Evaluation of the Efficacy of Epinephrine as a Vasopressor in the Management of Severe Sepsis: A Randomized Controlled Study.

Jyotishka Pal1, Abu Nadeem2, Syed Moied Ahmed3, Manazir Athar4

1Consultant, Rabindranath and Tagore Hospital, Kolkata, India.
2Assistant Professor, Department of Anaesthesiology & Critical Care, JNMC, Aligarh, India.
3Professor, Department of Anaesthesiology & Critical Care, JNMC, Aligarh, India.
4Senior Resident, Department of Anaesthesiology & Critical Care, JNMC, Aligarh, India.

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ABSTRACT

Background: Norepinephrine is the first-line vasopressor in the management of severe sepsis. Epinephrine may be added or act as a substitute. Aims: To evaluate the efficacy of epinephrine in management of severe sepsis. Settings and Design: Intensive Care Unit, randomised controlled prospective study. Methods: 50 adult patients of both sexes suffering from severe sepsis and septic shock were studied. The patients were randomized into two groups each comprising of 25 patients. Group A patients were treated with norepinephrine and Group B patients with epinephrine. The patients were managed based on the early goal-directed therapy of sepsis management. After the first 6 hours of therapy the study drugs were compared on the basis of Pulse rate, CVP, MAP, ScvO2, SOFA score, time taken to achieve target MAP and the LOS in ICU. Statistical analysis used: Mean (SD), Unpaired and Paired ‘t’ test Results: The pulse rate decreased significantly in Group A whereas it increased significantly in Group B (p < 0.01). The two groups showed statistically significant increment in CVP, MAP and ScvO2 after 6 hours of treatment. The decrease in SOFA score in both the groups was statistically significant (p < 0.001). The total intake and output of fluids (ml), length of ICU stay (LOS) and the time taken to achieve the target MAP were comparable between the two groups. Conclusion: Epinephrine is as effective as norepinephrine in the management of severe sepsis and septic shock. The beneficial aspect of epinephrine outweighs its adverse effects. It should be considered as a first-line drug especially in underdeveloped countries.

Keywords: severe sepsis, early goal-directed therapy, vasopressor, epinephrine

INTRODUCTION

The incidence of sepsis and sepsis related morbidity and mortality are on the rise so it is imperative that clinicians are knowledgeable about sepsis, signs, symptom, and management of sepsis. Previous iterations of surviving sepsis guidelines have recommended a protocolized quantitative resuscitation, otherwise known as early goal-directed therapy (EGDT), which was based on the protocol published by Rivers.[1] This recommendation described the use of a series of “goals” that included central venous pressure (CVP) and central venous oxygen saturation (ScvO2). This approach has now been challenged following the failure to show a mortality reduction in three subsequent large multicenter RCTs.[2]

In surviving sepsis campaign 2016 the researchers recommended norepinephrine as the first choice vasopressor (strong recommendation; moderate quality of evidence) and adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage. Current suggestion about using dopamine is to use as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias . Epinephrine, though considered a second line drug in management of severe sepsis, could be used as a first-line drug because of its easy availability and cheaper cost. Hence, the aim of the present study was to evaluate the efficacy of epinephrine in the management of...
patients with severe sepsis and septic shock and the protocol we have adopted is based on early goal-directed therapy principle.

MATERIALS AND METHODS

Study design and participants
We conducted randomized control study at Jawaharlal Nehru Medical College, Aligarh in India. The institutional ethical committee has approved the study protocol. B Braun and BD arterial pressure monitoring equipment was used. We recruited 50 patients in the ICU in whom sepsis was suspected clinically, who were 20 to 50 years of age and who have evidence of one or more end organ dysfunction, infection along with two or more of the following criteria: (1) body temperature higher than 38°C or less than 36°C, (2) heart rate (HR) greater than 90/min, (3) respiratory rate greater than 20/min, or arterial CO2<32 mm Hg, (4) WBC count > 12000/mm3, or < 4000/mm3 or > 10% immature band [3] along with systolic arterial blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) < 65 mm Hg and central venous pressure CVP ≤ 8 in non-ventilated patients or ≥ 12 in ventilated patients.

Study Interventions
Patients enrolled in the study were randomly allocated to two groups of 25 subjects each, using chit in the box technique. Baseline parameters were recorded at the moment when the study drug was initiated. This was taken as baseline 0 hour (study entry) reading. Group A patients were treated with norepinephrine and Group B patients with epinephrine. Exclusion criteria were absent peripheral pulse, non-recordable BP, age less than 18 years, pregnancy, acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury and trauma patients. The patients with initial CVP ≥ 8 or ≥12 cm H2O in non ventilated and ventilated patients respectively and with MAP ≥ 65 mm Hg was also not included in the study.

A central venous access was established via the central approach in the internal jugular vein on the right side and central venous pressure was noted. Venous blood sample was sent from the central venous line for blood gas analysis and central venous oxygen saturation (SvO2). Any complications during catheter insertion were recorded. Hemodynamic monitoring was done using continuous electrocardiogram (ECG) and invasive arterial pressure (B Braun and BD). The MAP was measured at end expiration. SOFA scoring was done at 0 hours i.e. on admission and at 6 hours or, at conclusion of study, whichever was later.

All subjects were mechanically ventilated with the target to maintain SpO2 ≥ 90 % and PCO2 ≤ 50. Sedation and analgesia was given by fentanyl and midazolam.

The target of therapy was to achieve all of the following parameters:
- SBP > 90 mm Hg
- MAP > 65 mm Hg
- CVP ≥ 8 in non-ventilated patients
- CVP ≥ 12 in ventilated patients

All the parameters were recorded every 15 minutes and increment in dose of studied drug was done if targets were not achieved. A fluid challenge @ 20ml/kg of 0.9% saline was administered over 30 minutes to patients with CVP of ≤ 8 in non-ventilated patients or ≥ 12 in ventilated patients with MAP ≤ 65 mm Hg, if target CVP is not attained then MAP was measured and maintenance fluid (0.9% NS) @ 2ml/kg/hr was started for those with MAP ≥ 65mm Hg and were excluded from the study.

If CVP target was achieved without achievement of MAP levels of ≥65mm Hg, maintenance fluids were started & simultaneously, vasopressor (norepinephrine @ 4µg/min or, epinephrine @ 2µg/min according to the concerned group) were initiated through the central venous route, but if CVP was not attained with first fluid challenge repeated fluid challenges were given each over 30 minutes with graded increment of vasopressor dose (2 µg/min for norepinephrine & epinephrine) till desired CVP & MAP levels were attained.

If MAP ≥ 90 mm of Hg, the vasopressor dose was reduced. Maintenance fluids were continued @ 2ml/kg/hr. After 6 hours of monitoring, CVP, MAP were measured & central venous blood sample was sent for SvO2. If maximum dose of vasopressors (20µg/min of norepinephrine and 10µg/min of epinephrine) was reached within 6 hours without attainment of target (CVP ≥ 8 or ≥ 12 cms of H2O & MAP ≥ 65 mm of Hg), central venous blood sample was sent for SvO2 & study was ended. Further modalities of treatment based on standard protocol were implemented accordingly after that.

RESULTS

Over a period of one year we enrolled 50 patients for the study, 25 patients in the epinephrine group and 25 in epinephrine group. The two groups were comparable with each other with respect to age, weight, SOFA score on the day of admission and sex ratio (Table 1). There was significant change in the pulse rate between pre treatment (0 hours) and post treatment (6hours) in both the groups (p < 0.01, [Table 2]. The two groups showed statistically significant increment in MAP from their pretreatment values (p < 0.001, [Table 2]). CVP reading at 0hrs and 6 hrs showed marked increase in
CVP in both the groups which was statistically significant (p < 0.001, [Table 2]). Both the groups registered a highly significant increment of ScvO2 (p < 0.001, [Table 2]). The baseline SOFA score in Group A and B were 9.85 ± 1.90 and 10.20 ± 1.67 respectively. The post treatment values in these groups were 8.70 ± 1.45 and 9.0 ± 1.65 respectively. The decrease in both the groups was statistically significant (p < 0.001, [Table 2]). When the change in Pulse rate, MAP, CVP and ScvO2 at 6 hours were compared between Group A and Group B, the mean pulse rate was highly significant (p < 0.001), whereas the MAP, CVP and ScvO2 was not statistically significant (p > 0.05, [Table 3]). There was no considerable difference in amount of fluid infusion given during the study phase in both groups. The length of stay (LOS) and the time taken to achieve the target MAP were also comparable between the two groups [Table 4].

Table 1: Demographic Data.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>37.55 ± 12.51</td>
<td>39.85 ± 12.11</td>
<td></td>
</tr>
<tr>
<td>Weight in kg</td>
<td>50.35 ± 10.96</td>
<td>53.25 ± 8.16</td>
<td></td>
</tr>
<tr>
<td>SOFA Score</td>
<td>9.85 ± 1.90</td>
<td>10.20 ± 1.67</td>
<td></td>
</tr>
<tr>
<td>Sex Ratio (Male: Female)</td>
<td>9:16</td>
<td>11:14</td>
<td></td>
</tr>
</tbody>
</table>

P<0.05 is significant, SOFA-sequential organ failure assessment

Table 2: Changes in pulse rate, CVP, MAP, ScvO2 and SOFA score within the groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (norepinephrine)</th>
<th>Significance (pre-post) P1</th>
<th>Group B (epinephrine)</th>
<th>Significance (pre-post) P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>131.4 ± 5.0</td>
<td>'t' = 5.72; p &lt; 0.001</td>
<td>125.3 ± 11.9</td>
<td>'t' = 3.86; p &lt; 0.01</td>
</tr>
<tr>
<td>CVP</td>
<td>121.8 ± 12.76</td>
<td>'t' = 21.87; p &lt; 0.001</td>
<td>7.10 ± 1.86</td>
<td>'t' = 11.43; p &lt; 0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>56.05 ± 5.0</td>
<td>'t' = 17.25; p &lt; 0.001</td>
<td>57.55 ± 4.10</td>
<td>'t' = 15.49; p &lt; 0.001</td>
</tr>
<tr>
<td>ScvO2</td>
<td>56.52 ± 5.0</td>
<td>'t' = 9.3; p &lt; 0.001</td>
<td>54.98 ± 9.28</td>
<td>'t' = 9.05; p &lt; 0.001</td>
</tr>
<tr>
<td>SOFA</td>
<td>9.85 ± 1.90</td>
<td>'t' = 4.36; p &lt; 0.001</td>
<td>10.20 ± 1.67</td>
<td>'t' = 4.54; p &lt; 0.001</td>
</tr>
</tbody>
</table>

P<0.05 is significant, CVP-central venous pressure, MAP-mean arterial pressure, ScvO2-central venous saturation, SOFA-sequential organ failure assessment, P1 and P2 – level of significance in Group A and Group B respectively

Table 3: Comparison in pulse rate, CVP, MAP, ScvO2 and SOFA score between Group A and Group B

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>Group A vs Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Rate</td>
<td>121.8 ± 11.75</td>
<td>133.8 ± 8.44</td>
<td>'t' = 3.64; p &lt; 0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>74.15 ± 6.05</td>
<td>74.20 ± 4.93</td>
<td>'t' = 0.029; p &gt; 0.05</td>
</tr>
<tr>
<td>CVP</td>
<td>9.10 ± 1.59</td>
<td>9.15 ± 1.48</td>
<td>'t' = 0.31; p &gt; 0.05</td>
</tr>
<tr>
<td>ScvO2</td>
<td>74.29 ± 10.48</td>
<td>71.06 ± 6.07</td>
<td>'t' = 1.19; p &gt; 0.05</td>
</tr>
</tbody>
</table>

DISCUSSION

The fundamental principles for the management of sepsis include early recognition, control of the source of infection, appropriate and timely administration of antimicrobial drugs, and resuscitation with intravenous fluids and vasoactive drugs. In the present study the CVP, MAP and ScvO2 increased significantly and the SOFA score improved after 6 hours of administration of norepinephrine (Group A) and epinephrine (Group B) in sepsis patients. However, pulse rate significantly decreased with norepinephrine contrary to the significant increase with epinephrine. The change in all the parameters was comparable between the groups except pulse rate. Further, the total intake and output of fluids (ml) between Group A and Group B during the study period was also comparable. The LOS and the time taken to achieve the target MAP were not significantly different between the two groups.

The aim of initial septic shock management is to rebalance the imbalance between oxygen delivery and demand. Mean arterial pressure (MAP) is one of the hemodynamic targets used to try to ensure that organs are adequately perfused. During initial resuscitation, a MAP level of greater than 65 mm Hg is recommended in the Surviving Sepsis Campaign guidelines. Although this goal may be acceptable in a global sense, a target MAP of 65 mm Hg is unlikely to be appropriate for many critically ill patients. However, intervention to achieve a higher MAP carries several risks. The optimal MAP level (or the optimal vasopressor dose) corresponds to the...
optimal balance between these risks. The Surviving Sepsis Campaign guidelines suggest that the optimal MAP should be individualized because it may be higher in selected patients such as those with atherosclerosis or previous hypertension. Nonetheless, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol: Central venous pressure 8–12 mm Hg, Mean arterial pressure (MAP) \( \geq 65 \text{ mm Hg} \), Urine output \( \geq 0.5 \text{ ml/kg/hr} \), Central venous (superior vena cava) oxygen saturation \( \geq 70\% \).

As per Surviving Sepsis Campaign, Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study. Resuscitation directed toward the previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce 28-day mortality rate. These studies showing the benefit of EGDT in adults presenting to the emergency department with septic shock have been observational and open to potential confounding. The three trials, ProCESS, ARISE and ProMISe were designed to address the effectiveness of EGDT in different countries and they concluded that in critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days. But none of these trials have questioned about the use and efficacy of inotropes and still the first line agent in sepsis is norepinephrine with epinephrine and vasopressin as effective alternatives.

With the above principles in mind, in the present series the patients presenting with severe sepsis or septic shock were subjected to vasopressor support in the form of norepinephrine or epinephrine when MAP remained \( \geq 65 \text{ mm Hg} \) in spite of adequate preload. The aim was to find out whether hemodynamic e.g. pulse rate, MAP and CVP and biochemically derived parameter ScvO2 were attained and or maintained by the concerned vasopressors and if there was any deducible good, better, best among the two drugs. SOFA score at the conclusion of the study i.e. at 6 hours was taken into account to find out if any particular vasopressor could lead to any significant immediate decrement i.e. betterment in the patient status. The intake for the entire 6 hours was also taken so as to get a surrogate marker of the effectiveness of the vasopressor and the cumulative output was taken as a marker of vital organ perfusion. The time taken for MAP to be attained was observed for each drug as was the length of stay in ICU (LOS) to get an idea of the efficacy, both short and long term, if any among the two drugs concerned.

Epinephrine, although not currently recommended by international organizations as first-line vasopressor therapy in sepsis, is a viable alternative. So, in our study, we have taken norepinephrine as a benchmark drug against which we tried to compare and evaluate with epinephrine. All the patients achieved target MAP (\( \geq 65 \text{ mm Hg} \)) with norepinephrine and epinephrine. The post treatment MAP was comparable with norepinephrine and epinephrine. Myburgh and colleagues performed a prospective, multicentered, double-blind, randomized controlled trial of 280 ICU patients comparing epinephrine with norepinephrine. They found no difference in time to achieve target MAP. There was also no difference in the number of vasopressor-free days between the two drugs. Our finding was also supported by Rudis, Basha, Zarowitz. They performed a MEDLINE search from 1985 to 1994 relating to all pertinent English and French articles dealing with hemodynamic support with selected vasopressors and inotropic agents in human sepsis and sepsis syndrome and found that epinephrine and norepinephrine uniformly increased hemodynamic values. Similar to the study of Bollauert et al, where epinephrine was effective in attaining MAP even in patients in whom dopamine had failed, our study also lends accreditation to the fact that epinephrine is a very effective vasopressor but there are three concerns regarding the use of epinephrine, 1) epinephrine increases myocardial oxygen demand; (2) epinephrine increases serum glucose and lactate, which is largely a calorigenic effect (increased release and anaerobic breakdown of glucose); and (3) epinephrine appears to have adverse effects on splanchnic blood flow. Concern about the effect of increased serum lactate and hyperglycemia has limited the use of epinephrine. However, it is unclear whether lactate is harmful in sepsis and concern regarding hyperglycemia appears to be fading. As mentioned by Levy, that despite an increase in oxygen consumption, no adverse cardiac side effects have been described in patients of septic shock by the use of epinephrine, our study also did not find any adverse cardiac events despite the tachycardia induced by epinephrine. Whether increasing myocardial oxygen consumption in sepsis is a good thing or a bad thing is unknown.

The significant increase in CVP as compared to the baseline with both the drugs in our series was in accordance to the study of Rivers et al. They used vasopressor in the form of norepinephrine, dopamine and epinephrine and observed significant improvement in the CVP values. The original EGDT study of Rivers et al in 2001 was based on SvO2 as a target parameter in assessing adequacy of resuscitation of patients in severe sepsis. In the present study ScvO2 was taken as a marker of
resuscitation. This was because to obtain SvO2, Pulmonary artery catheterization is a must. Insertion of PAC was not indicated in all our patients and also to avoid unnecessary complications of PAC as mentioned in various literatures. However, there are literatures where ScvO2 has been compared to ScvO2 and a value of 65% has been correlated with 70% for patients with sepsis. An important target parameter in the surviving sepsis campaign guidelines for assessment of adequacy of resuscitation is ScvO2. A value of ≥ 70% has been advocated. In our study, the target ScvO2 was attained in 13 out of 20 patients (65%) in norepinephrine group and 12 out of 20 (60%) in epinephrine group. However, there was no statistically significant difference in the values of ScvO2 between any of the vasopressors studied. Our findings are similar to the study of Rivers et al., who also found that norepinephrine, dopamine and epinephrine significantly improves ScvO2 values in patients of severe sepsis and septic shock. In the pioneering study of EGDT by Rivers et al., on 263 patients of severe sepsis or septic shock, the amount of i.v fluids in the first 6 hours was 4981 ± 2984 ml. Our study based on same EGDT protocol required less amount of i.v fluids. This could be probably because there has been no mention of body weight in the study of Rivers et al. The body weight in Indian perspective is generally less than Western perspective. However, there was no significant difference between norepinephrine (Group A) and epinephrine (Group B) regarding intake of fluids. In the present study, there was no significant difference in urine output in both the groups. Similarly, Schreuder et al. used norepinephrine in patients with septic shock and observed no difference in urine output. However, in our study use of epinephrine also led to no difference in urine output. This might be a reflection of the fact that by increasing MAP, epinephrine effectively preserved renal perfusion. Achieving the target MAP is the urgent need in patients with severe sepsis and septic shock. The time taken to achieve the target MAP following administration of the vasopressors may be dependent upon the efficacy of the two vasopressors. In the present study there was no significant difference in the time required by any of the drugs to attain the target MAP thereby indicating that the vasopressor potency was perhaps identical. The ultimate benefit of the use of vasopressors in severe sepsis and septic shock lies in reduction of mortality, decreased LOS in ICU and betterment of prognostic scores with time duration of therapy. In our study, each drug led to significant improvement in the post treatment values as compared to the baseline. Further, the post treatment SOFA scores were comparable between the two groups. Thus, irrespective of the vasopressor used, the immediate short term prognosis of the patients remained the same. The LOS was comparable in both the groups without any statistically significant difference. These findings are similar to the study of Annane et al., aimed at comparing the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock. In 330 patients, there was no significant difference between the two groups in time course of SOFA score as well as in mortality rates at discharge from intensive care, at hospital discharge, and by day 90. Every study has some weakness and strength. Similarly one of the weaknesses of the present study was that it could not be a blind study. This was not feasible in our setup and also because the increment of different vasopressor regimens were different which could not possibly be kept undisclosed from the attending physician. Also, measurement of blood lactate as a surrogate marker of organ perfusion could not be done because of paucity of appropriate equipments. This study would have been more powerful had it been a placebo control study. But for combating shock where vasopressors are essentially necessary, placebo control would have been unethical. However, the strengths of the study lie in the fact that this was a prospective, randomized and controlled interventional study. Also, the number of patients taken for this study and subsequently for each group under consideration was sufficient for adequate statistical analysis and significance.

CONCLUSION

epinephrine is as effective as norepinephrine in the management of patients with severe sepsis except that epinephrine caused a significant rise in pulse rate. Our studies alongside other contemporary studies have shown, the beneficial aspect of epinephrine outweighs those adverse effects which were more highlighted in the years gone by. It is time that epinephrine be used alongside both norepinephrine as a first-line vasopressor agent in the management of patients with severe sepsis and septic shock, particularly in the so called underdeveloped countries where availability and the cost of a drug matters ‘much’ to the patient.

REFERENCES