity of the various trials could be seen from the varying rates of mortality, ranging from 0%[11] to 20%[19], which probably reflects the range of sepsis severity in the patients recruited for the trials, as well as the resources and treatments available for these patients. In several of the studies, the researchers were hampered by the lack of resources including drugs (norepinephrine was not available in some European countries[20]) and monitoring devices[19]; in fact, terlipressin was tried as an alternative to vasopressin precisely because vasopressin was not available in those countries at that time[17–19].

There were a few limitations of the VASST trial, including the severity of sepsis at the point of vasopressin initiation, the exclusion of patients with poor cardiovascular conditions and the dose of vasopressin used, which limits the applicability of the results to general practices.

The VASST trial showed no significant difference in mortality and morbidity outcomes between the vasopressin and norepinephrine group, possibly attributable to a better than expected mortality rate in the study population, as the study was initially powered to detect an absolute difference in mortality rate of 10% from an expected 60%. Patients in the trial required a fairly low mean dose of norepinephrine (0.27 to 0.28 μg/kg/min) at randomisation, suggesting that the study population was less critically ill. Moreover, as vasopressin may be associated with cardiovascular adverse events, exclusion of patients with acute coronary syndromes or heart failure may have provided more favourable results in the vasopressin group.

Interestingly, the trial also showed a significantly lower mortality rate in the vasopressin group compared to the norepinephrine group in patients with less severe septic shock but not in patients with more severe septic shock. This was in contrast with the authors' secondary hypothesis that the beneficial effects of vasopressin would be more pronounced than those of norepinephrine in patients with more severe septic shock. One possible reason was the low dose of vasopressin at 0.01 to 0.03 units/min used in the trial, as patients with more severe septic shock might have required higher doses of vasopressin to maintain haemodynamic stability.

In the paediatric population, the addition of vasopressin appeared to double the 30-day mortality rate compared to placebo[16], although this did not reach statistical significance. The authors mentioned several reasons for the lack of clinical benefit of vasopressin use in the study, including insufficient dose of vasopressin used and inappropriate timing of vasopressin initiation. The difference in mortality rate was also thought to be due to chance, as there were higher incidences of non-septic causes of vasodilatory shock in the

vasopressin group. Furthermore, the study involved a small sample size (n=65), which makes it difficult to make any conclusion regarding the effect of vasopressin on paediatric mortality outcomes. Terlipressin use for refractory septic shock in the paediatric population[19] was non-conclusive in deciphering ICU mortality benefits and had some effect in reducing ICU stay in survivors. However, as with most of the other trials, small sample sizes were potential confounders.

For now, the mortality and morbidity benefit of vasopressin and terlipressin in both the adult and paediatric population still remains largely unknown and the group of patients likely to have long-term benefit is still uncertain. In addition, there are several other issues arising from vasopressin use that have yet to be resolved. Uncertainty exists regarding the doses and methods of administration, as well as when to initiate vasopressin and its analogues.

Dose and Administration

At the moment, the effective dose of vasopressin, as well as the dose and route of administration of terlipressin, for septic shock, is also not optimised. The Surviving Sepsis guidelines currently suggest a vasopressin dose of 0.03units/min (which is the dose used in VASST trial), but higher doses may be required for more severe septic shock, above and beyond the physiologic replacement doses[2].

The VASST trialists justified the dose of vasopressin used in the trial based on a case series[21] that reported an increase in cardiac arrests with vasopressin doses >0.04 units/min. However, these results were not replicated in a randomised, controlled, open-label trial[22] that compared 2 doses of vasopressin (0.033 versus 0.067 units/min) in patients with vasodilatory shock requiring norepinephrine doses >0.6 µg/kg/min, with the higher dose being more effective in restoring cardiovascular function without significantly increasing the incidence of cardiac events. Nevertheless, it should be noted that the patients included in both studies were relatively small in numbers and larger randomised, controlled trials are still required to conclude on the efficacy and safety of higher doses of vasopressin.

The dose of terlipressin, on the other hand, is even less well documented. Due to a long elimination half-life of 50 to 70 minutes and duration of activity of 4 to 6 hours[23], terlipressin is usually dosed as an intravenous bolus of 1 to 2 mg every 4 hours[8] for its licensed indication of acute variceal bleeding. Albanese *et al*[17] and Morelli *et al*[18] proceeded with a limited number (ranging from 1 to 2 doses) of terlipressin boluses of 1 mg while Yildizdas *et al*[19] used up to 17 doses of 20mcg/kg boluses given 6 hourly. However, a more recent paper by Morelli *et al*[20] used terlipressin as a continuous intravenous infusion of 1.3mcg/kg/hour to avoid vasoconstriction, subsequent drop in cardiac index and mixed venous oxygen saturation associated with high doses of bolus terlipressin.

Dobutamine, as a strategy to counter the reduction of cardiac index, was found to be effective mainly at high doses of 20 +/- 8 mcg/kg/min; however, this would open the patient to the deleterious effects of high catecholamine doses that terlipressin use was intended to spare. As such, the combination of dobutamine with terlipressin is probably unwarranted.

Up to now, there is no data on the long-term use of terlipressin, as all the studies have so far been limited to a maximum of 96 hours. The long term safety and efficacy of terlipressin use for this group of patients is as yet unknown. However, certain European groups are actively studying this issue[26] and there may be new data available to resolve this uncertainty within the next few years.

Timing of Initiation

Another issue lies with the timing of administration of vasopressin and terlipressin, i.e. whether these drugs should be initiated early in the treatment of septic shock or as an add-on in septic shock refractory to standard vasopressors.

The presence of hypotension and hypovolaemia stimulates the release of endogenous arginine vasopressin, but this vasopressin response in septic shock is biphasic[3,4]. During the first few hours of septic shock, serum vasopressin concentrations increase rapidly to help maintain blood pressure and organ perfusion. Hence, it is unknown whether initiating vasopressin early in septic shock may be helpful in restoring haemodynamic stability. Thereafter, serum vasopressin concentrations dramatically decline to physiologically normal levels. This is known as relative vasopressin deficiency, since serum vasopressin concentrations are expected to be high during hypotension under normal circumstances. Unfortunately, the exact time when this relative vasopressin

deficiency occurs varies between patients, making it difficult to determine the best time to initiate vasopressin. Although correlation between serum vasopressin levels and haemodynamic stability has been demonstrated, uncertainty exists as to exactly when or whether the use of serum vasopressin levels to guide vasopressin therapy is beneficial[24].

Most studies did not investigate the use of vasopressin as a first-line therapy for the treatment of vasodilatory septic shock. Patients included in the studies were already on vasopressors before being randomised in the trials to receive additional vasopressin versus placebo or continue with standard vasopressors such as norepinephrine. This is in accordance with the Surviving Sepsis Campaign 2008 guidelines, which recommend that vasopressin should not be used as the initial vasopressor in septic shock but be added on to norepinephrine to achieve effects similar to norepinephrine alone[2]. However, the dose of norepinephrine to serve as the threshold to add on vasopressin was not suggested. A cohort study found that norepinephrine requirements >0.5μg/kg/min was an independent risk factor for death from advanced vasodilatory shock treated with vasopressin[25]. Hence, it has been suggested that initiation of vasopressin before norepinephrine doses exceed 0.6 μg/kg/min may improve mortality outcomes.

The 4 studies using terlipressin varied widely in the types of patients recruited. These ranged from catecholamine-naïve patients and the refractorily hypotensive patients despite fluids and catecholamines. From these small studies, terlipressin seems to have some positive effect in both catecholamine-naïve (i.e. when used as first line) and catecholamine-refractory patients (as add-on therapy). The current role of terlipressin in septic shock seems to be as an add-on in refractory patients when alternatives are unavailable (such as in some European countries where vasopressin is not registered). However, larger trials with better power will hopefully provide a conclusion to this.

A European study group is currently conducting the TErlipressin in Septic Shock Trial, TESST-1, a randomised controlled trial similar to the VASST study, aiming to evaluate the safety and efficacy of terlipressin infusion compared with norepinephrine in the first line treatment of septic shock after fluid resuscitation[26]. We await the results of this study with great anticipation.

CONCLUSION

Catecholamines remain the gold standard for the treatment of vasodilatory septic shock. The evidence for vasopressin analogues is still sparse, but there seems to be a definite role for vasopressin analogues as add-on therapy. There is promising short-term data for vasopressin and terlipressin in terms of surrogate markers of septic shock. Vasopressin and terlipressin seem to be comparable to conventional agents in the maintenance of haemodynamic stability and organ function in vasodilatory shock. There also seems to be a catecholamine-sparing effect which may be useful.

However, as most trials were carried out for a very limited duration, the long-term benefits for vasopressin and terlipressin in vasodilatory shock remain unclear. Currently available mortality and morbidity data do not differentiate vasopressin and terlipressin from catecholamine vasopressors. Vasopressin and terlipressin seem to be useful as an add-on therapy to standard vasopressors but the current small trials with short term data do not justify their use as first-line therapy in the treatment of vasodilatory septic shock.

Additionally, the dosages used in the vasopressin and terlipressin trials were very heterogeneous. More data is needed for the optimal dosing regimen and timing of administration of vasopressin and terlipressin for septic shock, as well as the long-term outcomes and benefits for both drugs.

Given the choice of vasopressin or terlipressin in this patient population, it would be prudent to select vasopressin as the agent of choice for add-on to conventional catecholamine vasopressors in supporting septic shock, due to the larger body of evidence for this drug. The selection of terlipressin should only be in cases where vasopressin is not available, or within the auspices of a clinical trial.

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