Monitoring of the Effect of Synthetic Vasopressin in Vasodilatory Shock Using Esophageal Doppler Probe

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Abstract

Background: Septic shock is a form of vasodilatory shock characterized by arteriolar vasodilation; the objective of treatment is to elevate tissue perfusion and mean arterial pressure to allow adequate organ perfusion. Noradrenaline and dopamine were the usual catecholamines used in the treatment of septic shock. Loss of response was the common problem that lead to patient loss after large continuous dose of noradrenaline which was termed as catecholamines refractory septic shock. Recently vasopressin and its analog namely terlipressin used in the treatment of such catastrophic condition.

Methods and Results: In a prospective controlled study we included 40 patients with catecholamine resistant septic shock i.e. noradrenaline dose exceeded 0.7mg/kg/min divided into two groups 20 patients was treated conventionally according to surviving sepsis campagin 2008 served as control group and the other 20 patients treated conventionally and when noradrenaline dose exceeded 0.7mic/kg/min terlipresin in a dose of 1mg I.V bolus every 12 hours for a study time of 48 hours was started terlipressin therapy was associated with increased MAP from 58 ± 14mmHg at baseline to 73 ± 20 mmHg with p value: 0.008 after 48 hours that allowed significant reduction of noradrenaline dose from 50mic/min on day 0 to <25 ± 8 mic/min after 48 hours terlipressin therapy was associated with elevated systemic vascular resistant from 546 ± 260dyne.sec/cm–5 to 986 ± 390dyne.sec/cm–5 after 48 hour which represent normalized arterilor tone that expected to allow better organ bed perfusion.

There was reduction of both stroke volume and cardiac output 63 ± 16ml/beat to 51ml/beat and 78liter/m to 5.3litre/min, respectively this was not associated with abnormal organ perfusion marked by improved urine output from 49ml/hour to 133ml/h and improved global perfusion which was marked by improved base deficit which represent lactic acidosis from 9.3 ± 3mEq/L to 5.7 ± 3mEq/L p value: <0.002.

Terlipressin therapy was not associated with deleterious effect on PO2/FiO2 ratio 208 ± 74 to 211 ± 118 after 48 hours.

Yet there was significant reduction of oxygen delivery Do2 from 848ml/min to 610±47ml/min after 48 hours (p>0.02).

There was no effect on length of ICU stay in both groups which was 16±6 in the terlipressin group and 12±6 days in control group (p>0.06) shorter length of stay in control group may be due to the rapid deterioration of hemodynamics and death without terlipressin support. Which was true as mortality in control group was 70% versus 60% (12/20) in terlipressin group with absolute risk reduction 10% and relative risk reduction 25% regarding organ function terlipressin could improve SOFA score form 11 ± 3.2 to 8± 5 with p value: <0.02.

Conclusion: Terlipressin is a rather safe inexpensive easy to administer alternative in the treatment of septic shock—further studies are needed to propose the ideal timing for initiation of its therapy early Vs. late, adjuvant or as an initial treatment.

Key Words: Terlipressin – Catecholamine resistant septic shock.

Introduction

ENDOTOXIC shock is a syndrome of cardiovascular collapse and multiple organ failure in response to bacterial products [1].

The central characteristic of septic shock is systemic vasodilatation, the cause of which is multifactorial the most common cause is excessive nitric oxide synthesis and activation of vascular smooth muscle K+ ATP channel [2,3].

Vascular smooth muscle is poorly responsive to noradrenaline (NA) in septic shock Meadow, et al., [4] and vasopressin doesn’t play a significant role in the control of vascular smooth muscle in normal conditions Schwartz, et al., [5] but becomes critical when blood pressure is threatened [5].

Recent studies showed that some patients in advanced vasodilatory septic shock are exquisitely sensitive to the pressure effect of the exogenous vasopressin therapy.

This unexpected finding raised the possibility that endogenous plasma vasopressin is inappropriately low in these patients.

The most common theories for vasopressin deficiency is first, deficient baroreflex-mediated...
secretion of vasopressin i.e. primary autonomic failure Kaufmann, et al., [6] the second explanation is depletion of secretory stores of the neurohypophysis [7,8].

The above findings are the new concept of treatment of catecholamine resistant septic shock by replacement of the deficient vasopressin in this group of patients.

**Aim of work:**

*The aim of the work in this study was:*
- Evaluation the newly introduced long acting vasopressin analogue-terlipressin-in the management of catecholamine resistant septic or vasodilatory shock regarding its effect on organ function, length of stay and mortality.
- Evaluation of its safety on organ function.

**Patients and Methods**

The study is a prospective controlled study done on 40 patients in period of one year October 2007 to October 2008.

The study was performed in Critical Care Medicine Department which is multidisciplinary intensive care unit with 50 beds.

Informed consent was obtained from the patient first degree relative regarding the use of terlipressin as salvage treatment after failure of all other conventional measures.

**Inclusion criteria:**

1- Patient enrollment in study when showing criteria of severe sepsis which are:
- Tachycardia >90 BPM.
- Tachypnea PCO$_2$ <32mmHg or respiratory rate >20 breath per minutes.
- Fever >38 °C or hypothermia <35 °C.
- Leucocytosis >12x10$^3$/CC or <4x10$^3$/CC

2- Manifestations of organ dysfunction considered if:
- Metabolic acidosis with high anion gap as a sign of organ hypoperfusion.
- Hypoxemia PO$_2$/FiO$_2$ ratio less than 200.

3- Septic shock was defined if in addition to above criteria there are persistent hypotension despite adequate fluid resuscitation necessitating the use of vasoactive drugs with or without inotropic agent [9].

- All patients eligible for the study when showed the above criteria of septic shock in addition when noradrenalin dose required to maintain mean arterial blood pressure (MAP) around 70mmHg and/or reached 0.6 μg/Kg/min $\times$ (40 $\mu$g/min) despite adequate volume resuscitation CVP (8-12mmHg).

**Exclusion criteria:**

1- Age less than 18 years.
2- Pronounced cardiac dysfunction i.e. cardiac index <2.2 litre/min/m$^2$ or severe valvular dysfunction.
3- Patients with suspected coronary artery disease or previous coronary intervention or coronary artery bypass grafting for the fear of coronary flow insufficiency secondary to terlipressin therapy.
4- Pregnancy.
5- Suspected acute mesenteric occlusion.
6- Vasospastic diathesis e.g. Raynaud's syndrome or related diseases.
7- Terminal malignancy.
8- Because of the hemodynamic monitoring of patient was by the Esophageal Doppler monitoring, patients with esophageal pathologies e.g. cancer, achalasia and bleeding peptic ulcer or patients with significant bleeding tendencies also were excluded.

From 89 patients with septic shock screened, 40 patients were included.

All patient received mechanical ventilation using volume controlled mode the ventilatory setting remained unchanged throughout the study.

**Following admission all patients and controlled group were subjected the following:**

1- Full clinical evaluation: Including history and physical examination bed side chest X-ray, abdominal ultrasound or CT abdomen were done when needed.
2- Laboratory investigations:
- Complete blood count.
- Blood culture.
- Serum urea and creatinine.
- SGPT, SGOT, Alkaline phosphatase, albumin, globulin, total and direct bilirubin.
- Arterial and venous blood gases.
- Base deficit measurement.
3- All patients and control group evaluated using:
Acute physiology and chronic health evaluation
II score (APACHEII) and sequential organ
failure assessment (SOFA) score on day of enro-
llment to the study.

• Measurement:
Systemic hemodynamic monitoring of the patients
included:
1- Pulmonary artery catheter: 7.5 F. Baxter. Con-
tinuous cardiac output monitor ring using thermo
dilution technique Edward lifiscienceTM vigilance
CEDV.

Fig. (1): Position of pulmonary artery catheter pressure system.

Two methods for referencing the pressure system to the phlebo-
static axis are shown. The system can be referenced by placing the
air-fluid interface of either the in-line stopcock or the stopcock on
top of the transducer at the phlebostatic level. Redrawn from Bridges,

2- Esophageal Doppler monitor: We used custom-
ized Deltecx cardio Q system, which consist of
bedside monitor equipped to process continuous.
Doppler velocity output from an esophageal
probe. The monitor was modified specifically
by Deltecx to allow continuous acquisition of
the Doppler velocity envelope signal slave di-
rectly into our analogue to digital conversion
system (WIND-AQV 1.26, Dataq instruments
Akran, Ohio, USA).

The probe itself 90cm in length and has 2-4
megahertz Doppler transducers at the distal tip.

The technique of insertion and stability of the
probe has been previously described, briefly, we
inserted the probe into the esophagus and advanced
it to mid thoracic region.

After identifying descending aortic waveform,
the probe location was focused to give the optimum
peak velocity (PV) and waveform signals.

The probe was readjusted on necessary prior
to each data collection to maintain optimum peak
velocity and waveforms.

3- All the 40 patients underwent echocardiography
assessment using ATL HDI 5000, with 2.5MHz
phase array transducer.

1- For sake of excluding major cardiac dysfunction.
2- Regarding measurement of CO using the tran-
saortic Doppler flow.

Study design:
Forty patients showed criteria of catecholamine
resistant septic shock were included as shown. The
first consecutive 20 patients were grouped as (I)
to receive noradrenalin initial dose 0.2 µg/kg/min
with increment of 0.2 µg/kg/min till reaching 0.6
Fluid challenge using hydroxystrach 6% (volumen) was performed to maintain central venous pressure (CVP) around 10-12mmHg.

- Systemic hemodynamic measurements were done at baseline (0) and every 12 hours for 48 hours later.
- Surrogate variables of organ function were analyzed at baseline and scored in SOFA and APACHE II score.
- Target end point which are length of stay, complication regarding organ failure score (SOFA) at 48 hours and mortality was assessed at end of the study.

**Statistical measures:**
- Sigma state software (SPSS, Chicago, IL, USA) was used for statistics.
- All data expressed as mean and standard deviation (SD).
- Frequency table for all categorical data.
- Student t test (paired and unpaired) after checking normality for all continuous data.
- Chi square test for all categorical data to test for the presence of an association.
- p value of less than 0.05 was considered significant.

**Results**

Our study is a prospective controlled study done on 40 patients admitted to Critical Care Department, Cairo University from the period of August 2007 till October 2008.

The studied population sample diagnosed as patients with catecholamine refractory septic shock.

*The studied population were divided into two groups:*

**Group 1:** Twenty patients has been subjected to conventional treatment of septic shock according to surviving sepsis campaign 2008, plus adding terlpressin 1mg every 12 hours when noradrenaline dose exceeds 0.6mic/kg/min for 48 hours "treatment group”.

**Group 2:** Another twenty patients kept on conventional treatment of septic shock (control).

**1- Demographic data of treatment and the control group:**
- Age: The age of treatment group ranged from 28 to 80 years with mean 55 ± 14 years, and in
control group it ranged from 15 to 85 years with mean $50 \pm 18$ years.

There was no significant difference in age between the two groups.

Gender: Treatment group showed 9 females and 11 males while in the control group it was 6 females and 14 males.

Risk factors of sepsis:
Different risk factors of sepsis was present in both groups.

Source of sepsis:
Different source of sepsis was present in both groups.

Table (1): Mean age of group I and group II.

<table>
<thead>
<tr>
<th>Age</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>$55 \pm 14$</td>
</tr>
<tr>
<td>Group II</td>
<td>$50 \pm 18$</td>
</tr>
</tbody>
</table>

Table (2): Gender distribution in patients of both study group (group I, group II).

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Group II</td>
<td>14</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

Table (3): Different risk factors of sepsis in (group I, group II).

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Diabetes</th>
<th>Uremia</th>
<th>Immune suppression</th>
<th>Malignancy</th>
<th>Trauma</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Group II</td>
<td>8</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Table (4): Source of sepsis in both groups.

<table>
<thead>
<tr>
<th>Source of sepsis</th>
<th>Pulmonary</th>
<th>Genito urinary</th>
<th>Abdomen</th>
<th>Soft tissue</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Group II</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
II- Ability of the scoring systems for mortality evaluation:

The mean APACHE II score in group I was 28±6 ranged from 17 to 40 while in group II its was 32±10 with p value about 0.09.

Non significant difference between APACHE II score between the two group.

SOFA score:

SOFA score in group I ranged from 7 to 19 with mean 11±3 while in group II it ranged from 6 to 16 with mean 11.7±2.8.

There was no significant difference between the two groups.

APACHE II score and mortality:

There was significant difference between APACHE II score in survivors and non survivors.

SOFA and Mortality:

There was significant difference between SOFA score in survivors and non survivors.

Age and Mortality:

In the current study there was no correlation between age and mortality pearson correlation was −0.1 and p value was >0.6.

Gender and Mortality:

Also in the study we couldn't find correlation between gender and mortality. Mortality was 12 patients, 7 males and 5 females. Pearson correlation was 0.08 and p value was 0.7.

Table (5): Mean of APACHE II score in (group I and group II).

<table>
<thead>
<tr>
<th>Groups</th>
<th>APACHE II score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>28±6</td>
<td>0.09</td>
</tr>
<tr>
<td>Group II</td>
<td>32±10</td>
<td></td>
</tr>
</tbody>
</table>

Table (6): SOFA score in both groups.

<table>
<thead>
<tr>
<th>SOFA</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7</td>
<td>19</td>
<td>11±3</td>
<td>0.9</td>
</tr>
<tr>
<td>Group II</td>
<td>6</td>
<td>16</td>
<td>11.7±2.8</td>
<td></td>
</tr>
</tbody>
</table>

Table (7): APACHE II score in survivors and non survivors.

<table>
<thead>
<tr>
<th>Groups</th>
<th>APACHE II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>23±3.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Non survivors</td>
<td>31±57</td>
<td></td>
</tr>
</tbody>
</table>

Table (8): SOFA score in survivors and non survivors.

<table>
<thead>
<tr>
<th>SOFA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>8.8±1.2</td>
</tr>
<tr>
<td>Non survivors</td>
<td>12.4±3.4</td>
</tr>
</tbody>
</table>
III- Different hemodynamic variables and its relation with mortality:

Stroke volume (SV):

Cardiac output (CO):

The non survivors showed the classic pattern of CO in uncontrolled sepsis, early high CO then progressive drop when the sepsis cause significant myocardial depression, and hyperdynamic state into hypodynamic one.

Systemic vascular resistantance (SVR):

There was no significant difference in SVR between survivors and non survivors.

Table (9): Stroke volume in survivor and non survivors.

<table>
<thead>
<tr>
<th></th>
<th>SV0</th>
<th>SV1</th>
<th>SV2</th>
<th>SV3</th>
<th>SV4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>64±19</td>
<td>55±11</td>
<td>68±21</td>
<td>64±17</td>
<td>64±15</td>
</tr>
<tr>
<td>Non survivors</td>
<td>63±15</td>
<td>64±17</td>
<td>57±17</td>
<td>52±21</td>
<td>42±14</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Table (10): CO in survivors and non survivors.

<table>
<thead>
<tr>
<th></th>
<th>CO0</th>
<th>CO1</th>
<th>CO2</th>
<th>CO3</th>
<th>CO4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>7.4±2</td>
<td>6.3±1.4</td>
<td>6.3±1.5</td>
<td>6±1</td>
<td>6±1.2</td>
</tr>
<tr>
<td>Non survivors</td>
<td>8±2.2</td>
<td>7±2</td>
<td>6±1.5</td>
<td>5.3±1.5</td>
<td>4.8±1.8</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table (11): SVR in survivors and non survivors.

<table>
<thead>
<tr>
<th></th>
<th>SVR0</th>
<th>SVR1</th>
<th>SVR2</th>
<th>SVR3</th>
<th>SVR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>655±268</td>
<td>903±333</td>
<td>930±278</td>
<td>931±172</td>
<td>1000±199</td>
</tr>
<tr>
<td>Non survivors</td>
<td>473±243</td>
<td>723±353</td>
<td>824±243</td>
<td>921±422</td>
<td>977±769</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Monitoring of the Effect of Synthetic Vasopressin

IV- Monitoring of the terlipressin therapy effect on hemodynamic variables, oxygenation parameters mortality and length of stay:

1- Hemodynamic variables:

a- Stroke volume (SV).

b- Cardiac output (CO).

There was significant drop of cardiac output readings along the whole study time after the use of terlipressin yet the least mean reading value of CO was $5.3 \pm 1.7$ litre/min which still considered a normal range of CO.

c- Systemic vascular resistance (SVR):

There were significant elevation of SVR after the use of terlipressin along the whole study time.

d- Heart rate (HR):

There were significant drop of heart rate after the terlipressin therapy.

e- Mean arterial blood pressure (MAP):

There was significant increase in MAP after the use of terlipressin.

f- Base deficit:

There was significant improvement of tissue perfusion which was evident by progressive drop of base deficit which is a marker of lactic acidosis improvement.

g- Urine output (UOP):

There was significant improvement of UOP after the use of terlipressin.

Table (12): Effect of terlipressin on CO.

<table>
<thead>
<tr>
<th></th>
<th>Before terlipressin</th>
<th>After 12 hours</th>
<th>After 24 hours</th>
<th>After 36 hours</th>
<th>After 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>7.8±2.2</td>
<td>6.7±1.8</td>
<td>6.2±1.5</td>
<td>5.6±1.4</td>
<td>5.3±1.7</td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td>0.004</td>
<td>0.0001</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Table (13): Effect of terlipressin on SVR.

<table>
<thead>
<tr>
<th></th>
<th>Before terlipressin</th>
<th>12 hours</th>
<th>24 hours</th>
<th>36 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>546±263</td>
<td>795±348</td>
<td>867±256</td>
<td>925±338</td>
<td>986±592</td>
</tr>
<tr>
<td>p value</td>
<td>0.002</td>
<td>0.000</td>
<td>0.001</td>
<td>0.003</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table (14): Effect of terlipressin on HR.

<table>
<thead>
<tr>
<th></th>
<th>Before terlipressin</th>
<th>12 hours</th>
<th>24 hours</th>
<th>36 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>122±19</td>
<td>111±17</td>
<td>105±18</td>
<td>105±24</td>
<td>109±23</td>
</tr>
<tr>
<td>p value</td>
<td>0.000</td>
<td>0.001</td>
<td>0.003</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

Table (15): Effect of terlipressin on MAP.

<table>
<thead>
<tr>
<th></th>
<th>Before terlipressin</th>
<th>12 hours</th>
<th>24 hours</th>
<th>36 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>58±14</td>
<td>73±15</td>
<td>74±12</td>
<td>74±16</td>
<td>73±20</td>
</tr>
<tr>
<td>p value</td>
<td>0.002</td>
<td>0.001</td>
<td>0.003</td>
<td>0.008</td>
<td></td>
</tr>
</tbody>
</table>

Table (16): Improvement of base deficit with terlipressin therapy.

<table>
<thead>
<tr>
<th></th>
<th>Before terlipressin</th>
<th>After 24 hours</th>
<th>After 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base deficit</td>
<td>9.3±3 mEq/L</td>
<td>6.4±2.8</td>
<td>5.7±3.9 mEq/L</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.000</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

Table (17): Effect of terlipressin on UOP.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>12 hours</th>
<th>24 hours</th>
<th>36 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>UOP</td>
<td>49±32 ml/h</td>
<td>96±9.7</td>
<td>142.12</td>
<td>117±12</td>
<td>133±23 ml/h</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.05</td>
<td>0.004</td>
<td>0.02</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>
2- Liver functions before and after terlipressin:
   a- (ALT):
   b- Bilirubin:

   There was no significant difference between ALT and Bilirubin level before and after terlipressin.

| Table (18): ALT level before and after terlipressin. |
|-----------------------------------------------|-----------------|---|
| Mean ± SD                                    | p value         |
| ALT 0                                       | 53.2±24.8       | NS |
| ALT 1                                       | 47±15.8         |    |
### Table (19): Bil. level before and after terlipressin.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bil. 0</td>
<td>1.5±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Bil. 1</td>
<td>1.45±0.73</td>
<td></td>
</tr>
</tbody>
</table>

Fig. (22): ALT level before and after terlipressin.

**Fig. (23): Bilirubin. Level before and after terlipressin.**

3- Oxygenation parameter:

a- \(PO_2/FiO_2\) ratio:

There was no significant difference in \(PO_2/FiO_2\) ratio before and after the use of terlipressin.

b- Oxygen delivery (DO\(_2\)):

There was significant reduction of oxygen delivery after 48hrs of terlipressin therapy.

c- Oxygen consumption (VO\(_2\)):

There was significant drop of oxygen consumption with terlipressin therapy.

Table (20): Effect of terlirpessin on \((PO_2/FiO_2)\) ratio.

<table>
<thead>
<tr>
<th></th>
<th>Before 12 hrs</th>
<th>24 hrs</th>
<th>36 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PO_2/FiO_2)</td>
<td>208±74</td>
<td>207±79</td>
<td>218±100</td>
<td>224±101</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. (24): Effect of terlirpessin on \((PO_2/FiO_2)\) ratio.

Fig. (25): Effect of terlipressin on \(DO_2\).

Fig. (26): Effect of terlipressin in \(VO_2\).
Table (21): Effect of terlipressin on $\text{DO}_2$.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After 24 hours</th>
<th>After 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{DO}_2$ ml/min</td>
<td>848±72</td>
<td>793±53</td>
<td>610±47</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.48</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Table (22): Effect of terlipressin in $\text{VO}_2$.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After 48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{VO}_2$</td>
<td>252±119</td>
<td>229±96</td>
</tr>
<tr>
<td>$p$ value</td>
<td>&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

**4- Effect of terlipressin on weaning of catecholamine:**

*Noradrenaline NA dose in mic/min:*

There was significant reduction of NA dose after the use of terlipressin it's secondary to the elevation of MAP and CO as mentioned before.

**5- Effect of terlipressin on length of ICU stay (LOS):**

There was no significant difference between lengths of stay between the two groups.

**6- Effect of terlipressin on mortality:**

- Mortality in treatment group was 12/20 i.e. 60% mortality.
- While in control group was 70%.
- There is absolute risk reduction of mortality of 10% and 25% relative risk reduction of mortality.

**7- Effect of terlipressin on organ functions represented by SOFA score:**

*SOFA 0 i.e. before terlipressin therapy:*

**SOFA 1 after terlipressin therapy:**

There was significant improvement of SOFA score after terlipressin therapy which represents significant organ function improvement.

Table (23): Effect of terlipressin on weaning of noradrenalin.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>12 hrs</th>
<th>24 hrs</th>
<th>36 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA dose</td>
<td>50±1.9</td>
<td>32±1.4</td>
<td>30±6.7</td>
<td>24±6</td>
<td>25±8.5</td>
</tr>
<tr>
<td>$p$ value</td>
<td>0.000</td>
<td>0.009</td>
<td>0.000</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Table (24): Effect of terlipressin on LOS.

<table>
<thead>
<tr>
<th></th>
<th>Length of stay</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terlipressin group</td>
<td>16±6 days</td>
<td>0.06</td>
</tr>
<tr>
<td>Control group</td>
<td>12±6 days</td>
<td></td>
</tr>
</tbody>
</table>

Table (25): Effect of terlipressin on organ functions marked by improvement of SOFA score.

<table>
<thead>
<tr>
<th></th>
<th>SOFA 0</th>
<th>SOFA 1</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11±3.2</td>
<td>8.5±5</td>
<td></td>
<td>0.02</td>
</tr>
</tbody>
</table>

Fig. (27): Effect of terlipressin on weaning of noradrenalin.

Fig. (28): Effect of terlipressin on LOS.

Fig. (29): Effect of terlipressin on organ functions marked by improvement of SOFA score.
Monitoring of the Effect of Synthetic Vasopressin

Discussion

Septic shock is a form of distributive shock characterized by arteriolar and venous vasodilatation. The objective of treatment are to improve $O_2$ delivery to organ by increasing cardiac output and mean arterial blood pressure (MAP) to a level that allows distribution of cardiac output sufficient for organ perfusion.

Among the catecholamines, noradrenalin (NA) and dopamine are often favored. However, vascular responsiveness to them diminishes over time and patient may die in a state of intractable shock. The vascular hypo reactivity to catecholamiens is caused by:

1- Excessive nitric oxide (NO) formation associated with elevation of ATP-sensitive K-channels.

2- Reduction in calcium entry to vascular smooth muscle through voltage gated calcium channels.

3- Down regulation of beta receptors [3].

Thus the search for an alternative vasopressor was a priority.

The aim of the current study was to evaluate the efficacy of a vasopressin analogue namely lysine-vasopressin “terlipressin” as that alternative to catecholamines in patients with septic shock that become refractory to catecholamines.

The study was done in critical care medicine department on 40 patients in which 20 patients received NA and terlipressin and the control group was treated conventionally with (NA) only.

Supportive treatment was the same in the two groups including hydrocortisone 50mg every 6 hours according to surviving sepsis campaign 2008.

The major findings of the present study are that Terlipressin markedly increased mean arterial pressure (MAP) and reduced (NA) requirement. This finding was in accordance with previous clinical studies.

The first study was by O'Brien, et al. [10] in 2002 on a small number of patients (8 pts) used a single 1mg terlipressin dose in short lived time study (first 5 hours).

MAP elevated, cardiac output decreased and oxygen delivery subsequently. There were no reported side effects to the terlipressin especially, due to the short study duration.

In our study the increased of MAP from 58±14 to 74.5±15 on day 1 and up to 73.5±20 on day 2 allowed us to decrease or even stop the noradrenal, dopamine and or adrenaline in almost all patient which is considered a good therapeutic target as Luckner and colleagues in 2005 reported a positive correlation between high norepinephrine dose and morality [11].

This finding is in accordance to the study done by Morelli, et al. [12], in 2004 on only 15 patients with catecholamines resistant septic shock NA dose was ≥0.6 µg/kg/min, in the study terlipressin bolus 1mg was associated by increase in MAP and significant reduction in cardiac index and $O_2$ delivery and consumption.

In the current study also cardiac output (CO) decreased from 7.86±2.2liter/min on day 0 to 5.3±1.7liter/min on day 2, yet this drop of CO was not associated with global clinical signs of organ hypo perfusion regarding urine output (UOP) which increased from (49±32ml/hour) on day 0 to (133 ml/h) on day 2, also there was no signs of elevated liver enzymes during therapy of terlipressin in treatment group.

Base deficit improved from (9.3±3) on day 0 to (5±3mEq/L, $p<0.000$) on day 2 which considered a good global sign of preserved organ perfusion, and improvement of the previously present lactic acidosis.

The drop of CO may be a sign of reversal of hyper dynamic circulation of sepsis and low systemic resistance of dilated peripheral circulation which is blocked by the V 1 receptor activation of terlipressin that cause elevation of systemic vascular resistance from 546±263dyn/sec cm2 on day 0 to 986±590 at the end of the study.

The drop of cardiac output may be explained by a baroreceptor activation and increase in left ventricular after load according to Cowley, et al. [13], in 1983 regarding the role of vasopressin in cardiovascular regulation.

The most interesting finding in current study is the increase in urinary output despite the potential antidiuretic effect (Antidiuretic hormone) of terlipressin. This may be secondary to improvement of glomeular filtration rate by increase resistance of efferent glomeuralr arteriole without affecting the afferent one [14].

Also Tamaki T., et al. [15], in 1996 showedhat vasopressin cause vasodilation of afferent arteriole and increase glomeuralr filtration rate and hence urinary output Tanaki T., et al., [15]. Also terlipressin is less likely to produce antidiuretic effect due to higher V 1 selectively than vasopressin.
From those findings the drop of cardiac output and theoretical drop of oxygen delivery and SVO$_2$ shouldn’t be regarded as detrimental effect rather than surrogate of reduced metabolic demands secondary to possible reversibility of dynamics of sepsis.

Terlipressin therapy was also associated with drop of heart rate from 122 ± 19 BPM on day 0 to about 109 ± 23 BPM on day 2. This finding was evident by all previous studies on arginine vasopressin and terlipressin which is more pronounced from all other vasoconstrictors.

This effect is mostly mediated by V1 receptor in baroreceptors whether by increase in baroreceptor gain and excess vagal stimulation or resetting of the baroreceptor to a lower blood pressure level [16].

Regarding the safety of terlipressin, the twenty patients received the high bolus dose which is 1mg terlipressin every 12 hours for 48 hours without significant rise for liver enzymes nor renal chemistry which was actually improved during the therapy also there was no effect on coagulation profile. Two cases showed severe polyuria >300 ml/h, despite no signs of preceding ATN that was resolved after terlipressin cessation after 48 hours.

No effect on oxygenation Po$_2$/FiO$_2$ ratio day 0 was 208±74 to day 2 was (202±118) with no significant p value. These findings are in accordance with Obrien, et al., [10] and Morelli, et al., [12] in there studies regarding the safety on organ functions. However, Leone, et al., in his study in 2004 showed significant elevation of bilirubin, AST, ALT levels with terlipressin therapy.

Also in his study significant thrombocytopenia was encountered during the therapy.

Direct measurements of regional and local splancnic blood flow in septic shock patients would be invasive, and require special skills and instruments that not readily available at bed side. Thus the current study depend on global biochemical markers as liver profile and base deficit improvement and organ function score which is SOFA score that improved from (11 ±3.2 in day 0 to 8.5±5) after 48 hours of terlipressin therapy with p value of <0.02.

The current study evaluated the mortality in the treatment group (I) and control group both were 20 patients with septic shock in which (NA) requirement exceeded 0.6mic/kg/min.

Group II served as control group to compare mortality and length of stay to the group treated with terlipressin.

Group I mortality was 12/20 i.e. about 60% while in control group was 14/20 i.e. 70%.

This mortality is higher than the study done by Leone M. et al. [17], in 2004 on 17 patients were the mortality was 8/17 i.e. 47% this difference may be explained by the lower initial noradrenalin dose which was 0.2mg/kg/min Vs. 0.6mg/kg/min in our study which considered a marker of more poor prognosis in our study group and more severe form of catecholamine resistant septic shock.

Also the mortality in the study done by O’Brien et al. [10] in 2002 was 4/8 i.e. 50% yet the small number of the study group may be the cause. Overall mortality rate of 50-60% are quoted for septic shock, though anticipated mortality would be much higher in the subset of failure to respond with such higher doses of catecholamien and steroids especially in high APACHE II score in group I which was 28±6 on admission and SOFA score of 11±3.2 on day of admission, so terlipressin offers a potentially important and adjuvant in hypotensive septic patients not responding to high dose catecholamien which seems safe and easy to administer.

Length of stay in treatment group was 16.5±6.9 versus 12±6.8 days in control group. The p value was 0.06 yet the shorter length of stay in control group may be considered as a poor marker of sepsis control with failure to maintain hemodynamic support without terlipressin in contrary to terlipressin group.

Our study may be a leading one in using EDP in monitoring of CO and SVR in patients with septic shock patients receiving hemodynamic supportive drugs in addition to fluid replacement therapy. The other studies used EDP for intra-operative and postoperative purpose for monitoring volume status of patient underwent hip replacement, bowel resection or proximal femoral fracture [18-21].

Conclusion:

- Terlipressin can be used and be considered in patients with truly refractory septic shock i.e. high dose of catecholamine exceeding 0.6-0.9mic/kg/min despite adequate fluid resuscitation.
- So if the terlipressin is the last resort therapy, good selection of patients without significant cardiac.
dysfunction should be done to avoid the excessive increase in SVR against a failing heart.

- Terlipressin therapy was associated with good improvement in hemodynamic variables and organ functions.

- There was 10% absolute risk reduction and 25% relative risk reduction in mortality between the treatment and control group.

- From this, EDP could be an effective alternative to the PAC in bedside monitoring of critically ill patients.

Table (26): Clinical studies on bolus injection and case reports on continuous infusion of terlipressin in patients with septic shock.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Subjects</th>
<th>Interventions</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Brien et al.</td>
<td>8 patients with septic shock</td>
<td>1-2mg terlipressin</td>
<td>Increase in SAP, decrease in cardiac output.</td>
</tr>
<tr>
<td>Leone et al.</td>
<td>17 patients with septic shock</td>
<td>1-2mg terlipressin</td>
<td>Increase in SAP; decrease in cardiac output. and platelet count; increase in liver enzymes and bilirubin.</td>
</tr>
<tr>
<td>Morelli et al.</td>
<td>15 patients with septic shock</td>
<td>1mg terlipressin</td>
<td>Increase in SAP and gastric mucosal perfusion; decreases in cardiac output, DO2, VO2/PCO2 gradient.</td>
</tr>
<tr>
<td>Albanese et al.</td>
<td>20 patients with septic shock</td>
<td>1-2mg terlipressin Vs. titrated norepinephrine</td>
<td>Decreases in cardiac output, VO2, VO2.</td>
</tr>
<tr>
<td>Current study</td>
<td>40 patients with septic shock</td>
<td>Terlipressin Vs. conventional treatment</td>
<td>Increase mean arterial blood pressure and SVR decreased HR, SV, CO, DO2, VO2. 10% absolute reduction of mortality, no effect of length of stay, improved SOFA score at 48 hours.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Publication</th>
<th>Subjects</th>
<th>Interventions</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jolley et al.</td>
<td>1 patient with septic shock</td>
<td>0.25-0.5mg/h terlipressin</td>
<td>Increase in SAP; decrease in cardiac output.</td>
</tr>
<tr>
<td>Zeballos et al.</td>
<td>1 Infant with septic shock</td>
<td>0.7-1.4mg/70kg/h terlipressin</td>
<td>Increase in SAP.</td>
</tr>
<tr>
<td>Morelli et al.</td>
<td>3 patients with septic shock</td>
<td>0.09 and 0.18mg/70kg/h terlipressin</td>
<td>Increase in SAP without decrease in cardiac output or increase in PCO2 gradient at both doses; increase in liver enzymes, increase in bilirubin and skin necrosis only at the higher dose.</td>
</tr>
</tbody>
</table>


References


8- COOKE C.R., WALL B.M., JONES G.V., PRESLEY D.N. and SHARE L.: Reversible vasopressin deficiency


