Terlipressin Facilitates Transport of Septic Patients Treated with Norepinephrine

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Abstract

Background: Transport of hemodynamic unstable septic patients for diagnostic or therapeutic interventions outside the intensive care unit is complex but sometimes contributes to increasing the chance of survival.

Objectives: To report our experience with terlipressin treatment for facilitation of transport to distant facilities for diagnostic or therapeutic procedures in septic patients treated with norepinephrine.

Methods: We conducted a retrospective analysis of the records of our ICU, identifying the patients with septic shock who required norepinephrine for hemodynamic support.

Results: Terlipressin was given to 30 septic shock patients (15 females and 15 males) who were on high dose norepinephrine (10 µg/min or more) in order to facilitate their transport outside the ICU. The dose of terlipressin ranged from 1 to 4 mg, with a mean of 2.13 ± 0.68 mg. The dose of norepinephrine needed to maintain systolic blood pressure above 100 mmHg decreased following terlipressin administration, from 21.9 ± 10.4 µg/min (range 5–52 µg/min) to 1.0 ± 1.95 (range 0–10) ($P < 0.001$). No patients required norepinephrine dose adjustment during transport. No serious complications or overshoot in blood pressure values were observed following terlipressin administration. Acrocyanosis occurred only in eight patients receiving more than 1 mg of the drug. The overall mortality rate was 50%.

Conclusions: Our data suggest that terlipressin is effective in septic shock. Because it is long-acting and necessitates less titration it might be indicated for patient transportation.

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Septic shock is a life-threatening condition with a mortality rate above 50%. The main principles of patient management include identification and treatment of the source and the invading organism, intervention in the pathophysiology of severe sepsis (e.g., activated protein C, tight glucose control, corticosteroids), and maintenance of vital organ perfusion. Support for the failing cardiovascular system is a cornerstone in the therapy of septic shock [1].

The recommended drugs for this support are dopamine, epinephrine, norepinephrine, dobutamine, and phenylephrine, given alone or in combination. All these drugs have sympathetic activity. The principle difference between them is their affinity for α-1, α-2, β-1 and β-2 receptors. They have a very short half-life, so that discontinuation of treatment, even for a short time, can result in acute hemodynamic deterioration and death.

ICU = intensive care unit

Recently, terlipressin, a long-acting vasopressin analogue, was successfully used to provide hemodynamic support in adult patients with catecholamine-resistant septic shock. That report concluded with the recommendation that terlipressin be used in patients with norepinephrine-resistant septic shock [2]. No study has demonstrated the efficacy and safety of terlipressin in the treatment of septic unstable patients who needed to be transported outside the intensive care unit. In the present paper we present the results of a retrospective review of our experience over a 4 year period in administering terlipressin to septic shock patients who needed to be transported.

Patients and Methods

The Department of Critical Care at the Soroka University Hospital has a data collection system in a locally developed database (TOREN) that allows search by demographic variables, disease, syndrome, intervention, medication, complication, type of surgery, length of stay, and mortality [3]. We identified all patients treated with terlipressin for septic shock over a period of 4 years. From this population we selected the patients who needed to be transported outside the ICU. The study population was identified in the first stage by a computer search after which the medical records were reviewed to complete the study database. The recorded variables included the indication for terlipressin, the hemodynamic response, the reduction in norepinephrine dosage, adverse reactions to the drug, and outcome.

The statistical analysis was performed using the Epi Info 3:3™ Statistic Package (Centers for Disease Control, Atlanta, USA). The results are expressed as mean ± standard deviation.

Results

Thirty patients with the diagnosis of septic shock who required norepinephrine for hemodynamic support and needed transportation outside the ICU were identified and comprised the study population [Table 1]. The mean age of the patients was 64.2 ± 11.3 years (range 33–87). Fifteen patients were males and 15 females. The mean APACHE 2 was 23.3 ± 5.1 (range 19–28). Sixteen patients were transported from the ICU for computed tomography scans, one for a magnetic resonance imaging scan and one for nuclear imaging. Twelve patients were transported to the operating room for surgery.

Table 1. Summary of data

No. of patients	30	*P*
Male:Female	15:15	
Age (yrs)	63 ± 12.6 (33–88)	
APACHE 2	23.3 ± 5.1 (19–28)	
Norepinephrine dose before terlipressin injection (µg/min)	21.9 ± 10.4 (5–52)	<0.001
Norepinephrine dose after terlipressin injection (µg/min)	1.0 ± 1.95 (0–10)	
Terlipressin dose (mg)	2.13 ± 0.68 (1–4)	
Terlipressin time maximal effect (min)	15.0 ± 10.0 (5–29)	

Data expressed as mean ± SD (range)
APACHE = Acute Physiologic Age Chronic Health Evaluation

Terlipressin was administered as a bolus of 1–4 mg (for higher dose of norepinephrine we used higher dose of terlipressin). The mean dose of terlipressin was 2.13 ± 0.68 mg (range 1–4 mg). The dose of norepinephrine needed to maintain systolic blood pressure above 100 mmHg was reduced following terlipressin administration from 21.9 ± 10.4 µg/min (range 5–52 µg/min) to 1.0 ± 1.95 (range 0–10) ($P < 0.001$). The time that elapsed from terlipressin injection to the final reduction in the norepinephrine dose was 15.0 ± 10.0 minutes (range 5–29 min). The transport time was 2.1 ± 1.0 hours (range 0.5–4 hours). The dosage of norepinephrine was kept without adjustment for 3.5 ± 1.0 hours. No patients required adjustment of the norepinephrine dose or second bolus of terlipressin during their stay outside the ICU.

No serious complication or overshoot in blood pressure values was observed following terlipressin administration. Acrocyanosis was observed in eight patients. It is noteworthy that this complication was seen only in patients receiving more than 1 mg of terlipressin. The overall mortality rate was 50%.

Discussion

The provision of hemodynamic support in septic shock is a major challenge in intensive care medicine. The Society of Critical Care Medicine recommends the use of norepinephrine, epinephrine, phenylephrine, dobutamine, dopamine or a combination of these drugs to achieve this goal. Transport of critically ill patients is a difficult but essential part of the management of critically ill patients. As part of their workup or treatment, many patients with septic shock undergo diagnostic procedures or therapeutic interventions outside the ICU, including CT scans, MRI scans, nuclear medicine imaging, or surgery. At times intensivists decide not to take the risk of transporting a hemodynamically unstable patient from the ICU for an imaging procedure even though diagnosis or drainage of the source of sepsis might increase the chance of survival. Sometimes septic patients require extended surgical interventions that cannot be performed in the ICU, so they have to be transported to the operating room despite their unstable hemodynamic condition. The complication rate associated with the intra-hospital transport of septic patients ranges between 40 and 60% [4].

Stimulation of vasopressin V1-receptors in the brain induces vasoconstriction and enhances the effects of norepinephrine on vasculature [5]. Septic shock is associated with vasopressin deficiency and hypersensitivity to its exogenous administration [6]. There have been some reports on the use of vasopressin in septic shock, but its limited use has never showed any survival benefit over other vasopressors. [7]. Terlipressin is a potent vasopressin analog with a more selective vasoconstrictor effect than vasopressin [8] and a prolonged vasopressor effect that lasts for close to 5 hours.

Terlipressin demonstrates second-order pharmacokinetics, with an alpha half-life of 8–9 minutes and a beta half-life of 51–66 minutes. Its volume of distribution is 0.6–0.9 L/kg [9]. The main active metabolite of terlipressin is lypressin and approximately 1% of the administered dose is found unchanged in the urine.

Terlipressin has been shown to improve renal function in patients with the hepatorenal syndrome [10]. Some clinical studies have demonstrated its superiority over other medications in treating bleeding esophageal varices [11]. Terlipressin is also recommended to counteract severe anesthesia-induced hypotension in patients receiving renin-angiotensin system inhibitors [12].

The hemodynamic effects of terlipressin have been studied in animal models. Hansen and co-workers [13] showed that portal venous blood flow decreased significantly, and hepatic arterial flow increased by 81%, with an overall decrease of 12% in hepatic blood flow, following intravenous terlipressin administration in anesthetized healthy pigs. Some studies reported that administration of terlipressin raised arterial blood pressure and the systemic vascular resistance index in healthy and septic ewes. The increase in the systemic vascular resistance index was more accentuated in septic animals and only in this group was an increase seen in the pulmonary vascular resistance index [14].

Terlipressin has been used previously in the treatment of catecholamine-resistant septic shock in adults and children [2,15-20]. The major concern related to its use is a reduction in splanchnic blood flow caused by its strong splanchnic vasoconstriction effect, potentially resulting in ischemia that could jeopardize an already severely ill patient [21,22]. However, animal and human studies had shown that terlipressin can restore arterial blood pressure while reversing splanchnic hemodynamic derangements [23,24].

We have been using terlipressin for the last 4 years as a vasopressor in some of our septic shock patients who are treated with high dose of norepinephrine. In contrast to other studies, the decision to administer terlipressin in the present study was related to the clinical judgment of the attending physician (who felt strongly that the dose of norepinephrine should be adjusted frequently), rather than the absolute dose of norepinephrine infused. Thirty of our patients received the drug prior to their transport outside the ICU.

The results of our study show that terlipressin is effective in improving systemic blood pressure in septic shock. Its administration allowed a significant reduction in or even withdrawal of norepinephrine and facilitated the transport of unstable septic patients outside the ICU for critical diagnostic or therapeutic procedures.

There were no life-threatening events following terlipressin administration. The main adverse reaction was acrocyanosis,

without evidence of irreversible ischemic damage to the skin or limbs. Despite the theoretical risk of reduced splanchnic blood flow there was no evidence of intestinal ischemia.

The finding with the greatest potential importance in this study was that terlipressin can facilitate the transport of critically ill patients from the ICU for remote diagnostic or therapeutic procedures, because it raises the blood pressure and produces a prolonged stabilization. That obviates the need to make frequent adjustments of short-acting vasopressors given as continuously administered infusions.

Another benefit of terlipressin is that norepinephrine can be reduced in dose or even discontinued in some patients following the administration of a single dose of terlipressin, after which patients can remain on terlipressin support only.

In the first three patients of our series we gave 4 mg of terlipressin (the dose recommended by the manufacturer for bleeding esophageal varices). However, we reduced the dose to 1–2 mg IV due to the appearance of acrocyanosis. We believe that the optimal dose is 2 mg in IV push. We did not see any cases of severe or long-lasting hypertension following terlipressin administration.

Terlipressin is more expensive than other pressors for septic shock (costing about 10 times more than norepinephrine in Israel). However, financial considerations should not be a factor when it is mandatory to transport a critically ill patient [25].

Our data support previous studies that terlipressin is an effective drug for patients with septic shock. As a long-acting drug it requires less frequent titration and is safer for patients in transport. However, there are serious limitations to this study, being a retrospective study with a small population and incomplete data (e.g., complete hemodynamic profile). Thus, it is impossible to conclude from these findings that terlipressin represents a breakthrough in the management of norepinephrine-treated septic patients; the overall mortality (50%) was almost what we expected. We believe that a larger, controlled prospective study is warranted to clarify its role in the management of these patients. In the meantime we believe that it is feasible to try terlipressin in norepinephrine-dependent septic patients, especially if they require transportation outside the intensive care unit for diagnostic or therapeutic procedures.

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