The effectiveness of a beta-blocker in patients with septic shock

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Abstract

Background: The incidence of sepsis continues to increase. Septic shock is a major cause of mortality in the United States and throughout the world. An adverse outcome of sepsis is cardiac dysfunction. Tachycardia increases the workload on the heart, which increases the metabolic demands required. It is imperative to identify new treatment options to help alleviate and manage the symptoms of sepsis. There are many potential benefits of beta-blockers for acutely ill patients. This includes a decreased oxygen demand related to a decreased heart rate (HR). This also results in reduced blood pressure and decreased workload of the heart. Will the administration of beta-blockers be effective at controlling heart rate and mitigating the harmful effects of beta-adrenergic receptor stimulation in patients with septic shock?

Methods: An extensive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: beta-blocker and septic shock. The search was narrowed to only articles in English published within the last two years. Articles that were relevant for data evaluating the use of beta-blockers in septic shock were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Results: Two studies met inclusion criteria and were included in this systematic review. A randomized clinical trial with 336 participants demonstrated a decrease in 28-day mortality for septic shock patients receiving esmolol infusion. It also showed that esmolol was effective at reducing heart rate and maintaining it within desired levels while avoiding unwanted outcomes. A prospective observational pilot study evaluated 25 septic shock patients in the ICU. The study demonstrated a controlled heart rate with a titrated infusion of esmolol. It made evident a reduction in norepinephrine dosage, while maintaining microvascular blood flow and stroke volume.

Conclusion: A titrated infusion of esmolol has been shown to reduce mortality in patients with septic shock. These studies data support that the titrated administration of esmolol, a short acting beta-blocker, reduces HR and maintain it within a target range of 80-94bpm. Secondary outcomes support its use in patients with septic shock without significantly compromising the cardiac output of the patient and maintaining the microcirculation of blood flow.

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The Effectiveness of Beta-Blocker Use in Patients with Septic Shock

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
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Faculty Advisor: James Ferguson, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Steve Liddiard is a native of Utah. He received a Bachelor of Science degree in Biology from Utah Valley University in 2011. He also received an AS and AAS from UVSC where he completed the fire academy and paramedic program. Prior to PA school he worked for seven years as a Firefighter/Paramedic for the city of Provo. He is married and has four children.
**Abstract**

**Background:** The incidence of sepsis continues to increase. Septic shock is a major cause of mortality in the United States and throughout the world. An adverse outcome of sepsis is cardiac dysfunction. Tachycardia increases the workload on the heart, which increases the metabolic demands required. It is imperative to identify new treatment options to help alleviate and manage the symptoms of sepsis. There are many potential benefits of beta-blockers for acutely ill patients. This includes a decreased oxygen demand related to a decreased heart rate (HR). This also results in reduced blood pressure and decreased workload of the heart. Will the administration of beta-blockers be effective at controlling heart rate and mitigating the harmful effects of beta-adrenergic receptor stimulation in patients with septic shock?

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**Conclusion:** A titrated infusion of esmolol has been shown to reduce mortality in patients with septic shock. These studies data support that the titrated administration of esmolol, a short acting beta-blocker, reduces HR and maintain it within a target range of 80-94bpm. Secondary outcomes support its use in patients with septic shock without significantly compromising the cardiac output of the patient and maintaining the microcirculation of blood flow.

**Keywords:** beta-blocker, septic shock
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To my family: Thank you for your help, support, and love during PA school. I appreciate your sacrifices during this journey.
# Table of Contents

Biography.................................................................................................................. 2
Abstract ...................................................................................................................... 3
Acknowledgements ..................................................................................................... 4
Table of Contents ......................................................................................................... 5
List of Tables ............................................................................................................... 6
List of Abbreviations .................................................................................................. 6
BACKGROUND ......................................................................................................... 7
METHODS ................................................................................................................. 9
RESULTS ................................................................................................................... 9
DISCUSSION ............................................................................................................. 14
CONCLUSION ........................................................................................................... 16
References .................................................................................................................. 17
Table 1. Characteristics of Reviewed Studies ........................................................... 17
Table 2. Summary of Results ..................................................................................... 20
List of Tables

Table 1: GRADE Quality of Assessment
Table 2: Summary of Results

List of Abbreviations

HR  Heart Rate
CI  Cardiac Index
MI  Myocardial Infarct
CHF  Congestive Heart Failure
CAD  Coronary Artery Disease
bpm  Beats per Minute
ICU  Intensive Care Unit
BMI  Body Mass Index
MAP  Mean Arterial Pressure
MFI  Microvascular Flow Index
ATP  Adenosine Triphosphate
CVP  Central Venous Pressure
PAOP  Pulmonary Arterial Occlusion Pressure
GFR  Glomerular Filtration Rate
AUCs  Areas Under the Curve
RCT  Randomized Control Trial
PPVs  Proportion of Perfused Vessels
PRBCs  Packed Red Blood Cells
SIRS  Systemic Inflammatory Response Syndrome
MODS  Multiple Organ Dysfunction Syndrome
GRADE  Grading of Recommendations, Assessment, Development, and Evaluations
The Effectiveness of Beta-Blocker Use in Patients with Septic Shock

BACKGROUND

There has been a dramatic increase in the incidence of sepsis in recent years.\textsuperscript{1} In the 1970’s there was an estimated 164,000 cases of sepsis in the United States annually.\textsuperscript{2} Recent estimates report more than 1.6 million cases of sepsis every year in the United States.\textsuperscript{2,3} There is a mortality rate greater than 200,000 per year for patients with septic shock.\textsuperscript{4} This increase in incidence among the population is linked to an increasing aging population, comorbidities, multidrug-resistant infections, and immunosuppression.\textsuperscript{5}

Sepsis is a clinical syndrome that complicates severe infection. It results from a dysregulated inflammatory response to an infection. In sepsis we see a continuum of severity, which may result in systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). The body’s attempt to compensate for changes related to sepsis will be manifest in physiologic and clinical responses. Sepsis is often characterized by fever, tachycardia, tachypnea, altered mental status, and the cardinal signs of inflammation.

Shock is defined as a condition of severe impairment of tissue perfusion leading to cellular injury and dysfunction. There are several types of shock, but each results in hypo-perfusion, which leads to an inadequate delivery of oxygen to cells. With the less than required oxygen the cells start to dysfunction and release inflammatory mediators. These mediators set off a cascade of events that make perfusion even more inadequate due to changes occurring at the microvascular level. This often leads to a maldistribution of blood flow, which eventually leads to end organ damage and often death.\textsuperscript{4} With all types of shock the body tries to adapt to the hemodynamic changes placed on it.
The progression of sepsis and septic shock is multifactorial. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. There is a significant decrease in systemic vascular resistance; to maintain perfusion there is often an increase in cardiac output. A detrimental side effect in patients with sepsis is cardiac dysfunction,\(^6\) increasing the rate of mortality to 70\%.\(^7\) Tachycardia increases the workload on the heart, which increases the metabolic demands required. Sepsis creates a perfusion problem that leads to an imbalance between oxygen supply and demand.\(^8\) In sepsis the metabolic demands are high and this leads to a rapid depletion of adenosine triphosphate (ATP) and energy supply at the cellular level.\(^9\) Tissue hypoxia and inadequate perfusion are increased when the energy demand exceeds the actual supply.\(^8\)

The production of cellular energy is decreased by damage to mitochondria, compromise of the circulatory system, and microcirculatory alterations.\(^10\) Adrenergic stimulation leads to increased protein and fat catabolism, hyperglycemia develops from gluconeogenesis and glycolysis, and all require increased energy demands.\(^11\) This higher increased expenditure contributes to organ dysfunction.\(^11\) To prevent irreversible organ damage and cell death, it is important to investigate and conduct studies to find improved ways to manage and treat septic shock quickly and effectively, thereby decreasing the mortality rate.

There are many potential benefits of beta-blockers for acutely ill patients. This includes a decreased oxygen demand related to a decreased heart rate (HR). This also results in reduced blood pressure and decreased workload of the heart.\(^12\) Esmolol is an effective beta-blocker that has a short half-life and has been used in CHF, CAD, and MIs with great success.\(^13\) What is the effectiveness of using a beta-blocker to control heart
rate and mitigate the harmful effects of beta-adrenergic receptor stimulation in patients with septic shock?

METHODS

An extensive search was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: beta-blocker and septic shock. The search was narrowed to only articles in English published within the last two years. Articles that were relevant for data evaluating the use of beta-blockers in septic shock were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

RESULTS

The initial search yielded 232 articles with many of the articles ranging back to the 1960’s. After evaluating relevant articles for high quality data and human studies, a total of two articles met inclusion criteria. These articles included a randomized control clinical trial and a pilot study. See Table 1 and 2.

A Randomized Clinical Trial

This clinical trial was an open-label, randomized phase 2 study, to evaluate the use of esmolol to regulate heart rate and reduce the damaging effects of catecholamines while maintaining hemodynamic stability in patients with septic shock. The trial was performed in an ICU in a university hospital during the time frame of November, 2010 to July, 2012. There were 336 patients who were initially evaluated for the study. For various reasons 182 patients were excluded. A computer based random number generator was used to randomly assign the remaining 154 patients’ treatment with or without continuous infusion of esmolol. Seventy-seven patients were randomly allocated to each
of the treatment groups. The two groups were prognostically balanced, especially in regards to age, gender, body mass index (BMI), and preexisting conditions.¹⁵

Eligibility criteria consisted of the presence of septic shock requiring norepinephrine to maintain a mean arterial pressure (MAP) greater than or equal to 65 mm Hg even after attempts to improve pressure with volume resuscitation. Additional inclusion criteria were a heart rate of 95 beats per minute (bpm) or greater, central venous pressure (CVP) ≥ 8 mm Hg, and pulmonary arterial occlusion pressure (PAOP) ≥ 12. Patients that were excluded from the study were those younger than 18 years of age, who were pregnant, with valvular heart disease, who had been given beta-blocker therapy prior to selection, or who had displayed severe cardiac dysfunction.¹⁵

The primary endpoint was to see if the administration of esmolol, an effective short acting beta-blocker, could decrease HR to less than 95 bpm and achieve a target HR between 80 and 90 bpm during their residence in the ICU. Secondary endpoints included 28-day mortality, organ function, norepinephrine dosages, and oxygenation and cardiorespiratory indices. Acid-base balance, hemodynamics, and oxygenation were all monitored, evaluated, and assessed. This included radial and pulmonary artery catheterization, electrocardiography, labs, thermodilution technique to measure cardiac index, and the use of standard formulas to calculate ventricular stroke work, oxygen extraction, and oxygen delivery. Each variable was recorded at 24, 48, 72, and 96 hours after eligibility and randomization were completed. For 28 days after starting the clinical trial, data was recorded for all unfavorable side effects including death.¹⁵

A two-sided t test was used to determine the sample size. It was found that 64 patients would be needed for each group. To compensate for worst-case scenario, the
Wilcoxon Mann-Whitney test showed that the sample size needed to be increased to 75 patients for each group. Baselines were compared with demographic data using a $\chi^2$ test. AUCs (areas under the curve) calculations were used to avoid multiple comparisons. $\chi^2$ test was also used to compare 28-day mortality of the different groups. A multivariable Cox regression model was used to account for cofactors.

The authors of the randomized clinical trial (RCT) concluded that esmolol was effective at reducing HR and maintaining it within desired levels while avoiding unwanted outcomes. The achieved HR was significantly lower during the intervention time frame in the esmolol group. In the RCT the 28 day mortality was decreased in the esmolol group with 38 deaths compared to 62 deaths in the control group.

The authors identified five limitations of their study. Instead of an individualized HR for each patient a random set point was used. The use of esmolol titration required to control HR made the study so that it was non-blinded. The area in which the study was conducted had multidrug-resistant bacterial strains. It was difficult to determine if the non-cardiac actions of esmolol attributed to the witnessed decrease in mortality or if it was related to decreased HR. The authors were also unable to determine if the large difference between mortality of the two groups was due to confounding factors or a chance finding. Further clinical trials are needed to confirm the data and help resolve the limitations of the study.

**Pilot Study**

This prospective observational pilot study evaluated the effects of beta-blockers to control heart rate and decrease the negative effects of catecholamines in patients with septic shock. It was preformed in a multidisciplinary intensive care unit (ICU) at the
University of Rome and evaluated 25 septic shock patients in the ICU. The study used a case cross over design, which is an analytical epidemiological approach, in which the patients’ serves as their own control. It is used to investigate the effects of an intermittent exposure on the onset of acute outcomes. The study was conducted to evaluate the possible benefits of using a cardio selective beta-1 blocker, esmolol, to maintain heart rate within a target range and assess secondary benefits of beta-blocker therapy on hemodynamic stability.

Due to the patient’s condition, informed consent was obtained from the patients’ family. Selection criteria included patients who, even after sufficient fluid resuscitation, required norepinephrine to maintain a mean arterial pressure (MAP) equal to or greater than 65 mm Hg, and displayed a heart rate (HR) greater than 95 beats per minute (bpm). These patients were administered a continuous infusion of esmolol, with the goal to achieve a HR between 80 and 94 bpm. All 25 selected candidates were ventilated and given midazolam and sufentanil for sedation. Patients were excluded for the following reasons, if they were younger than 18 years of age, were pregnant, had advanced valvular heart disease, or had significant cardiac dysfunction.

Hemodynamic and microcirculation were assessed and monitored. Hemodynamics was monitored by pulmonary and radial artery catheterization. Heart rate was recorded by continuous telemetry. Blood gases were analyzed for each patient and stroke volume and oxygen indexes were calculated using standard formula. An optical probe was applied to the underside of the tongue to assess the microvascular blood flow. This was done using imaging from MicroScan that had five-fold magnification lens. The use of “De Backer Score” was used to calculate vessel density and the total number of
vessels lengths based on size (small, medium and large). Dividing these up into horizontal and vertical lines on the screen a score was calculated by dividing the number of lines by the length of the lines. This score was the microvascular flow index (MFI) that had a range of 0-3, with 3 being normal, 2 sluggish, 1 intermediate, and 0 absent. A formula multiplying the proportion of perfused vessels (PPVs) by vessel density was used to calculate perfused vessel density.

Patients were given a titrated continuous infusion of esmolol beginning with a rate of 25mg/hr, maxing out at 2000mg/hr, to maintain a HR or 80-95 bpm. In addition to esmolol, the patients were provided standard treatment including fluid challenges, packed red blood cells (PRBCs) as needed, and administration of norepinephrine to maintain MAP. Each patient was reevaluated after 24 hours of esmolol infusion.

A significant finding from the study showed no negative affect on microvascular blood flow, even after the reduction in HR from the administration of esmolol. The change in MFI following administration of esmolol was the primary endpoint for statistical analysis, with a correlation of 0.99, achieving 90% power was specified. Data was considered statistically significant for $p$ value less than 0.05. After 24 hours of esmolol administration HR and cardiac index (CI) were significantly reduced. HR went from a baseline of 117 to 86 bpm. Cardiac index decreased from a baseline of 4.0 to 3.1. The amount of norepinephrine needed was also greatly decreased from 0.53 $\mu$g/kg/min to 0.41 $\mu$g/kg/min. There was improvement in acid-base homeostasis and oxygenation. The consumption index and the demand for oxygen delivery decreased. The MFI data showed significant increase from 2.8 to 3.0.

This was the first clinical study to assess the effects of esmolol to reduce and
maintain heart rate in patients with septic shock. To ensure the safety of the patient a
case-cross over design was used, therefore the patient acted as the control. No control
group was present in the study and therefore the findings might be related to the patient’s
own improvement, rather than the benefits of a decreased HR from the administration of
a beta-blocker. The sample size was small, but the data does support a positive outcome
from esmolol.16

DISCUSSION

In the United States the incidence of severe sepsis and septic shock is greater than
1.6 million per year2,3 with a mortality of more than 200 000 per year.4 The incidence
continues to rise as patients now live longer and present with more comorbid conditions
that are being managed with greater efficiency by modern medicine. In view of the
epidemiology, it is imperative to continue to investigate additional options to help treat
septic shock and decrease mortality.

Esmolol provides a reasonable approach to treat patients’ with septic shock. In the
clinical trial15 data illustrated that esmolol was effective in decreasing HR while
maintaining MAP (see Table 2). In addition, secondary outcomes were identified and
determined to be beneficial. The group who received esmolol demonstrated a decrease in
the dosage of norepinephrine administration to maintain MAP.15,16 The concern with the
administration of esmolol was that decreased HR would decrease cardiac output, which
would have an adverse effect on MAP.8 This was shown not to be the case. The findings
suggest that a decreased HR allowed for greater ventricular filling during diastole.15 This
resulted in notable improvement in stroke volume and left ventricular stroke work indices
in the esmolol group.15 The need for IV fluid administration was also decreased in the
esmolol group.\textsuperscript{15,16}

Statistical analysis of the data from the clinical study also showed an increase in pH and a decrease in lactate concentration,\textsuperscript{15} which indicates a decrease in aerobic metabolism. Kidney function was also shown to have a positive improvement in the esmolol group.\textsuperscript{15} Glomerular filtration rate (GFR) for those being treated with esmolol was 14ml/min/1.73m\textsuperscript{2} compared to the control group with a GFR of 214ml/min/1.73m\textsuperscript{2}. The partial pressure of O\textsubscript{2} to inspired oxygen fraction ratio also increased for the esmolol group.\textsuperscript{15} The esmolol group had myocardial injury bio-markers, troponin and creatine, that were lower.\textsuperscript{15}

A significant outcome in the study was improved survival rate in the esmolol group. The 28-day mortality was almost double for the control group when compared to those receiving esmolol (49.4\% vs 80.5\%).\textsuperscript{15}

While both studies\textsuperscript{15,16} demonstrated that a titrated infusion of esmolol was effective in reducing HR and maintaining it in a target range, without adversely affecting MAP, stroke volume, lactate levels, or norepinephrine requirement; both studies had limitations. In the clinical trial\textsuperscript{15} it would be difficult to use a placebo in place of esmolol to regulate heart rate. Many patients were excluded from the study because they did not have tachycardia. As with all drugs, the administration of beta-blockers, does not happen without a myriad of possible adverse reactions.\textsuperscript{20} There is still debate about whether treating tachycardia in septic shock is recommended.\textsuperscript{8,15} Tachycardia is a main mechanism to overcome decreased cardiac output in the early phase of septic shock.\textsuperscript{21} The ideal heart rate and timeframe are still undetermined. A major limitation of the pilot study was the small sample size. Both studies had a high risk for selection bias because
there were conducted in only one University.

CONCLUSION

The studies\textsuperscript{15,16} data supports the titrated administration of esmolol, a short acting beta-blocker, to reduce HR and maintain it within a target range of 80-94 bpm. Secondary outcomes support its use in patients with septic shock without significantly compromising the cardiac output of the patient and maintaining the microcirculation of blood flow.\textsuperscript{15,16} Notable improvement was seen in stroke volume, MAP, decreased dosage of norepinephrine, and less deleterious effects to organ function.\textsuperscript{15} The evidence for the use of esmolol in septic-shock patients is positive and data demonstrated an increased survival rate. There was a 30\% decrease in 28 day mortality in the RCT.\textsuperscript{15} The overall combined quality of the studies reviewed is low based on the GRADE criteria. More studies need to be conducted to see if the use of a beta-blocker earlier in the treatment of patients’ with sepsis is beneficial. Further research is also required to investigate the effects of beta-blockers on clinical outcomes.
References


### TABLE 1 GRADE evidence profile: Esmolol use in patients with septic shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized Controlled Trial(^{15})</th>
<th>Observational Pilot Study(^{16})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate (<em>/min)</em></strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>114</td>
<td>117</td>
</tr>
<tr>
<td><strong>24 hours</strong></td>
<td>84</td>
<td>86</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>114</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>28-day Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment group</strong></td>
<td>38/77 = 49.4%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td>62/77 = 80.5%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Nor-epinephrine dosage (µg/kg/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment group</strong></td>
<td>0.4</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td>0.4</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Mean Arterial Pressure (mm Hg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment group</strong></td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td>72</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Stroke Volume (mL/beat/m(^2))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment group</strong></td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td>34</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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**No blinding in the RCT\(^{15}\) and both studies\(^{15,16}\) contained a high risk for selection bias because it was conducted in just one University.

\(^{a}\)Small sample size in the observational pilot study\(^{16}\)

\(^{b}\)Failure to capture individualized HR in the RCT\(^{15}\)