Characteristics of Patients Given Terlipressin in Catecholamine Supported Septic Shock Patients at Cardinal Santos Medical Center (January 2015-December 2017) - A Retrospective Pilot Study

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Abstract

Background: Sepsis is known worldwide as a clinical syndrome with high considerable rate of mortality and morbidity. Over the past decades, studies conducted on this life-threatening disease have discovered that septic shock, which causes organ failure and injury as a consequence of responding to infection, may lead to certain changes in the body's hemodynamic response. Consequently, about 30% of patients with sepsis develop a multiple organ dysfunction syndrome. A 20% mortality rate has been observed in sepsis patients which further increases to 60% to 80% mortality rate, among septic shock patients. Refractory septic shock has also been observed to increase the 28-day mortality rate despite aggressive therapy. Patients with persistent hypotension and end-organ dysfunction, often require high doses of vasopressor support.

Objectives: This study aims to evaluate the effectiveness of using Terlipressin as a rescue therapy in patients who remain hypotensive despite conventional catecholamines. Terlipressin is a synthetic, long-acting analogue of Vasopressin which also has an effect on the vascular smooth muscle. During the early years, Terlipressin was used in patients with Hepatorenal syndrome (HRS). Recent studies showed that Terlipressin is seen both as a major advancement and a complementary treatment for septic shock. The purpose of this study is to determine and assess whether or not there will be a reduction of catecholamine dose in septic shock patients after the infusion of Terlipressin, which may decrease the potential side effects of catecholamine among patients and increase their rate of survival.

Methods: A descriptive retrospective cohort study was applied in this study. An extensive review of medical records of Filipino septic patients admitted to Cardinal Santos Medical Center Philippines, from January 2015 to December 2017, was conducted. The patients' characteristic profiles and reasons for admission were determined. A repeated measures ANOVA (RMANOVA) was used to determine whether or not the following parameters varied across different time points: MAP, heart rate, urine output, norepinephrine dose, dopamine dose, bilirubin levels, SGOT levels, SGPT levels, platelet count, and Pao2/fio2 ratio.

Results: A total of 173 patients, admitted from January 2015 to December 2017, and were infused with Terlipressin during the time of their admission comprised the database sample for this study. 45 patients with refractory hypotension despite adequate catecholamine infusion (norepinephrine and dopamine) were selected, based on the inclusion and exclusion criteria. The median age of admission was 71 years old and majority of the participants were females at 55 years old. Hypertension and malignancy were the majority of comorbidities. The infusion of Terlipressin has shown to have improved, reaching the target MAP of the patients on the first 6 hours of infusion and decreasing the dose of Norepinephrine +/I-Dopamine, which prevents untoward adverse effects. A significant increase of the MAP on the 12th and 24th hour of infusion of Terlipressin was observed. There was a reduction of the mean dose requirements of norepinephrine and dopamine. During Terlipressin infusion, the effect on organ injury did not show any correlation.

Conclusion: Terlipressin may be used as an effective vasopressor agent that could be an alternative or complementary therapy in patients with refractory septic shock. However, the addition of Terlipressin to high doses of catecholamines may induce incidence of tachyarrhythmia.

Key words: *Terlipressin, sepsis, infection, Vasopressin, septic shock, Catecholamines, catecholamine, resistant, Philippines, Norepinephrine, Dopamine, mortality*

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Introduction

Septic shock is the leading cause of death in intensive care units with a mortality rate of up to 60%. Resuscitation strategies include the administration of intravenous fluids and the use of catecholamine such as norepinephrine, epinephrine, dopamine, and dobutamine.[(1)] Although largely effective in reestablishing minimally acceptable mean arterial pressures to maintain organ perfusion, catecholamine has important adverse effects that may increase mortality rates. For example, norepinephrine, a potent and commonly used α-adrenergic agent in cases of septic shock, may decrease cardiac output, oxygen delivery, and blood flow to vulnerable organs despite adequate perfusion pressure.

Catecholamines,especially norepinephrine, is often the first choice in effectively achieving and maintaining an adequate MAP in septic shock patients [(2).] However, despite facilitation in high doses, some patients fail to have their blood pressure and hemodynamic stability restored. The use of alternative vasopressors, such as epinephrine is practiced, but is not effective in stabilization. [(3)(4)] Terlipressin is a new drug that mediates vasoconstriction via V1 receptors, coupled to phospholipase C. It increases intracellular Ca2+ concentration [(3)] which the v1 receptors did not impair during sepsis. Thus, Terlipressin has been shown to effectively reverse catecholamine-resistant hypotension in septic shock patients. [(3) (7)]

The TERLIVAP trial supported the use of Terlipressin monotherapy while the VAAST trial supported the early use of vasopressin as a rescue or “add-on” therapy for better patient outcomes. Terlipressin has been explored as a potentially new rescue therapy that may be considered as an alternative treatment for patients with septic shock. [5 6] As a conclusion of these trial studies, it was asserted that the use of Terlipressin is associated with a significant increase in MAP in study patients with severe hypotension, despite the use of high-dose norepinephrine, dopamine, and fluid resuscitation. Concomitantly, a decrease in heart rate and Cardiac index was observed and was accompanied by a decrease in intravenous oxygenation in patients who were given Terlipressin. Renal function also improved with a significant increase in creatinine clearance.

However, a number of limitations have been observed in these studies. First, is that the study duration investigated only a small number of septic shock patients treated over a relatively brief period (of 48 hours) and focused on indices of hemodynamic stability and measures of organ function. Another

limitation is the reduction of norepinephrine dose as the primary endpoint. In this regard, it has to be emphasized that there is no reliable evidence to support that a reduction in catecholamine requirements may lead to an improved outcome. No major side effect was noted during the TERLIVAP and VASST studies, only associations with transient self-limiting side effects, including crampy abdominal pain in two patients and self-limiting cardiac arrhythmias in three patients. [7] However, the improvement of survival is still on investigation. Few international studies have reported that the infusion of Terlipressin effectively administered through a bolus dose improved the hemodynamics of septic shock patients, leading to higher probability of survival. [2 3 4]

This study aims to determine whether or not there will be a reduction of catecholamine dose in septic shock patients after the infusion of Terlipressin, which may decrease the potential side effects of catecholamine and ensure better patient survival. As this is the first local study on Terlipressin in the Philippines, it is of valuable importance among septic shock patients in the country.

Materials and Methods

STUDY DESIGN

A single center, retrospective descriptive study was performed on adult, septic shock patients who remain hypotensive with conventional catecholamines in CSMC, from January 2015 to December 2017.

STUDY PARTICIPANTS

Patients who were considered for enrolment are from ages 18 years old and above, diagnosed with septic shock during their admission at Cardinal Santos Medical Center. Septic shock was defined by the presence of two or more diagnostic criteria for the systemic inflammatory response syndrome[1]. Proven or suspected infection, and hypotension was observed despite adequate fluid resuscitation as seen by the inability to maintain a mean arterial pressure (MAP) and 'high catecholamine doses' (at least 1 µg/ kg/min norepinephrine and/or dopamine [12]. All cases were screened by reviewing their medical charts. Patients admitted due to Hepatorenal syndrome, active liver diseases, active cardiovascular problem, including patients with incomplete data and outcome were excluded, since these characteristics may improve or alter the results.

DATA COLLECTION

The review of records was conducted among admitted patients in CSMC, from January 2015 to December 2017. The following variables were collected: age, sex, comorbidities, source of infection, and outcome. The presence of norepinephrine or dopamine doses were collected during the time Terlipressin was started. Dose adjustments associated with changes in MAP levels, heart rate, and urine output, were observed using their vital signs sheet and urine output monitoring. Follow-up period was from the 6th hour, 12th hour, and 24th hour infusion of Terlipressin. Blood test monitoring or evidences of adverse effects (peripheral ischemia, acute ACS, arrhythmias, liver injury and thrombocytopenia) of both catecholamines and/or Terlipressin were observed before and after the 24th hour of infusion. Data obtained were tabulated in the Microsoft Office XP Excel worksheet.

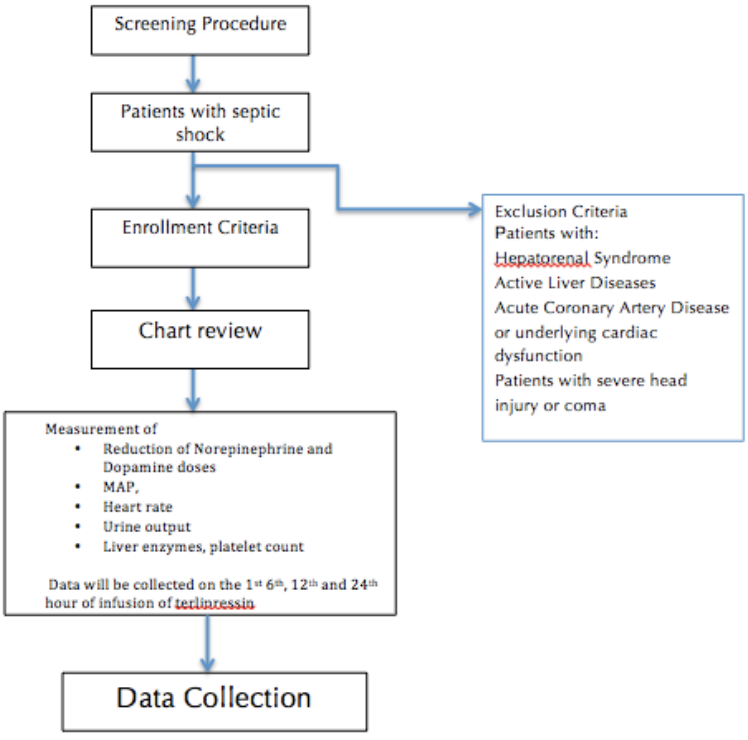


Figure 1. Data Collection Process

Study Outcomes

The main outcome of this study focuses on Terlipressin being used for refractory septic shock, that can improve mortality in admitted patients and secondary outcome improvement of MAP. This study also examines the reduction of norepinephrine doses among these patients and determines the incidence rate of fatal adverse effects.

Sample Size

All 45 study patients, admitted from January 2015 to January December 2017, at the Cardinal Santos Medical Center, due to refractory septic shock to norepinephrine or dopamine, were all reviewed.

Statistical Treatment of Data

For the profiling of patients, quantitative variables (e.g. age, urine output, etc.) were described using the mean and standard deviation, while qualitative variables (e.g. sex, hypertension status, etc.) were summarized using frequencies and percentages. The proportion of patients who experienced a particular adverse event was determined for weeks 5, 9, and 13 of the study.

Repeated measures ANOVA (RMANOVA) was used to determine whether or not the following parameters varied across different time points: MAP, heart rate, urine output, norepinephrine dose, dopamine dose, bilirubin levels, SGOT levels, SGPT levels, platelet count, and Pao2/fio2 ratio. The Box correction factor for violations in the sphericity assumption was applied to the RMANOVA results. Post-hoc comparisons using Bonferroni's Method were performed when the result of RMANOVA was statistically significant. A 5% level of significance was used to test all the hypotheses of this study. Stata IC 12 was used to generate descriptive statistics and perform the test of hypotheses.

Table 1. Profile of the Patients (n=45)

Characteristics	**Mean**
Age	71.13
	Percent
Sex	
Male	44%
Female	55%
Hypertension	68.89%
Diabetes Mellitus	40%

Results

With	40%
CAD	28.89%
Malignancy	26.67%

During the 3-year period, a total of 173 patients were given Terlipressin infusion. After a careful assessment, 128 patients were excluded in the study. Out of 128, 42 patients were infused with Terlipressin before norepinephrine and/or dopamine, 43 patients were infused with Terlipressin due to active liver disease (Hepatorenal syndrome and upper gastrointestinal bleeding secondary to bleeding esophageal varices), 10 patients used Terlipressin for cardiogenic shock and myocardial infarction, 17 patients expired on the first 24 hours of admission, 13 patients had incomplete data/chart, and 3 patients had prolonged Terlipressin use of over 1 month.

A total of 45 patients met the inclusion criteria of this study. Most of them were female patients (55%) with the mean age of 71.13 years. The youngest and oldest patients were aged 34 and 91 years, respectively. Most patients involved in this study have hypertension (68.89%), underlying malignancy (26.67%), underlying stable CAD (28.89%), and Diabetes Mellitus (40%).

Hemodynamic Variables

Systemic hemodynamic variables were summarized in Tables 2 and 3. Clinical and hemodynamic measurements at the beginning of the interventions, varied significantly between the study. Mean MAP levels of the patients significantly varied across time points (p=0.0036) with patients given Terlipressin during their admission. There was a significant effect on the 6^{th} and 12^{th} hour of infusion, p= 0.001 and 0.020, respectively. However, on the 24^{th} hour, there was no significance as compared to the baseline. Overall, the mean MAP levels of the patients at the 6^{th} and 12^{th} hour of infusion, was significantly higher than their mean MAP levels at the 24^{th} hour (p=0.001). Likewise, there were variations of heart rate during this study, which showed no significant change during Terlipressin infusion (0.015) (See Table 2).

Table 2. Comparison of the Mean MAP levels of Patients across Different Time Points

Time Point	Mean	SD	p-value
0	71.0455	13.17848	0.0036
6	92.75	14.88737	
12	84.9302	29.87944	

24	74.8409	35.31516	

Table 3. Comparison of the Mean Heart Rate of Patients Across Different Time Points

Time Point	Mean	SD	p-value
0	108.864	24.91996	0.015
6	102.636	26.04387	
12	97.2791	32.94969	
24	86.7674	41.97155	

Norepinephrine and Dopamine Dose Requirements

Treatment with Terlipressin showed a significant reduction in the norepinephrine infusion rate, from the mean range of 1.5 µg/kg/min pre-Terlipressin administration, to 1.2 µg/kg/min, 12 hours after TP administration, and to 0.9µg/kg/min 24 hours later ($P < 0.001$) (See Table 5). However, on the first 6 hours of infusion, the rates did not significantly decrease ($p=0.237$) the infusion requirements from the baseline. Dopamine requirements did not have a significant reduction, after Terlipressin infusion on the 6^{th}, 12^{th} and 24^{th} hour (See Table 6).

Table 5. Comparison of the Mean Norepinephrine Dose of Patients Across Different Time Points

Time Point	Mean	SD	p-value
0	1.5181818	0.6779836	<0.0001
6	1.2863636	0.7331331	
12	0.98883721	0.7859638	
24	0.68659091	0.7605779	

Table 6. Comparison of the Mean Dopamine Dose of Patients Across Different Time Points

Time Point	Mean	SD	p-value
0	9.06818	9.158545	<0.0001
6	7.83333	8.290214	
12	4.13953	6.868082	
24	3.85227	7.122336	

Variables of Organ Function and Injury

Measurement of the mean urine output of the patients did not significantly vary across time points (p value =0.0964) (See Table 4). There was no significant difference between the bilirubin and SGPT/SGOT levels from the norepinephrine infusion and once given with Terlipressin (<0.0562 and <0.1563 respectively). Platelet count has been reported to be affected in Terlipressin administration. [6,7] It also observed that the decreasing platelet count had a significant lowering of mean platelet count from the baseline, on the 12th and 24th hour of infusion (p value- 0.0006).

Table 4. Comparison of the Mean Urine Output of Patients Across Different Time Points

Time Point	Mean	SD	p-value
0	28.2558	50.88694	0.0964
6	48.1395	68.33133	
12	61.7442	83.01839	
24	52.6585	75.47437	

Table 10. Comparison of the Mean Platelet Count of Patients Across Different Time Points

Time Point	Mean	SD	p-value
0	170.977	138.5506	0.0006
12	90.1053	88.25632	
24	84.8462	106.5592	

Causes of Sepsis

The most common causes for septic shock in admitted patients are *pneumonia* (18 patients), *peritonitis* (12 patients), *urinary tract infection* (4 patients), *pancreatitis* (2 patients), *diabetic foot (*2 patients), *acute gastroenteritis* (2 patients), *sacral ulcer* (1 patient), *surgical site infection* (1 patient) and other *unknown source of infection* (4 patients).

New Onset Tachyarrhythmias

One adverse effect noted during this study was the new onset tachyarrythmia. There were 15 out of the 45 enrolled patients who had an incidence of new onset (i.e., atrial fibrillation) tachyarrhythmias, during the introduction of Terlipressin, within the first 24 hours. Out of 45 patients, 66% of patients (about 30 patients) during their admission expired, and only 33% survived.

Discussion

Septic shock is a very complex condition characterized by circulatory failure. Its treatment has been based, in addition to antibiotic therapy, on aggressive volume resuscitation and cardiocirculatory support by means of the vasopressor and inotropic effects of catecholamines. [13] Despite taking the aggressive approach and utilizing all available resources, chances of mortality and survival did not improve. New therapies which target other factors need to be discovered.

In the treatment of septic shock, [2] it is essential to preserve sufficient tissue oxygenation (3). This goal can only be achieved, with an appropriate MAP and an adequate cardiac index. In the study of O'Brien et al., [3] it was observed that septic shock patients experienced a decrease in cardiac index after the injection of Terlipressin, although no data was reported on oxygen delivery. As asserted by Morelli et. al., Terlipressin is associated with a significant reduction in cardiac output and oxygen delivery [10-16].

An important consideration with the use of Terlipressin is its effects on regional hemodynamics and organ function. [20] Due to the invasiveness of the procedure, the researchers failed to observe mesenteric perfusion, although some abnormalities in liver function test have been observed. As seen in this study, there was no significant change in the Bilirubin, AST, ALT and platelet count.

In line with previous clinical trials, [13-15] the urinary output increased over time in Terlipressin-treated groups, as compared to those treated with norepinephrine, despite potential antidiuretic effects. In this context, it is important to note that vasopressin analogues (Terlipressin) may increase glomerular filtration rate, by increasing resistance of efferent glomerular arterioles without constricting afferent arterioles. In this study, urine output and oxygen delivery showed no significant effect on patients.

Renal function was assessed by monitoring urine output on the 6^{th}, 12^{th} and 24^{th} hour of infusion, which proved insignificant. This is in contrast to recent studies which asserted that Terlipressin was

already established to be beneficial and was proven to show improvement in the Glomerular perfusion rate of patients. [6-12]

Emerging RCT studies have been accomplished on the value of Terlipressin in sepsis and septic shock. In line with other studies, it was observed that Terlipressin caused an improvement of MAP and it allowed significant weaning from norepinephrine [18] [19], all of which were reflected in this study. However, it is still necessary to investigate if the improved effects on patients was entirely due to Terlipressin or was caused by antibiotics and norepinephrine.

Many of these patients have underlying diseases such as diabetes, hypertension, and stroke that probably resulted in reduced ventricular compliance. Consequently, it could be suggested that the researchers did not sufficiently expand the volume of patients. However, it was ensured that the management of patients is in accordance with the standard guidelines of managing septic shock patients. A continuous, low-dose infusion of Terlipressin may prevent these unwanted side-effects.[18, 19]

In this study, 30% of patients developed new onset tachyarrhythmia. Previous reports showed that serious ischemic adverse events were associated with Terlipressin, such as skin ischemia. One probable reason for the high rate of Terlipressin-associated digital ischemia in septic shock patients is the simultaneous administration of Terlipressin and norepinephrine, which increases the incidence of vasoconstriction. However, since only 30% of patients survived in this study, Terlipressin may also be considered a contributory factor on the progression of mortality.

Conclusion

The overall survival rate of 40–50% is estimated for septic shock patients, although the anticipated mortality was set at a higher rate, especially to those who failed to respond to high-dose norepinephrine and aggressive fluid therapy [3]. In line with recent studies abroad, it is important to emphasize that Terlipressin has a role in patients who were persistently hypotensive, despite the use of first line catecholamines in septic shock. Terlipressin may be used as additional therapy in increasing or achieving the target MAP to maintain hemodynamic stability and improve organ function.

Based on the key findings of this study, Terlipressin was tested to be safe and easy to administer, despite some established adverse effects in patients. The patients' response to a single dose within 24 hours of administration showed vascular improvement, and thus, enhanced sensitivity to endogenous and

exogenous catecholamines. Thus, the use of Terlipressin may be considered in patients with refractory septic shock, despite adequate fluid resuscitation and high-dose conventional vasopressors. [21] However, if Terlipressin is to be the last resort therapy, then its advantages (e.g., increased MAP, and improved renal function and perfusion of gastric mucosa) [10-18] should be weighed against unresolved issues, namely, its effects on other organs and risks for severe and irreversible ischemia. It must also be re-assessed in terms of its (unknown) effects on microcirculation. [20]

The main outcomes of this study were intended to shed light on the use of Terlipressin, not only in Hepatorenal syndrome but also in septic shock patients who were not responding to conventional therapy and treatment. These findings also provide adequate data that may be used in studying the effects of Terlipressin in all septic shock patients across the country. Nevertheless, the improvement of survival rates upon the infusion of Terlipressin alone in septic shock patients, is still to be determined, especially if it does change the final prognosis for patients.

Limitations

A number of limitations were observed in this study. First, is the use of a limited sample size and sample population, which restricted the methods of data collection. A far greater number of patients is necessary to demonstrate a potential survival benefit. Secondly, the study adopted an open-label design with no control group; thus, a time effect with a favorable evolution of the patients cannot be ruled out. Third, the study duration was short and was mainly focused on indices of hemodynamic stability and measures of organ function. Also, no conclusion may be drawn from the present study on whether or not, Terlipressin does increase the survival of septic shock, as compared to conventional catecholamine therapy. Direct measurements on regional and local splanchnic blood flow in septic shock patients would be invasive, and may require special skills and instruments that are not readily available at the bedside (CVP, swan ganz catheter). Fourth, although other studies reported a positive correlation between high norepinephrine doses and mortality, it remains unclear whether the reduction of norepinephrine dosages per se represents a therapeutic target. [17] And lastly, this study is limited as there is no established data on the specific dosage or route of Terlipressin, which is deemed most efficacious in septic shock patients.

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