Original Article

Systematic review of use of β-blockers in sepsis

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Abstract

Background and Aims: We proposed a review of present literature and systematic analysis of present literature to summarize the evidence on the use of β-blockers on the outcome of a patient with severe sepsis and septic shock.

Material and Methods: Medline, EMBASE, Cochrane Library were searched from 1946 to December 2013. The bibliography of all relevant articles was hand searched. Full-text search of the grey literature was done through the medical institution database. The database search identified a total of 1241 possible studies. The citation list was hand searched by both the authors. A total of 9 studies were identified.

Results: Most studies found a benefit from β-blocker administration in sepsis. This included improved heart rate (HR) control, decreased mortality and improvement in acid-base parameters. Chronic β-blocker usage in sepsis was also associated with improved mortality. The administration of β-blockers during sepsis was associated with better control of HR. The methodological quality of all the included studies, however, was poor.

Conclusion: There is insufficient evidence to justify the routine use of β-blockers in sepsis. A large adequately powered multi-centered randomized controlled clinical trial is required to address the question on the efficacy of β-blocker usage in sepsis. This trial should also consider a number of important questions including the choice of β-blocker used, optimal dosing, timing of intervention, duration of intervention and discontinuation of the drug. Until such time based on the available evidence, there is no place for the use of β-blockers in sepsis in current clinical practice.

Key words: β-blockers, cardiac index, heart rate control, mortality, sepsis, systematic review

Introduction

Sepsis is a clinical syndrome that arises from an inflammatory response to infection. The response from the host is associated with immune, hormonal, metabolic, bioenergetics, and autonomic nervous system modification. This is associated with an overall catabolic state, excessive adrenergic stimulation, high catecholamine levels, and myocardial depression. Myocardial injury in sepsis is mediated via excessive catecholaminergic action and cytokine production.[1] β-blockers modulate both these pathways. There are several studies that have shown the benefits of β-blockers in sepsis. Animal studies have shown benefits of β-blockers.[2-4] Until date, there is no published systematic review on the effect of β-blockers in sepsis. We sought to summarize the evidence from all human studies on the effect of β-blockers in sepsis.

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Material and Methods

Methods of inclusion and analysis were developed in accordance with the Cochrane collaboration guidelines.[5]

Search methods

We identified references for this systematic review using Medline, EMBASE and the Cochrane register of controlled trials with search terms sepsis (MeSH term) OR "β-blockers" (MeSH term) OR "β-adrenergic blocking agent*" (all fields) OR

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"β-antagonist*" (all fields) OR "β-adrenergic antagonist*" OR "β-adrenoreceptor antagonist*" (all fields) OR "β-adrenergic receptor antagonist* (all fields). Appendix 1 shows the search strategy. No language or publication date restriction was imposed. Medline was searched from 1946 and EMBASE from 1947. Bibliographies of all selected articles were searched. We also searched the grey literature via the medical university database. An additional search was done on the clinical trial database.[6]

Study selection and data extraction

All potential relevant studies were obtained and critically appraised. We used the following inclusion criteria:

1. Diagnosed sepsis.
2. On β-blockers or treated with β-blockers during their Intensive Care Unit (ICU) admission.
3. Adult population (age >18 or older).

Exclusion criteria were:

1. Pediatric patients.
2. Animal studies.
3. Nonseptic patients.

The eligible studies were heterogeneous and, therefore, did not permit statistical pooling.

Appendix 1
Sources searched: Cochrane, EMBASE, Medline
Search strategy used:
Search History:

1. MEDLINE; exp SEPSIS/; 93873 results.
2. MEDLINE; sepsis.af; 88127 results.
3. MEDLINE; 1 OR 2; 132947 results.
4. MEDLINE; exp ADRENERGIC BETA-ANTAGONISTS/; 79054 results.
5. MEDLINE; ("β-blockers" OR "β-blockers" OR "β-adrenergic blocking agent*" OR "β-antagonist*" OR "β-adrenergic antagonist*" OR "β-adrenoreceptor antagonist*" OR "β-adrenergic receptor antagonist*").ti,ab; 21035 results.
6. MEDLINE; 4 OR 5; 87584 results.
7. MEDLINE; 3 AND 6; 171 results.
8. MEDLINE; 7 NOT animals/; 71 results.
9. EMBASE; exp SEPSIS/; 157125 results.
10. EMBASE; sepsis.af; 128218 results.
11. EMBASE; 9 OR 10; 183205 results.
12. EMBASE; exp BETA ADRENERGIC RECEPTOR BLOCKING AGENT/; 220234 results.
13. EMBASE; ("β-blockers" OR "β-blockers" OR "β-adrenergic blocking agent*" OR "β-antagonist*" OR "β-adrenergic antagonist*" OR "β-adrenoreceptor antagonist*" OR "β-adrenergic receptor antagonist*").ti,ab; 28021 results.
14. EMBASE; 12 OR 13; 224302 results.
15. EMBASE; 11 AND 14; 1198 results.
16. EMBASE; 15 NOT animals/; 1171 results

Data extraction

After independent review of the finalized articles, the following information was extracted. Year of publication, sample size, study population, heart rate (HR) control, mortality rate, adverse incidence and change in metabolic parameters with the administration of β-blockers. The papers were reviewed to confirm the initial diagnosis of sepsis. Individual authors were contacted to clarify overlapping of patients between studies. Authors were also contacted for data on subgroup analysis.

Study selection

Our electronic database search identified 1242 studies for initial abstract review. We identified 31 texts for full-text review. Of these, 19 were excluded because they did not meet the inclusion/exclusion criteria; 10 editorial reviews, 2 non-β-blockers (calcium channel blockers) 5 animal trials and 2 pediatric population [Figure 1]. Three studies which included 2 case series and 1 randomized controlled trial (RCT) were excluded after clarifying that they referred to the same cohort of patients.[7-9] This was confirmed from personal correspondence with the author[7] and by identifying identical methodology and patient cohort in 2 studies.[8,9] We requested the author of one study[10] for subgroup analysis, but they did not respond.

Study description

A total of 9 studies were included; of which, 7 were interventional and 2 were observational. These can be further classified as follows: One single center RCT,[11] 2 retrospective observational studies,[12,13] 1 pilot study,[14] 1 retrospective analysis of β-blocker administration,[15] and 4 case series.[16-19] Table 1 contains analysis of all included studies.

Results

Hemodynamic parameters

HR reduction was the primary outcome measure in 6 of the 7 interventional studies.[11,14-16,18,19] The 2 retrospective studies[12,13] did not provide data on HR control. Table 2 contains data on HR control. In total 179 patients were administered β-blockers and 173 had achieved target HR. In

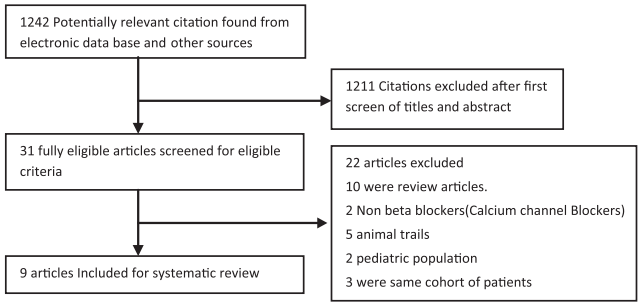

Figure 1: Search flow diagram

Table 1: Characteristics of reviewed studies

First author, year of publication (reference)	Number of patients	β-blocker	Outcomes	Study type	Initiation and duration of administration of β-blockers
Morelli *et al.*, 2013[11]	77	Esmolol	100% target HR achieved, improved mortality	RCT	24 h till D/C
Morelli *et al.*, 2013*[14]	25	Esmolol	100% achieved target HR, improved markers	Pilot	24 h for 24 h
Balik *et al.*, 2012[16]	10	Esmolol	100% achieved target of reduction in HR by 20%	Case series	24 h for 24 h
Macchia *et al.*, 2012[12]	1061	Variable	Improved mortality	Retrospective analysis	Not applicable
Misonoo *et al.*, 2009[18]	21	Landiolol	76% achieved target HR improved arrhythmia	Case series	Not disclosed
Gutierrez *et al.*, 2009[13]	83	Variable	No difference in mortality	Retrospective analysis	Not applicable
Schmittinger *et al.*, 2008[15]	40	Metoprolol	97.5% of patients achieved target HR of 20% reduction	Retrospective analysis of β-blocker administration	17.5±15.5 h, duration not disclosed
Gore and Wolfe, 2006[19]	6	Esmolol	100% of all patients achieved target HR of 20% reduction, increase in oxygen consumption, no change in energy expenditure	Case series	Initiation not disclosed. 3 h duration
Berk *et al.*, 1973[17]	11	Propranolol	Better HR control	Case series	Initial dose 2-3 h then 6-7 h later

**4 patients were repeated in the previous trial by same author. HR = Heart rate, RCT = Randomized controlled trial*

one study,[17] HR data were presented on 4 of the 11 included patients; 3 had better HR control. This is summarized in Table 2.

Stroke volume and stroke volume index

Five studies presented data on stroke volume or stroke volume index.[11,14-16,19] These are summarized in Table 3. All values were not statistically significant. Of the interventional studies 2[17,18] had not looked at stroke volume or stroke volume index, 2 retrospective observational studies[12,13] did not provide data on stroke volume or stroke volume index.

Cardiac index

The data on the cardiac index are summarized in Table 4. Two studies had statistically significant decrease in cardiac output. In one of the case series,[17] cardiac output data were published on 3 of the 11 included patients; of these, cardiac output decreased in 2 patients and in 1 patient cardiac output increased. There were no data on cardiac output or cardiac index presented in 3 studies.[12,13,18]

Norepinephrine requirement

There was statistically significant decrease in norepinephrine requirement in one retrospective study[15] and a nonsignificant decrease in three studies.[11,12,16] The other studies have not commented on the norepinephrine requirements.

Metabolic variables

The majority of the studies suggest improvement in metabolic variable/s. Data are summarized in Table 5. Gore and Wolfe[19] have reported an increase in adenosine triphosphate/total adenosine phosphate, as well as a statistically significant decrease in glucose, palmitate oxidation, and respiratory quotient. One retrospective analysis[13] reported an initial decrease in serum lactate but a subsequent rise in serum lactate in the β-blocker group as compared to control group. The authors did not comment on the time frame in which the analysis or the intervention compared between the groups. Three studies[12,17,18] did not comment on the metabolic parameters.

Mortality

The RCT[11] showed a statistically significant reduction in mortality in the β-blocker group. One retrospective analysis of patients on β-blockers[12] showed improved survival from 17.8% to 22.1% respectively. This study had not scored the severity of sepsis in both groups. The other retrospective analysis of patients on β-blockers[13] showed no difference in mortality rate with a trend toward the worse outcome, but did not reach statistical significance. One retrospective interventional group[15] and one case series[16] quoted a mortality rate of 33% and

10%, respectively. One case series[17] 7 of the 11 patients had survived. The other studies have not commented on mortality.

Table 2: Heart rate control in reviewed studies

Study	Number of patients administered β-blockers	HR control achieved	HR control not achieved
Morelli *et al*., 2013 (JAMA)	77	77	0
Morelli *et al*., 2013 (CCM)	25	25	0
Balik *et al*., 2012*	10	10	0
Macchia *et al*., 2012	Data not presented		
Gutierrez *et al*., 2009	Data not presented		
Misonoo *et al*., 2009	21	16	5
Schmittinger *et al*., 2008	40	39	1
Gore and Wolfe, 2006*	6	6	0
Berk *et al*.	4	3	1

**This study titrated esmolol to decrease in HR to 20% of base rate. HR = Heart rate*

Table 3: Stroke volume change in reviewed studies

Study	Change in stroke volume/index	Time of measurement
Morelli *et al*., 2013 (JAMA)	Increased	96 h
Morelli *et al*., 2013 (CCM)	Increased	24 h
Balik *et al*., 2012	Increased	30 h
Macchia *et al*., 2012	Data not presented	
Misonoo *et al*., 2009	Data not presented	
Gutierrez *et al*., 2009	Data not presented	
Schmittinger *et al*., 2008	Increased	96 h
Gore and Wolfe, 2006	Increased	3 h
Berk *et al*., 1973	Data not presented	

Table 4: Cardiac index in reviewed studies

Studies	Cardiac index (L/min/m^3) mean	Time of measurement
Morelli *et al*., 2013 (JAMA)	Decreased	96 h
Morelli *et al*., 2013 (CCM)*	Decreased by 0.9	24 h
Balik *et al*., 2012	Decreased by 0.2	30 h
Macchia *et al*., 2012	Data not presented	
Misonoo *et al*., 2009	Data not presented	
Gutierrez *et al*., 2009	Data not presented	
Schmittinger *et al*., 2008	Increased by 1.6	96 h
Gore and Wolfe, 2006 *	Decreased by 1.0	3 h
Berk *et al*., 1973	Data not presented	

**Statistically significant*

Adverse outcome

The retrospective interventional study[15] reported asymptomatic bradycardia in 2 patients, increased norepinephrine requirement in 9 patients and increase in milrinone requirements in 6 patients.

The pilot study[14] administered 500 ml of 6% hydroxyethyl starch in 6 patients. A case series[17] described the use of temporary pacing wire in 1 patient, discontinuing β-blocker because of asymptomatic bradycardia and administration of atropine. This study initiated treatments at HR of 100. The case series[16] reported rebound tachycardia after cessation of esmolol. The rest of the studies have not mentioned significant adverse incidents.

Discussion

This systematic review has revealed some evidence for the benefit of β-blocker in sepsis with limited adverse outcomes. The 9 included studies described 1090 patients on β-blocker prior to ICU admission and 186 patients being administered β-blockers during their ICU stay. β-blocker therapy led to improvement in HR control in 6 studies. There was no significant detrimental effect on MAP. Esmolol was the most commonly used agent in the included studies. Infusions of esmolol had a statistically significant improvement in HR control in 4 studies.[11,14,16,19] Studies that have used esmolol have significantly better HR control than those that used other agents; 100% compared with 89.2%. HR control may be the primary target in future trials as using this target has improved mortality with the limited adverse outcome. However, the target HR value is not yet known; some of the studies targeted a HR of 90 beats per minute, and others targeted a 20% reduction in HR from baseline HR. Increased HR causes shortening of diastolic relaxation time and impairment in diastolic function compromising coronary perfusion thereby leading to cardiac ischemia. Studies have shown that tachycardia is associated with increased incidence of cardiac events in critically ill high-risk patients.[20-22] The contribution of HR control alone to the improvement of outcomes in septic patients is currently being addressed by the MODIfY trial (reducing elevated HR in patients with the multiple organ dysfunction syndromes by Ivabradine MODIfY (RCT).

Table 5: Metabolic changes in reviewed studies

Studies	pH	Lactate (mmol/L)	Time of measurement
Morelli *et al*. 2013 (JAMA)	pH higher in esmolol versus control	Mean decrease of 0.4 mmol/L between esmolol versus control	96 h
Morelli *et al*. 2013 (CCM)	Increase from 7.33 to 7.38*	Mean decrease of 0.4	24 h
Balik *et al*. 2012	Data not presented	Mean increase of 0.1	30 h
Schmittinger *et al*. 2008	7.36-7.42*	Mean decrease of 0.66	96 h

**Statistically significant*

There was a trend toward improvement in stroke volume or stroke volume index[11,14,15,19] and decrease in cardiac output.[11,14,15,18,19] Tachycardia worsens myocardial impairment in sepsis, and diastolic filling thereby leading to a decrease in stroke volume.[20] The improvement in stroke volume and stroke volume index in this review could be because the lowering of HR improves diastolic filling and thereby leads to an improvement in stroke volume. HR control also improves myocardial contractility improving stroke volume. Decreases in HR have a comparable decrease in cardiac output possibly because in sepsis cardiac output is predominately dependent on HR.

The β-adrenergic system has a range of effects on cardiac, immune, metabolic and coagulation function. These functions are altered during sepsis.[23] In the pathogenesis of sepsis, there is impairment of oxygen utilization at the mitochondrial level[23,24] and decrease in oxygen delivery to the cellular level. This leads to anaerobic metabolism and hyperlactatemia. In the reviewed studies, there has been an overall trend toward improvement in lactate levels. The mechanism of this could decrease in cellular oxygen expenditure. Improvement in microvascular flow was reported in one study,[14] which could imply an improvement in cellular oxygen delivery.

Catecholamine mediated the hypermetabolic response in septic shock caused increase in resting energy expenditure, extensive protein, and fat catabolism and hyperglycemia. β2-blockers effects include lowering gluconeogenesis, hyperglycemia, proteolysis and resting energy expenditure.[25] β-blockers have been shown to reduce muscle catabolism in burns;[26] it could be postulated that β-blockers have a similar effect in sepsis. However, one study showed that there was no change in muscle catabolism.[19] It is difficult to draw a conclusion on the exact effect of β-blockers in modulating septic metabolic dysfunction.

β adrenergic system modulates the immune system. β2 pathways up regulate the synthesis of anti-inflammatory cytokine and down regulates the synthesis of pro-inflammatory cytokines.[27] The adrenergic system has an effect on monocyte production and immune system apoptosis.[28] Studies have shown a variable effect of β-blockers on the immune system.

Sepsis associated coagulation dysfunction is partly mediated by the adrenergic system. Platelets express adrenoceptors on their surfaces.[29] α2-adrenoceptors enhance platelet aggregation, and β2 receptors reduce platelet aggregation. β-blockers have been demonstrated to decrease platelet aggregation and adhesion.[30] The action of β-blocker is likely to be by multiple mechanisms.

In most studies, β-blockers were started after 24 h of ICU admission based on the theory that the initial compensatory mechanism of sepsis included increase in sympathetic drive to increase HR and systemic vascular resistance and this mechanism would be required during the initial period. However, patients on chronic β-blockers have shown an improvement in mortality.[12] Animal studies showed improvement in survival with early β-blocker therapy[31] prior to the septic insult. This raises the question on the optimal timing of initiation of β-blocker therapy. The duration of infusion of β-blockers has varied from 3 h to the time of discharge in the studies reviewed. This raises the question on what duration should therapy be continued.

The major limitation of the review is that due to the heterogeneous nature of the study it does not permit statistical analysis.

Conclusion

This review of the available evidence suggests that β-blockers may have a role in sepsis. However, at present, we would not recommend the routine use of β-blockers in sepsis until more robust evidence becomes available. This should take the form of a large multi-centered appropriately powered RCT. This trial should also consider the following important aspects in its methodological design:

1. Choice of drug,
2. Timing of initiation of therapy,
3. Duration of therapy, and
4. Choice of physiological endpoint to target.

This systematic review of the available evidence to date provides the reassurance that such a trial is necessary and feasible.

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Conflicts of interest

There are no conflicts of interest.

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