Do \( \beta \)-Blockers Decrease the Hypermetabolic State in Critically Ill Children With Severe Burns?

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**BACKGROUND AND OBJECTIVES:** Severe burns result in a hypermetabolic state that is associated with increased morbidity and mortality. We reviewed the literature to determine if there is strong evidence that short-term \( \beta \)-blockers reduce the hypermetabolic state or mortality and length of stay (LOS) compared with no therapy in patients with severe burns.

**METHODS:** A literature search of PubMed, Embase, the Cochrane Database of Systematic Reviews, and BestBETs was conducted on the use of adrenergic \( \beta \)-antagonists in burn patients.

**RESULTS:** Six randomized controlled trials met the inclusion criteria. Five pediatric trials found that \( \beta \)-blockers reduced the hypermetabolic state (as defined by reduction of cardiac work, rate pressure product, resting energy expenditure, central deposition of fat, and bone mineral loss) and were associated with an improvement in lean muscle mass in patients with severe burns. However, there was no change in LOS or mortality in these children. One adult study in burn patients found shorter LOS in patients treated with \( \beta \)-blockers but no difference in mortality rate. \( \beta \)-blockers were relatively well tolerated, with no differences in adverse effects reported.

**CONCLUSIONS:** \( \beta \)-blockers seem to reduce the hypermetabolic state in pediatric patients with burns, but there is insufficient evidence to suggest they have an impact on mortality rates or LOS.
Children with severe burns (>40% total body surface area) develop a metabolic rate of 180% above baseline during the acute admission. This hypermetabolic rate remains elevated at 150% after wound closure and is still at 110% of the baseline metabolic rate 1 year after the injury. This surge in metabolism is driven by supraphysiologic elevations in stress hormones, catecholamines, and inflammatory mediators; it enables increased metabolic demands to be met by mobilizing energy substrates at the expense of excess tissue catabolism. After a burn injury, metabolic activity and tissue perfusion immediately decrease for 2 to 3 days. This reaction is soon followed by the hypermetabolic response, which has been shown to persist for up to 3 years after injury.

The hypermetabolic response (Fig 1), evident from elevated resting energy expenditure (REE), can lead to the physiologic consequences of lipolysis, catabolism of muscle and bone, hepatic steatosis, increased susceptibility to infections, insulin resistance, and growth retardation in severely burned children. The hypermetabolic response also results in tachycardia and increased cardiac output, cardiac work, and REE without a proportional increase in stroke volume. Prolonged increases in cardiac work can decrease the efficiency of oxygen delivery by the heart and may lead to cardiac failure.

Free fatty acids from lipolysis that are not used may be deposited in the liver or peripheral muscle, leading to dysfunction in these tissues. Proteolysis can lead to an extensive reduction in lean body mass, which may result in immune dysfunction, delayed wound healing, and increased morbidity and mortality.

Because of the central role of adrenergic “overdrive,” β-adrenergic receptor antagonists (eg, propranolol) have been used to mitigate the actions of plasma catecholamines and thus reduce the hypermetabolic state in patients with acute burn injuries. However, β-blockers have also been shown to increase the release of cytokines and suppress cellular immunity, which may be detrimental during sepsis. We examined the available evidence regarding the efficacy of β-blockers in reducing the hypermetabolic state and improving length of stay (LOS) and mortality in burn patients.

**STRUCTURED CLINICAL QUESTION**

In a patient with burns [patient], do short-term β-blockers during hospitalization [intervention] reduce the hypermetabolic state [primary outcome] or mortality and LOS [secondary outcome] compared with no therapy [control]?

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**FIGURE 1** A simplified flowchart on hypermetabolism in burns.
SEARCH STRATEGY AND OUTCOME

The following databases were searched: PubMed, Embase, Web of Science, the Cochrane Database of Systematic Reviews, and BestBETs. We used the Medical Subject Headings of the National Library of Medicine key word search terms of (‘adrenergic β-antagonist’), (‘β blocker’), (‘β-blocking agent’), (‘propranolol’), AND (‘burns’), (‘trauma’).

The study included prospective and retrospective trials of both pediatric and adult patients with severe burns, which compared the effectiveness of patients treated with and without β-blockers. Studies were excluded if they were not written in English, included <10 patients, or involved concomitant administration of another drug that can affect metabolism. No restrictions were placed on the age of patients, mode of administration, time of initiation, or duration of β-blocker usage.

Two independent reviewers assessed all studies identified in the database search for relevance based on the title and abstract. Articles that met the inclusion criteria were retrieved. Two independent reviewers assessed all retrieved studies for relevance. In case of disagreement, a third independent reviewer made the final decision. References from full-text articles were also reviewed for potential suitable studies.

RESULTS

Search Results

The literature search identified 446 references, and 142 full-text articles were retrieved (Fig 2). Six articles that met all the inclusion criteria were included in the present review (Table 1).

Primary Outcomes

With regard to the metabolic outcomes, 3 studies17–19 showed that β-blockers led to a significant reduction in hypermetabolism (as measured according to REE) in children with severe burns. The physiologic consequences of hypermetabolism, which involve loss of peripheral lean body mass and bone mineral content, were decreased in 2 studies.17,18

Another physiologic consequence of hypermetabolism is lipolysis and hepatic steatosis. In 2 pediatric randomized controlled trials (RCTs), the surrogate outcome for these changes (ie, central mass) was determined by measuring the mass of organs such as the liver, spleen, kidneys, and mesenteric fat by using dual-energy X-ray absorptiometry18 or ultrasound.20 Two studies found that central mass was significantly decreased at 3 months when patients were maintained on β-blocker therapy.18,20

In addition to the effects on metabolism, the ramifications of short-term β-blockade on cardiovascular outcomes were also evaluated in 2 studies. Rate pressure...
### TABLE 1 Characteristics of Studies Reviewed

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study Group</th>
<th>Study Type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Key Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herndon et al18, 2012</td>
<td>179 children</td>
<td>RCT (Level 1b)</td>
<td>Propranolol 4 mg/kg/d vs no propranolol for 12 mo Initiated 3 ± 2 d after admission</td>
<td>Mortality</td>
<td>No difference</td>
<td>Mode of administration of propranolol unclear Randomization, allocation concealment, and blinding were not clear</td>
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<tr>
<td></td>
<td>90 given propranolol; 89 control subjects</td>
<td></td>
<td></td>
<td>LOS</td>
<td>No difference</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Rate pressure product (95% CI)</td>
<td>Decrease of 1706 mm Hg × beats/min at 2 wk (1200–2212 mm Hg × beats/min)</td>
<td>Intention-to-treat analysis performed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Percent predicted REE (95% CI)</td>
<td>Decrease of 11% in the propranolol group at 2 wk (8%–27%)</td>
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<td></td>
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<td></td>
<td>Peripheral lean mass (95% CI)</td>
<td>Increase of 664 g at 3 mo (22–1350 g)</td>
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<tr>
<td>Herndon et al17, 2001</td>
<td>25 children</td>
<td>RCT (Level 1b)</td>
<td>Oral propranolol (average: 6.3 mg/kg/d) vs no propranolol for 2–4 wk</td>
<td>Mortality</td>
<td>Not reported</td>
<td>Time of initiation of propranolol not clear Randomization conducted Allocation concealment and blinding not clear Small study and insufficient power Baseline characteristics of 2 groups varied</td>
</tr>
<tr>
<td></td>
<td>13 given propranolol; 12 control subjects</td>
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<td></td>
<td>LOS</td>
<td>Not reported</td>
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<td></td>
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<td></td>
<td>REE (95% CI)</td>
<td>Decrease of 349 kcal/d in propranolol group (181–517 kcal/d)</td>
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<td></td>
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<td></td>
<td></td>
<td>Lean body mass (95% CI)</td>
<td>Increase of 5.6% in propranolol group (4%–7%)</td>
<td></td>
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<tr>
<td>Williams et al21, 2011</td>
<td>406 children</td>
<td>RCT (Level 1b)</td>
<td>Oral propranolol (4–6 mg/kg/d) vs no propranolol</td>
<td>Mortality</td>
<td>Not reported</td>
<td>Randomization, allocation concealment, and blinding were not clear Duration of therapy not clear</td>
</tr>
<tr>
<td></td>
<td>171 given propranolol; 235 control subjects</td>
<td></td>
<td></td>
<td>ICU LOS</td>
<td>No difference</td>
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<tr>
<td></td>
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<td></td>
<td>Stroke volume (95% CI)</td>
<td>Increase of 18% for the propranolol group (17.2%–18.8%)</td>
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<td></td>
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<td></td>
<td></td>
<td>Rate pressure product (95% CI)</td>
<td>Decrease of 1500 mm Hg × beats/min (1331–1669 mm Hg × beats/min)</td>
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<tr>
<td>Jeschke et al,19, 2007</td>
<td>245 children</td>
<td>RCT (Level 1b)</td>
<td>Oral propranolol (2–6 mg/kg/d) vs normal saline placebo for &gt;3 d</td>
<td>ICU LOS</td>
<td>No difference</td>
<td>Randomization, allocation concealment, and blinding were not clear Intention-to-treat analysis performed</td>
</tr>
<tr>
<td></td>
<td>102 given propranolol; 143 control subjects</td>
<td></td>
<td></td>
<td>Mortality</td>
<td>No difference</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Infections and sepsis</td>
<td>No difference</td>
<td>Intention-to-treat analysis performed</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Percent predicted REE</td>
<td>Decrease of 20% (P &lt; .05)</td>
<td>Time of initiation and duration of therapy not clear</td>
</tr>
<tr>
<td>Barrow et al20, 2008</td>
<td>98 children</td>
<td>RCT (Level 1b)</td>
<td>Oral propranolol (12–6 mg/kg/d) vs placebo started after second operation</td>
<td>Liver size</td>
<td>6% reduction in liver size in propranolol group (P &lt; .001)</td>
<td>Allocation concealment and blinding were not clear Time of initiation and duration of therapy not clear</td>
</tr>
<tr>
<td></td>
<td>44 given propranolol; 54 control subjects</td>
<td></td>
<td></td>
<td>Lean body mass</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Mohammadi et al22, 2009</td>
<td>79 adults</td>
<td>RCT (Level 1b)</td>
<td>Oral propranolol (2–7.92 mg/kg/d) vs starch powder placebo started on day 4 of admission</td>
<td>Hospital LOS (95% CI)</td>
<td>Decrease of 6.5 d (3.3–7.8 d)</td>
<td>Randomization was performed Allocation concealment and blinding were not clear Intention-to-treat analysis performed</td>
</tr>
<tr>
<td></td>
<td>37 given propranolol; 42 control subjects</td>
<td></td>
<td></td>
<td>Mortality</td>
<td>No difference</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sepsis</td>
<td>No difference</td>
<td>Duration of therapy not clear</td>
</tr>
</tbody>
</table>

CI, confidence interval.
product, a correlate of myocardial oxygen consumption, is the product of mean arterial pressure and heart rate. Rate pressure product was found to be significantly decreased with short-term β-blocker therapy in 2 studies.\textsuperscript{16,21} Stroke volume, as determined on echocardiogram, was also significantly increased with β-blocker therapy.\textsuperscript{21}

**Secondary Outcomes**

One RCT in adult burn patients reported shorter LOS in patients treated with β-blockers compared with patients receiving placebo.\textsuperscript{22} Four RCTs examined LOS as secondary outcome measures. Only 1 adult study demonstrated a significant decrease in hospital LOS (6.5 days [95% confidence interval: 5.3–7.8]). Of the 6 RCTs included in this study, 3 reported mortality rates as secondary outcomes. One adult\textsuperscript{22} and 2 pediatric\textsuperscript{8,18} studies found no statistical difference in mortality rates between the 2 groups.

**Adverse Events**

In terms of safety outcomes, β-blockers were relatively well tolerated with no significant differences in blood pressure between the intervention and control groups. However, a small number of patients in the intervention group required omission of ≥1 dose of the β-blocker due to low blood pressure. Immunologically, β-blockers have been shown to increase cytokine release and suppress cellular immunity, which may be detrimental during sepsis.\textsuperscript{14,15} However, in 2 studies, no significant difference in the incidence of infection was found in patients treated with and without β-blockers.\textsuperscript{16,22} In fact, 1 study found a significantly shorter wound-healing time with β-blockers ($P = .04$).\textsuperscript{22} Another study reported incidences of hypoglycemia, bradycardia, cardiac arrhythmia, and respiratory compromise in patients treated with β-blockers.\textsuperscript{16} It is noteworthy that none of the studies was powered to detect differences in the incidence of these adverse effects.

**Study Quality and Bias**

The trials included\textsuperscript{17–22} in our review unfortunately have a high risk of bias. Three of the RCTs did not clearly state the method of randomization.\textsuperscript{18,19,21} Allocation concealment and blinding of patients, caregivers, and outcome assessors were also not explicitly described in any of the studies. Baseline characteristics of the treatment and control groups were similar in all RCTs except for the study by Herndon et al.\textsuperscript{17} In this study, the percentage of total body surface area burned, weight, age, and gender distribution differed between the intervention and control arms. Attrition rates were also not reported in 2 studies.\textsuperscript{19,21} None of the studies was powered to detect differences in the primary outcomes. Six studies were conducted in Shriners Hospitals for Children in Texas, with overlap in the time period that 4 of the studies were conducted, raising concerns about the possibility of duplication of results. There was also variation in the route of administration (parenteral or oral), dosage, time of initiation, and duration of β-blockers administered.

**DISCUSSION**

The epidemiology of burn injury varies according to the region, socioeconomic status of the country and population, race, and ethnicity. The decline in incidence of burns in the United States has led to a 25% decrease in the number of burn centers.\textsuperscript{23} Thus, the present review may be of interest to primary care providers who only occasionally encounter a burn patient.

Studies in which patients were treated with other drugs such as oxandrolone, insulin, and growth hormone were excluded because these drugs can attenuate some effects of the hypermetabolic state. This approach makes it difficult to draw conclusions on which drug has affected the outcomes of interest. Two studies specifically noted that no other anabolic drugs were used.\textsuperscript{18,19} A retrospective study\textsuperscript{14} assessed adult patients who were already taking β-blockers before the burn injury compared with patients who were not on β-blockers before the burn injury. This study was not included due to potential bias, with the matched control patients having a higher incidence of inhalation injury and higher percent body surface area burns compared with the patients on β-blockers. This imbalance of clinical characteristics can potentially confound the outcomes of hospital LOS and mortality.

The evidence reviewed in the present article suggests that hypermetabolism, as measured by using REE,\textsuperscript{17,18} may be decreased in patients treated with β-blockers. In children, the physiologic consequences of hypermetabolism that may be improved with β-blocker treatment include loss of weight, peripheral lean body mass, and bone mineral density and an increase in lipolysis and hepatic steatosis.\textsuperscript{17,18,20} The effect of β-blockers on pertinent clinical outcomes related to these physiologic changes (eg, bone fractures, final height) were not reported in any of the studies reviewed. However, clinical significance of the reduction in central mass (which is believed to correlate with extent of hepatic steatosis) remains uncertain. Studies examining the long-term incidence of hepatic steatosis and cirrhosis in burn patients will be an important focus for future research to more fully understand the consequences of the hypermetabolic state as well as the therapeutic role of β-blockers. The limited evidence currently available also demonstrates that β-blockers may be beneficial in reducing cardiac work and rate pressure product with improvement of stroke volume.\textsuperscript{18,19} However, the importance of these cardiovascular effects with respect to mortality and LOS has not been established.

Our review highlights a concerning lack of data regarding the effect of short-term β-blocker use on the clinically important outcomes of LOS and mortality. Because mortality in children with severe burn injury has decreased drastically over the last decade,\textsuperscript{25} larger trials are needed to be sufficiently powered to detect differences in mortality rates.

The available evidence found that β-blocker use in pediatric burn patients is not associated with significant adverse effects. Specifically, there was no significant increase in the incidence of hypotension or infection in patients treated with β-blockers. However, the studies reviewed were not powered to detect differences in other adverse effects.
CLINICAL BOTTOM LINE
Short-term β-blockers are a useful therapeutic option in reducing the hypermetabolic state in patients with burns. There is insufficient evidence to suggest that short-term β-blockers will be useful in decreasing mortality rates and hospital LOS, however. Because this therapy may be an effective option for reducing the negative outcomes associated with the hypermetabolic state in these patients, clinicians should weigh the risks and benefits of β-blockade.

REFERENCES
Do β-Blockers Decrease the Hypermetabolic State in Critically Ill Children With Severe Burns?
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