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The efficacy and safety of adrenergic blockade post burn injury: A systematic review and meta-analysis

Efficacy and safety of adrenergic blockade post burns

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ABSTRACT

Background: The hypermetabolic state after severe burns is a major problem that can lead to several pathophysiological changes and produce multiple sequelae. Adrenergic blockade has been widely used to reverse these changes and improve outcomes in burned patients, but has not been rigorously evaluated. The aim of this systematic review is to investigate the efficacy and safety of use of adrenergic blockade post burn injury.

Methods: The databases MEDLINE via OVID, Pubmed, EMBASE, CINAHL, Cochrane Library and Web of Science were searched from inception to December 2014 with search terms including "burns" and "Beta-Blockers" with appropriate synonyms. Articles were restricted to those published in English, French or Spanish. Randomized controlled trials, non-randomized controlled trials and systematic reviews were screened. After an independent screening and full text review, ten articles were selected and an appraisal of risk of bias was performed.

Results: From 182 articles screened, nine randomized controlled trials and one non-randomized controlled trial met the inclusion criteria. Pooled analyses were performed to calculate effect sizes and 95% confidence intervals. There was a positive effect favouring propranolol use that significantly decreased resting energy expenditure (g=-0.64; 95% CI -0.8,-0.5; p<0.001) trunk fat (g=-0.3; 95% CI -0.4,-0.1; p<0.001); improved peripheral lean mass (g=0.45; CI 0.3, 0.6; p<0.001) and insulin resistance (g=-1.35; 95% CI -2.0,-0.6; p<0.001). Occurrence of adverse events was not significantly different between treated patients and controls.

Conclusions: Limited evidence suggests beneficial effects of propranolol post burn injury and its use appears safe. However further trials on adult population with a broader range of outcome measures are warranted.

Registered at PROSPERO. Registration number CRD42014015115.

Level of Evidence: Systematic review and meta-analysis, Level III

Type of Study: Therapeutic

Keywords: Burns, adrenergic blockade, beta blockade, propranolol, hypermetabolism

BACKGROUND

Worldwide, there were nearly 11 million severe burn injuries requiring medical care in 2004 (1). Mortality due to burn injuries has been reduced from an age-standardised death rate (per 100,000) of 5.9 in 1990 to 3.5 in 2013. This represents a median change of -41.9 (-50.85 to -29.74) % in the whole period (2) and as a result, a burn injury is emerging as a challenging chronic disease, with 20 (12-32) years living with disability per 100,000 individuals in the world population (3).

Changes to systemic metabolism drive the majority of the pathological problems. The hypermetabolic response following burns is characterized by an elevated metabolic rate, hyperdynamic circulation, increased oxygen and glucose consumption, muscle and bone hypercatabolism. Evidence also suggests higher rates of infection even after three years post burn (4).

Catecholamines play a role as primary mediators of the hypermetabolic response in severe burns (5). Early after the burn injury, a 10-fold increase in plasma catecholamine concentration can be observed in patients and this dramatic rise could explain the increased muscle protein catabolism and the elevated metabolic rate (6).

Several pharmacological studies involving anabolic steroids, recombinant human growth hormone (rhGH), insulin, and metformin have examined the efficacy of these drugs on the reduction of hypermetabolic response post burn injury (7, 8). Similarly, adrenergic blockade, specifically the non-selective adrenergic beta antagonist propranolol, has been utilized to minimise the effects of the elevated level of plasma catecholamine concentrations. This

hypothetically results in an anticatabolic effect thereby reducing the catecholamine-induced hypermetabolic response (7).

Furthermore, administration of beta-antagonists may produce short (immunosuppression in acute stress conditions or haemodynamic compromise) or long term side effects, such as attenuation of the immune function (9, 10). However, to date, there has not been a systematic evaluation of the benefits and safety of propranolol following burn injury.

Therefore, the purpose of this systematic review is to assess the quality of evidence supporting the efficacy and safety of use of beta-adrenergic blockade in adults and children affected by burn injuries.

METHODS

A protocol for the systematic review was created (see protocol, Supplemental Digital Content 1, http://links.lww.com/TA/A672) and registered at PROSPERO database (registration number CRD42014015115). The PRISMA statement (11, 12) was followed to assure the quality of reporting (see checklist, Supplemental Digital Content 2, http://links.lww.com/TA/A673).

Paper Identification and Selection

To search the databases, a population, intervention, comparison, outcomes and study design (PICOS) approach was performed to select and define keywords. Population was defined as adults or children in any phase of burn injury. Beta Blockers in general or propranolol as the specific drug were defined as the exclusive intervention; consequently, combined intervention

studies were excluded. We did not make comparisons with any other treatment and outcomes were defined as any endpoint showing changes in efficacy and safety after intervention.

Studies were identified by searching Medline via OVID, Pubmed, CINAHL, Cochrane Library, Embase and Web of Science databases using the key words "Burn", "Burns", "Burned", "Burn injury" or "Thermal Injury" for population and "Beta-Blockers", "Adrenergic Beta-Antagonists" or "Propranolol" for intervention. The searching process was restricted to studies performed in humans and by study design (Systematic Reviews, Randomized Controlled Trials or Non-Randomized Controlled Trials). The searching period was from database inception until December 2014 and restrictions were applied to select articles published in English, French or Spanish languages (see search strategy for PubMed Supplemental Digital Content 3, http://links.lww.com/TA/A674).

Disagreements between reviewers (OF, JP) were resolved by consensus by a third reviewer (KS). Citation tracking and key author searches were also completed with no further studies identified (Figure 1).

A data extraction sheet was developed, and one author (OF) extracted the data from selected articles, completed the data sheet and tabulated the information. Five authors were contacted to request further information. One author provided figures that had been presented in graphical form in the published report. Information was extracted from each article including: a) characteristics of participants (age, gender, severity of injury) b) modality of treatment (length, dose, administration via) and c) outcome measures.

To appraise the risk of bias on selected reports, two reviewers (OF, JP) working independently, used a modified and updated version of the method for assessing the quality of Randomized

Controlled Trials published by Chalmers et al (1981) (13). This scale determined the adequacy of randomization process, allocation concealment, use of placebo medication in the control group, blinding of patients and researchers and the quality of reporting.

Data Analysis

A quantitative approach was used to analyse the data at a group level, if there were two or greater trials with homogenous outcomes. To compare results between trials, for continuous outcomes the unbiased effect size estimators (Hedges g) with 95% confidence intervals was calculated, using Comprehensive Meta-analysis™ software. Dichotomous outcomes were expressed as risk ratios with 95% confidence intervals. The data was pooled using the fixed effects model, however when heterogeneity was statistically significant (Q statistic $p<0.01$), the data was re-analysed using the random effects model.

RESULTS

The searching of the six databases provided a total of 282 citations. After duplicates were removed, 182 references were screened by two reviewers (OF, JP) using title and abstract information. One hundred and fifty three were discarded because they did not match the inclusion criteria. Twenty nine were reviewed in full text to check eligibility. Nineteen studies were excluded in this phase (thirteen because design did not match inclusion criteria, three for using a combined intervention, two because participants did not match inclusion criteria and one conference abstract where the outcomes assessed were not relevant for this systematic review) (Figure 1). Ten studies published between 2001 and 2012 were finally selected for the review,

nine of them were randomized controlled trials and one was a non-randomized controlled trial (14). No current systematic reviews on this topic were found.

Intervention

The length of the intervention ie beta-adrenergic blockade varied from ten days to twelve months with the median time of 21 days. Treatment was started from 24 hours to twelve days post burn injury. All trials used propranolol as the adrenergic-blockade agent. Dose, frequency and administration route varied among the selected studies (Table 1).

Demographics and setting

The included studies recruited a total number of 451 patients (range 4 to 125 patients) in the treatment arm, and 611 (range 4 to 215 patients) in the control arm. Seven studies (15-21) were completed in the paediatric population, one involved exclusively adults (22) and the remaining two studies (14, 23) used both paediatric and adult subjects. All trials were performed in single-centre settings and eight out of ten trials were performed in the same paediatric burn research centre. Detailed demographic data of the included studies can be observed in Table 1.

Quality assessment

The risk of bias for each study is detailed in Supplemental Digital Content 4 (see risk of bias, Supplemental Digital Content 4, http://links.lww.com/TA/A675). Of nine items analysed, three (random sequence generation, appropriate statistical analysis and complete non-selective reporting) were completed by 90% of the studies selected. Eight of ten studies advised of the selection description and reject log, while only 30% reported complete outcome data and figures (14, 19, 22). Only one (22) of 10 studies was explicit in use of blinding methods for both patients

and personnel. Assessor blinding was reported for one study (22), whilst allocation concealment and an *a priori* estimation of sample size were not reported by any study included in this systematic review. Only four studies (15, 17, 20, 22) reported using a placebo medication for the control group.

As eight out of ten selected studies were completed in the same centre and trials had different outcomes and methodology, completing meta-analysis for the majority of measures was difficult.

Outcome Measures

Cardiac effects

Heart rate – percentage change, percentage of predicted and absolute values

From ten studies incorporated in this review, changes in heart rate post propranolol treatment were reported in five trials (18, 19, 21-23). Two studies (18, 21) found a decrease of 18-20% in the treatment group compared to controls (Table 2).

Herndon et al (19), examined heart rate expressed as a percentage of predicted according to reference values in a paediatric population. Data reported at four different time points was used to calculate effect sizes using the fixed effect model (i^2=0.00, Q= 2.4, p=0.493). There was a significant reduction in predicted heart rate at various time points favouring propranolol (pooled Hedges's g=-0.258; 95% confidence interval -0.4, -0.1; p=0.001) (see Supplemental Digital Content 5, http://links.lww.com/TA/A676, heart rate % predicted forest plot graph).

Heart rate measured by mean beats per minute (bpm) was examined in two studies performed in paediatric and adult populations (22, 23). Mohammadi et al (22) in an adult population reported a significantly decrease in heart rate after propranolol treatment, while Morio et al (23) in subjects

with ages ranged from 5.8 to 56.5 years (mean 21.7±18.9 years) also demonstrated a significant decrease associated to propranolol administration (Table 2).

Cardiac Output

Cardiac Output (% of predicted) was included as an outcome measure in one paediatric study (21) showing a decrease favouring the intervention group ($p<0.05$) (Table 2).

Metabolic outcome measures

Liver Size

Incidence of increased liver size was investigated in one study (15) to evaluate the efficacy of propranolol on reducing hepatomegaly after burn injury. From 49 children analysed receiving a placebo, 39 (80%) showed an increase in liver size compared to 5 (14%) in the propranolol group. Difference between groups was statistically significant χ^2 (1, N=85) = 35.87, $p<0.01$ (Table 2).

Metabolic Rate

Five studies, all performed in a paediatric population (16-20) included metabolic rate as a variable and all of them used resting energy expenditure (REE) as the outcome measure. One study (17) did not report the results obtained in this outcome, while another one (16) did not provide figures but reports a significant decrease in REE after propranolol use ($p<0.05$).

Herndon et al. (18) reported REE as mean change in kcal/day and found a significant decrease in the propranolol group compared to controls ($p=0.001$). Detailed data is available in Table 2.

Jeschke et al (20) in varied treatment times found a significant effect ($p<0.05$) of propranolol administration on reduction of metabolic rate (Table 2).

One paediatric study (19) calculated REE as a percentage of predicted from Harris-Benedict equations at different time points. A fixed effects model was used to pool data ($i^2=46.1$, $Q=5.5$, $p=0.134$) and a significant decrease in REE at each time point was found favouring propranolol use (Figure 2).

From the ten studies included in this review, one used oxygen consumption (ml/min) as an outcome measure (18), finding a significant decrease ($p=0.002$) in propranolol treated children compared with controls (Table 2).

Muscle wasting and body composition

Protein kinetics

Muscle protein net balance was measured in two paediatric studies (17, 18) showing a significant improvement in protein net balance after propranolol administration (Table 2).

Additionally, Herndon et al (18) reported a trend towards significance in muscle protein synthesis ($p=0.07$) but no significant effect on muscle protein breakdown ($p=0.2$) after two weeks of propranolol treatment in children. Detailed data is shown in Table 2.

Body composition

Body composition was measured in a paediatric population in three studies (15, 18, 19) by whole-body potassium scanning or dual-energy x-ray absorptiometry using lean body mass, peripheral lean mass, fat free mass, total body fat and trunk fat as outcomes.

Lean body mass was included in two studies (15, 18) as an outcome measure. One study (15) described no significant change between the propranolol group and controls while Herndon et al. (18) found statistically significant improvements (p=0.01) post propranolol treatment.

Two studies (15, 18) incorporated fat free mass (FFM) as an outcome measure with conflicting results. Barrow et al (15) reported non-significant decreases between groups, while Herndon et al (18) found a significant difference (p=0.003) in loss of FFM between the control (9%) and propranolol group (1%).

Total body fat was measured in one study (15), with no statistically significant effects found between the propranolol group and controls.

Two studies (15, 19) examined trunk fat as an outcome measure and one (19) provided data at four different time points. A fixed-effects model (i^2=0.000, Q=1.261, p=0.73) found a significant reduction in trunk fat favouring propranolol use over time (Figure 3). Barrow et al (15) also obtained trunk fat measures, with no significance between groups.

Of ten studies selected, only one (19) investigated peripheral lean mass as one of the outcome measures for body composition and provided data obtained at four different time points. To illustrate the over time, effect sizes using a a fixed-effects model (i^2=0.000, Q=0.08, p=0.99) were calculated and a significant improvement was found after propranolol treatment (Figure 4).

Blood, plasma, serum hypermetabolism markers

Insulin resistance

Ackay et al (14) investigated changes in insulin resistance after one and two weeks of adrenergic blockade treatment in a mixed sample of children and adults. Data was pooled using a fixed-

effects model (i^2=0.000, Q=0.3, p=0.55) and a significant decrease in insulin concentration was found at the two time points (pooled Hedges's g =-1.358; 95% confidence interval -2.0,-0.6; p<0.001) that favoured propranolol use (see Supplemental Digital Content 6, insulin resistance forest plot graph, http://links.lww.com/TA/A677; figure 6).

Hart et al (16) compared insulin dose (units/hour) used to control hyperglycaemic episodes with no significant differences between groups.

Metabolism substrates, hormones, inflammatory markers

Herndon et al. (18) measured several markers of hypermetabolism after two weeks of propranolol treatment, and found no significant changes between groups for serum glucose (p=0.67), serum potassium (p=0.05), insulin like growth factor I (p=0.56), growth hormone (p=0.26), cortisol (p=0.58) or insulin (p=0.29).

Changes in plasma triglycerides concentration were analysed in one study (15). A significant increase of 54% was found between baseline and post values in those receiving the placebo (p<0.0001), while the increase of 12% on triglycerides concentration post propranolol treatment was not significant (p=0.12).

Epinephrine, norepinephrine and dopamine plasma levels examined in a trial (14) were found to be elevated in patients randomized to the propranolol group, but the differences compared with controls were not statistically significant.

Jeschke et al (20) analysed cytokine expression profile and found that propranolol significantly decreased serum TNF and IL-1 β at one time point when compared with controls (p<0.05). No

differences were found for IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 and macrophage inflammatory protein 1-β between groups (Table 2).

Wound healing

One adult study analysed the effects of propranolol on wound healing (21) and found significant differences favouring propranolol use in healing time ($p<0.004$), time ready to graft ($p=0.007$), area needed for the skin graft ($p=0.006$) and length of hospital stay ($p=0.004$) (Table 2).

Gene expression

Of ten studies incorporated in this systematic review, two used mRNA expression of genes in adipose (15) or muscle (17) tissue after burn injury and propranolol treatment. Barrow et al. (15) compared mRNA expression of three genes between control and propranolol groups. Comparison of monoamine oxidase-A favoured propranolol ($p<0.05$) and changes founded in osteopontin favoured control group ($p<0.05$). No significant differences between groups were found in the expression of IGF-1.

Herndon et al (17) reported changes in mRNA expression of HSP70 with differences favouring the propranolol group ($p<0.05$) (Table 2).

Adverse events

Mortality

Three studies (19, 20, 22) used mortality as an outcome measure, two of them in paediatric populations (19, 20) and one (22) in adults. No differences in mortality rates were found in any of these trials (Table 2).

Incidence of sepsis

Incidence of sepsis was investigated in four trials (16, 18, 20, 22) performed in children and adults subjects, and accepted (24, 25) criteria for the diagnosis was stated in three (16, 18, 20). Sepsis was not defined in one study (22). No significant differences in sepsis incidence were reported in studies involving paediatric or adult populations (Table 2).

Hypotension

Of ten studies analysed, only two (18, 19) investigated whether beta blockade caused hypotension. No statistically significant differences in mean arterial blood pressure (MAP) were found after two weeks of treatment in the first trial (18) ($p=0.7$). Although Herndon et al (19) found a significantly lower mean arterial blood pressure (MAP) in the intervention group at two ($p=0.01$) and four ($p=0.01$) weeks post institution of treatment, this was not clinically significant. Detailed data is shown in Table 2.

Hart et al (16) reported no clinically relevant hypotension or bronchospasm after propranolol use in their sample.

Four studies incorporated description of adverse events as outcome measures. Three of them (15, 17, 18) reported that mechanical ventilation was not required in either control and propranolol groups except for brief perioperative periods. These trials also reported absence of pneumonia in both groups.

Psychological health

No studies included in this systematic review incorporated psychological health and particularly anxiety or posttraumatic stress disorder measures as outcomes.

DISCUSSION

Beta-adrenergic blockade has been used to improve outcomes in patients suffering burn injuries for at least 35 years (5). The American Burn Association Consensus statement in 2013 (26) specified beta-blockade as one of the pharmacologic approach to modulate the stress response after burns, and recognizing the potential benefits associated with beta-blockade on several outcomes related with postburn hypermetabolism. However, they also claimed that a higher level of evidence is necessary to accurately address benefits and safety

This systematic review and meta-analysis has found some limited evidence that there are consistent benefits on cardiac function, liver function, metabolic rate, body composition and wound healing after adrenergic-blockade treatment following burns. Moreover, evidence found from these studies suggests that beta-blocker use is safe and does not cause adverse effects.

The efficacy of adrenergic blockade on cardiac function outcomes of burned patients has been described in a number of studies from the initial observations of Wilmore et al (5) in 1974. Most of the trials performed consistently showed a negative chronotropic effect (5, 15-23, 27-29) and consequently, the benefits of a reduction of cardiac stress without affecting delivery of oxygen (27, 28, 30). This emphasizes the potential role that beta blockade could play in prevention of catecholamine-induced cardiac impairment (28, 30). Increased levels of norepinephrine and epinephrine have been observed in paediatric burn patients even after two years and sixty days respectively (31), and the magnitude of the stress response is related to the size of the burned area (32). The non-selective activity of propranolol on β1 and β2 adrenergic receptors theoretically counteract the increased levels of catecholamines, by binding to adrenergic

receptors and blocking the positive inotropic and chronotropic effect of the sympathetic system (33).

Most of the studies describing effects of propranolol in patients with burns have been performed in paediatric populations while a dearth of trials showing effects in adults was noted. In an adult population a clinical trial comparing both oral and parenteral route administration has shown significant reductions in metabolism and heart rate by both methods (29). Arbabi et al (34) in a retrospective cohort study found that pre morbid use of beta blockers improved outcomes and mortality in adult burned patients. However, caution should be adopted in accepting the results as a requirement for beta blocker use indicated pre morbid co-morbidities.

Despite absence of evidence describing signalling pathways in burned humans treated with beta-adrenergic blockade, animal models provide further evidence as to the mechanism of decreased hypermetabolism post beta blockers (35). Catecholamines were shown to induce endoplasmic reticulum (ER) stress in various cell types through inhibition of the phosphatidylinositol 3-kinase (PI3K)/Akt signalling cascade (35). The actions of the catecholamines appeared to be mediated through the beta-adrenergic receptors, since blockade of these receptors by the beta-blocker propranolol attenuated post burn hepatic ER stress and improved PI3K/Akt signalling (35).

The assumption that metabolic rate could be controlled under an adrenergic-blockade protocol was also examined in this review. A decrease in metabolic rate after propranolol use could be explained by two major reasons.

Breitenstein et al (29) hypothesized that attenuation of circulatory effects, reducing cardiac work and hyperdynamic circulation could explain part of this positive effect. Additionally, elevated concentrations of catecholamines cause increased lipolysis and subsequently, increased plasma

fatty acid levels (36). Increased triglyceride fatty acid cycling and metabolic rate on children and adults post burn injury were further demonstrated by Wolfe et al and a reduction on both cycling and metabolic rate by propranolol use was also observed in this population (37).

Body composition is regarded as a crucial outcome to assess the effects of hypermetabolism on muscle, bone and fat tissue (37, 38). The meta-analysis demonstrated efficacy of propranolol in decreasing trunk fat, which could lead to a reduction in cardiovascular risk (39) and a positive effect on peripheral lean mass.

Evidence from two studies (17, 18) confirms the positive effect of propranolol treatment on muscle protein net balance. Furthermore, one of the studies (18) also investigated the muscle protein synthesis and breakdown. Surprisingly, the complete improvement in protein net balance can be explained by a large increase in protein synthesis in the propranolol group, with the protein breakdown elevated in both treated and untreated patients. Herndon et al (17) found a relationship between the increase in muscle protein synthesis and improvements on mRNA expression of HSP70 gene, which is involved in muscle metabolism, and this mechanism could explain some of the benefits associated with propranolol use. It was also hypothesized that propranolol leads to an improvement in the myocyte intracellular recycling of free amino acids incorporating more substrates for protein synthesis (18). Finally, the effect of propranolol on reduction of metabolic rate could play a role by reducing the substrate oxidation, and avoiding energy substrate release from protein and fat stores.

Benefits related to wound healing were found in an adult population, and is supported by animal models (40, 41). Beta blockade with propranolol is claimed to reduce local inflammatory response and accelerate the process of wound healing (40). The effect of propranolol stimulating

the synthesis of nitric oxide could also assist wound healing by improving collagen deposition and myofibroblastic differentiation (40).

Finally, the data analysed suggests that propranolol does not increase mortality based on data from three studies (19, 20, 22) and confirms the neutral effect of this treatment on the incidence of sepsis. However, caution should be adopted, as the studies were underpowered for these outcomes.

Limitations

This systematic review and meta-analysis has some limitations namely the heterogeneity of treatment regimens and measurement of outcome measures.

Although the criteria used for inclusion of studies was strict, the quality of the studies varied. It must be noted that none of the selected studies followed a concealment allocation of patients and only one (22) explicitly used blinded patients and researchers. However, as most trials were paediatric inpatients, blinding of patients and use of a placebo may have been irrelevant. We also found incomplete outcome data in seven of ten reports,. For this reason, meta-analysis was completed on changes over time for some outcomes and biases within individual studies were described, but not included for further analysis.

Another source of bias could come from the fact that the same research group published eight out of ten studies included in this review, with more than 90% of included subjects.

Additionally these results should not be generalized as most of the trials included only a paediatric population.

Conclusions

Current evidence analysed in this report suggest that the use of beta blockers and specifically propranolol provide limited benefits on cardiac function, liver function, metabolic rate, body composition, muscle protein kinetics and wound healing. There were no reported adverse effects.

Future trials should incorporate adult populations and also psychological and functional outcome measures after adrenergic blockade.

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Figure Legends

Figure 1. PRISMA-Based Flow Diagram: description of the literature search process. *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

Figure 2. Resting Energy Expenditure (% predicted). Changes over 12 months' time period.

Figure 3. Trunk fat (gr). Changes over 12 months' time period.

Figure 4. Peripheral Lean Mass (gr). Changes over 12 months' time period.

Supplemental Digital Content

SDC 1. The efficacy and safety of adrenergic blockade post burn injury: systematic review protocol.

SDC 2. PRISMA 2009 Checklist. Efficacy and safety of adrenergic blockade post-burns.

SDC 3. Search strategy for PubMed.

SDC 4. Risk of Bias.

SDC 5. Heart Rate (% predicted). Change over 12 months' time period.

SDC 6. Insulin Resistance. Changes over 2 weeks' time period.

Figure 1

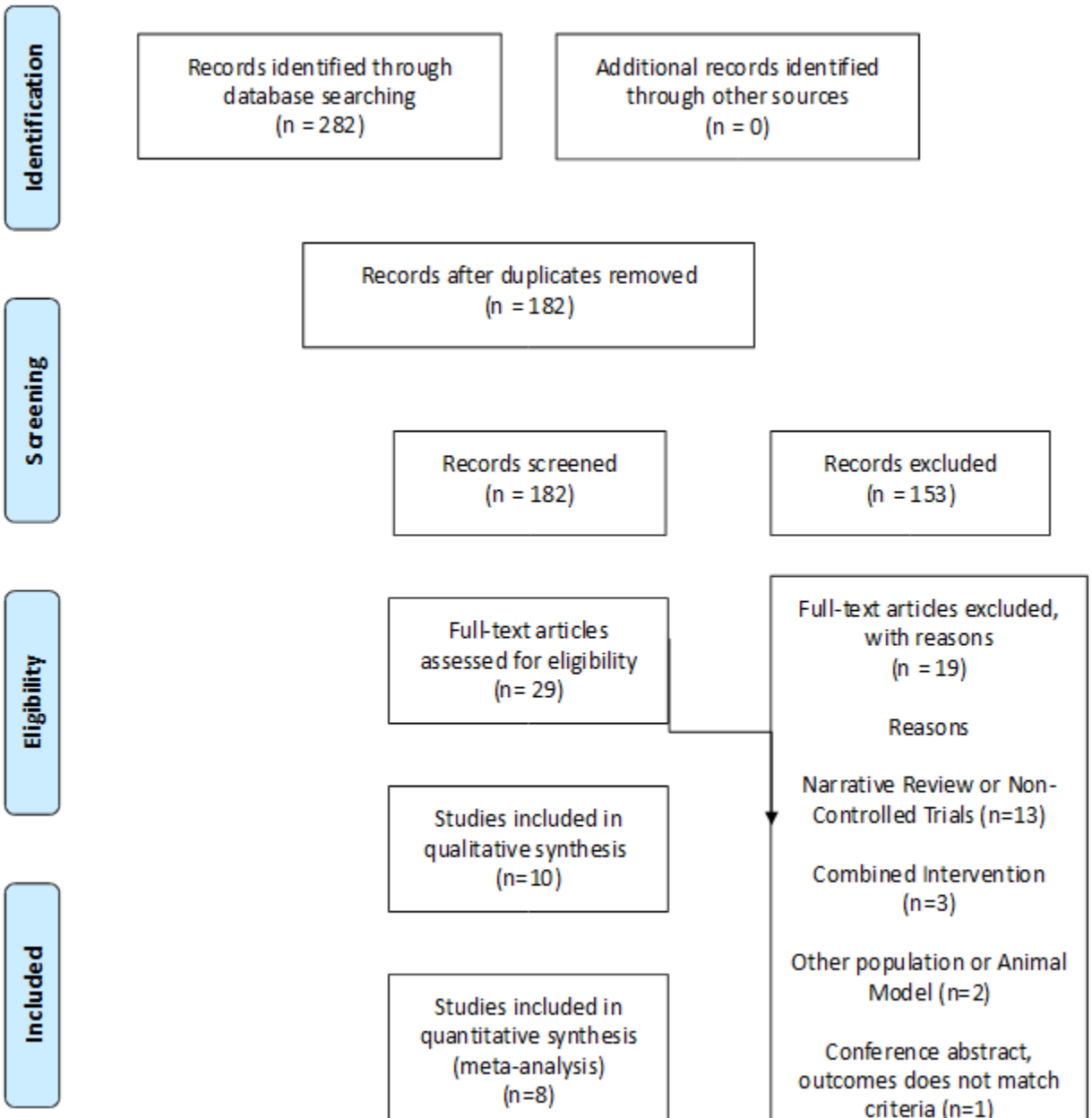

Figure 2

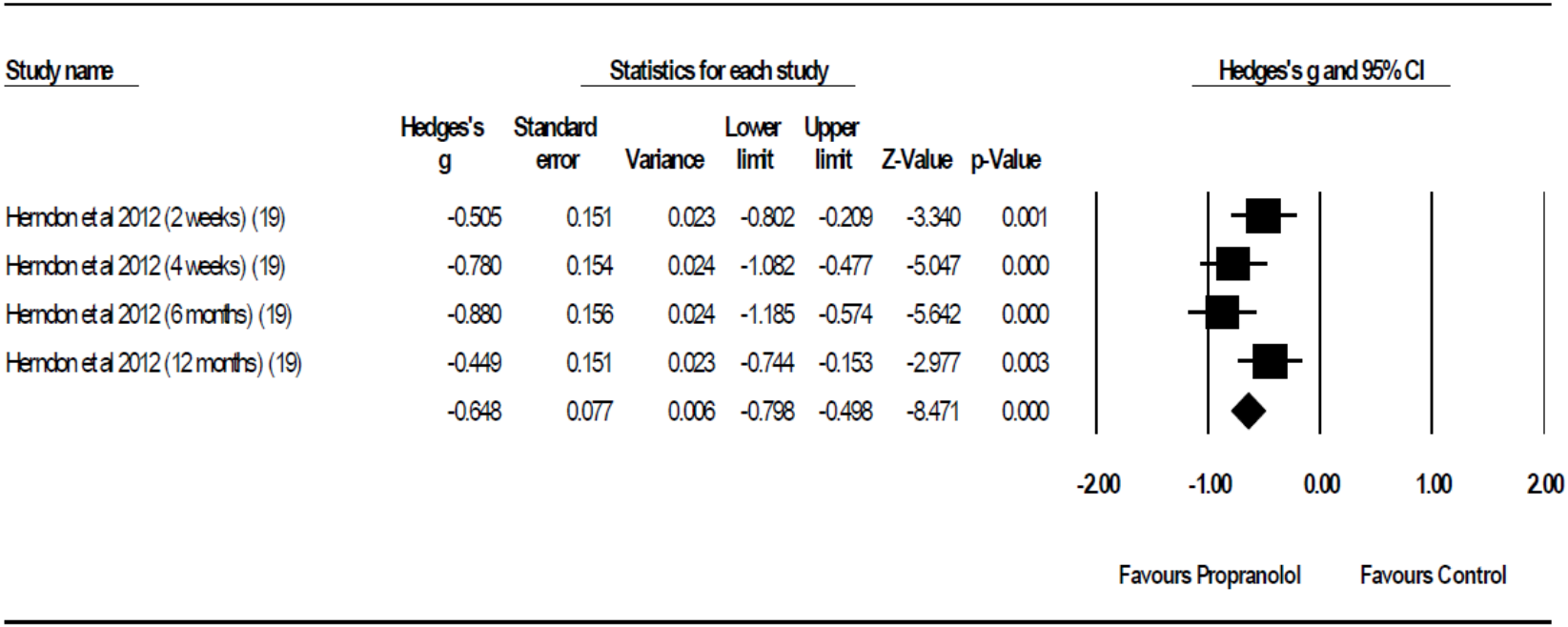

Figure 3

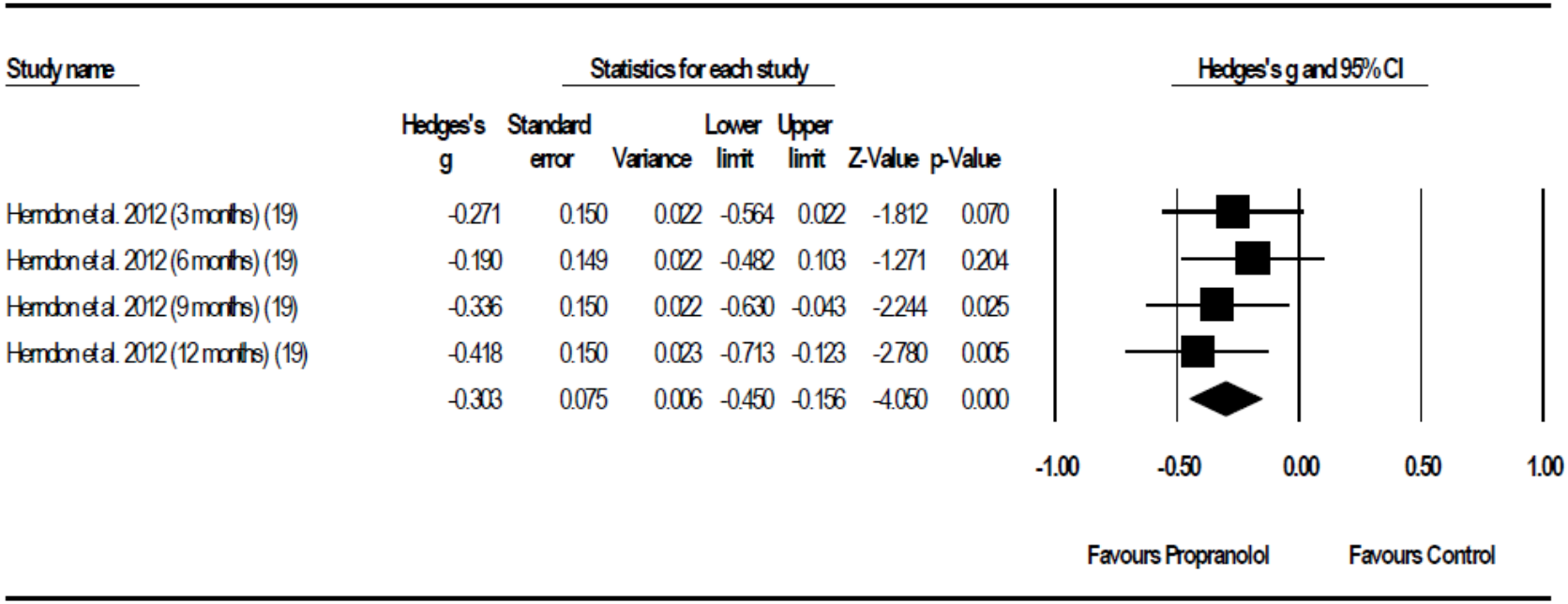

Figure 4

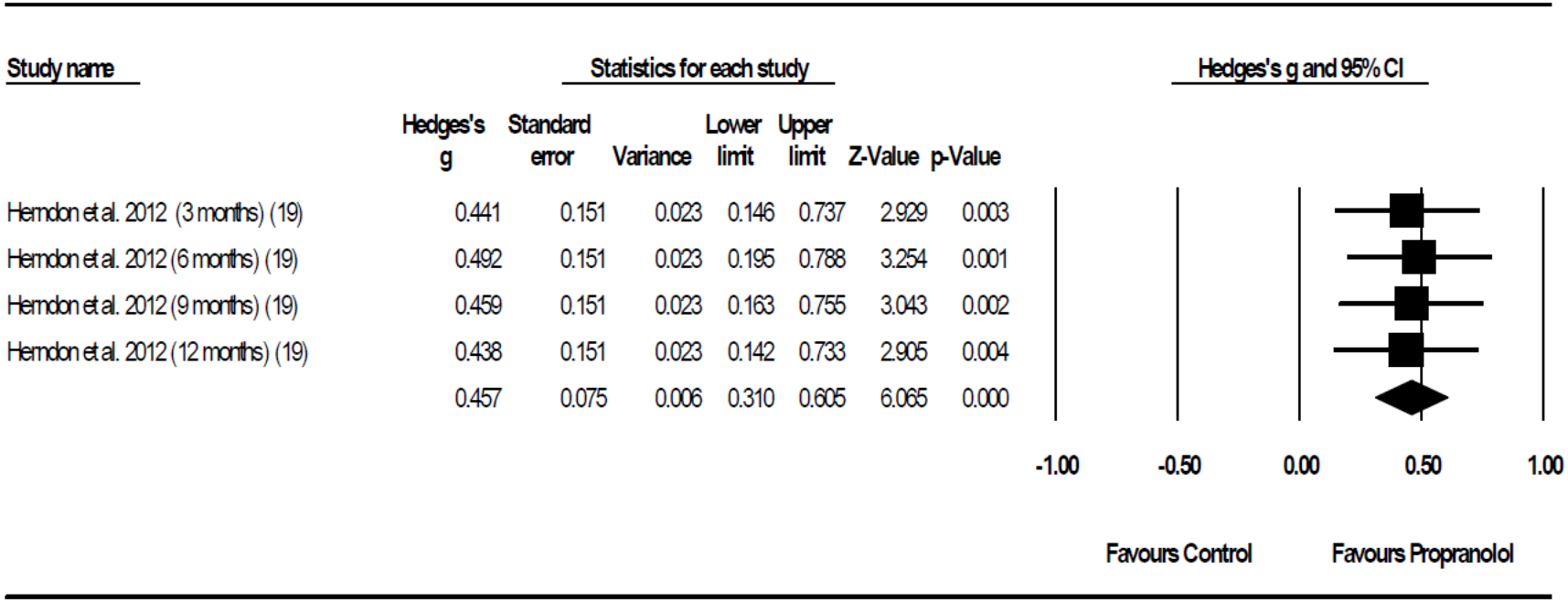

Table 1. Demographics of Selected Studies

AUTHORS	POPULATION	AGE (Mean years±SD)	GENDER (% Males)	TBSA (%)	Third Degree Burn (%TBSA)	Treatment Length	Dose/Route Administration
Akcay,M et al (14) (2005)	CHILDREN/ADULTS Control Group n=10 Propranolol Group n=10	Controls 32.3±3.6 Propranolol 31.4±3.1	Controls 60% Propranolol 80%	Controls 31.8±2.9 Propranolol 30.9±3.4	Unstated	Two weeks	2 mg/kg/day/oral
Barrow, RE et al (15) (2006)	CHILDREN Control Group n=54 Propranolol Group n=44	Controls 8.4±0.6 Propranolol 6.7±0.6	Controls 69% Propranolol 68%	Controls 59±2 Propranolol 56±2	Controls 46±3 % Propranolol 42±3 %	Unstated	0.3 to 1 mg/kg every four or six hours. Dose adjusted to achieve 12 to 15% reduction on HR/enteral
Hart, DW et al (16) (2002)	CHILDREN Control Group n=19 Propranolol Group n=12	Controls 8.4±1.6 Propranolol 7.0±1.5	Controls 68% Propranolol 66%	Controls 58±4 Propranolol 56±4	Controls 46±5 % Propranolol 46±6 %	10 days	0.3 to 1 mg/kg every four or six hours. Dose adjusted to achieve 12 to 15% reduction on HR/oral
Herndon, DN et al (18) (2001)	CHILDREN Control Group n=12 Propranolol Group n=13	Controls 7.8±1.4 Propranolol 6.6±1.5	Controls 75% Propranolol 61%	Controls 47±4 Propranolol 57±4	Controls 39±5 % Propranolol 41±5 %	Two weeks	0.33 to 1.05 mg/kg every four hours to achieve 20% reduction on HR/oral
Herndon, DN et al (17) (2003)	CHILDREN Control Group n=23 Propranolol Group n=14	Controls 10.2±1.1 Propranolol 9,2±1,1	Controls 64% Propranolol 66%	Controls 51±28 Propranolol 61±4,4	Controls 39±4.9 % Propranolol 47±6.4%	Unstated	0.3 to 1.0 mg/kg every four or six hours to achieve 10-15% reduction on HR/enteral
Herndon, DN et al (19) (2012)	CHILDREN Control Group n=89 Propranolol Group n=90	Controls 7±5 Propranolol 7±5	Controls 63% Propranolol 74%	Controls 57.5±13.5 Propranolol 55.7±16.5	Controls 45.6±22.7 % Propranolol 42,9±24 %	12 months	4 mg/kg/day to achieve 15% reduction on HR/not reported
Jeschke, MG et al (20) (2007)	CHILDREN Control Group n=143 Propranolol Group n=102	Controls 7.8±0.4 Propranolol 7.2±0.6	Unstated Propranolol 58%	Controls 55±1 Propranolol 54±2	Controls 43±2 % Propranolol 44±3%	Unstated	0.5 to 1.5 mg/kg every six hours/oral
Mohammadi, A et al (22) (2009)	ADULTS Control Group n=42 Propranolol Group n=37	Controls 24.54±12.06 Propranolol 27.71±9.73	Controls 91% Propranolol 59%	Controls 33.61±8.76 Propranolol 31.42±7.95	Controls 19.09±6.75 % Propranolol 17.48±6.09%	Unstated	1 to 1.98 mg/kg/day to achieve 20% reduction on HR/oral

Morio, B et al (23) (2002)	CHILDREN/ADULTS Control Group n=4 Propranolol Group n=4	Controls 28.3±22.0 Propranolol 15.1±15.3	Unstated	Controls 77.3±12.3 Propranolol 78±19.9	Controls 70.0±19.8 % Propranolol 74.3±21.5%	Three weeks	2 mg/kg/day to achieve 25% reduction on HR/oral
Williams, FN et al (21) (2011)	CHILDREN Control Group n=215 Propranolol Group n=125	Controls 8±5 Propranolol 7±5	Controls 59% Propranolol 71%	Controls 55±15 Propranolol 55±15	Controls 40±24 % Propranolol 42±22%	30 ± 20 days	4 mg/kg/day to achieve 15% reduction on HR/enteral

Table 2. Details and Results on Outcomes for Selected Studies

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Heart Rate (description)	Herndon et al (2001) (18)	Decrease of 20 % compared with baseline and control group	p=0.001	Propranolol
	Williams et al (2011) (21)	Decrease of 18% compared to control group	p<0.001	Propranolol
Heart Rate (% Predicted)	Herndon et al (2012) (19)	168±14 vs 152±14 (two weeks)	p<0.001	Propranolol
		162±17 vs 150±17 (four weeks)	p<0.001	Propranolol
		127±19 vs 116±19 (six months)	p<0.01	Propranolol
		119±16 vs 110±16 (twelve months)	p<0.01	Propranolol
Heart Rate (mean bpm)	Mohammadi et al (2009) (22)	116.45±12.75 vs 83.91±13.19	p<0.001	Propranolol
	Morio et al (2002) (23)	135.2±13.6 vs 123.0±22.9	p<0.05	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Cardiac Output (% predicted)	Williams et al (2011) (21)	158±8 vs 135±5	p<0.05	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Increased Liver Size (incidence)	Barrow et al (2006) (15)	79.59% vs 13.88%	p<0.01	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Resting Energy Expenditure (mean change in kcal/day)	Herndon et al (2001) (18)	140±67 vs -422±197	p=0.001	Propranolol
Oxygen Cosumption (ml/min)	Herndon et al (2001) (18)	236±33 vs 187±24	p=0.002	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Muscle Protein Net Balance (nmol Phe/min/100cc leg)	Herndon et al (2001) (18)	-42±16 vs 35±11	p=0.001	Propranolol
	Herndon et al (2003) (17)	-14.3±12.9 vs 69.3±34.9	p=0.012	Propranolol
Muscle Protein Synthesis (nmol Phe/min/100cc leg)	Herndon et al (2001) (18)	142±34 vs 337±61	p=0.07	NS
Muscle Protein Breakdown (nmol Phe/min/100cc leg)	Herndon et al (2001) (18)	184±30 vs 287±48	p=0.2	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Lean Body Mass	Barrow et al (2006) (15)	No significant change between groups	NS	NS
	Herndon et al (2001) (18)	73.5±1.5 vs 79.1±1.2	p=0.01	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Fat Free Mass	Barrow et al (2006) (15)	No significant change between groups	NS	NS
	Herndon et al (2001) (18)	9% vs 1% lost on FFM	p=0.003	Propranolol
Total Body Fat	Barrow et al (2006) (15)	4% vs 6% increase on TBF	NS	NS
Trunk Fat (% Change)	Barrow et al (2006) (15)	11% vs 16% increase on Trunk Fat	NS	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Insulin Resistance (μU/ml x fasting glucose value)	Ackay et al (2005) (14)	23.28±12.43 vs 18.31±9.91 (one week)	Unstated	NS
	Ackay et al (2005) (14)	24.27±13.68 vs 14.02±7.52 (two weeks)	p<0.05	Propranolol
Serum glucose concentration (mg/dl)	Herndon et al (2001) (18)	114±4 vs 115±3	p=0.67	NS
Serum potassium concentration (mg/dl)	Herndon et al (2001) (18)	3.72±0.08 vs 3.76±0.13	p=0.05	NS
Insulin like Growth factor I (ng/ml)	Herndon et al (2001) (18)	123±16 vs 112±19	p=0.56	NS
Plasma Triglycerides Concentration (% Change)	Barrow et al (2006) (15)	54 vs 12	p<0.001	Propranolol
Growth Hormone (ng/dl)	Herndon et al (2001) (18)	2.0±0.9 vs 1.1±0.4	p=0.26	NS
Cortisol (μg/dl)	Herndon et al (2001) (18)	10.2±2.3 vs 9.8±1.3	p=0.58	NS
Insulin	Herndon et al (2001) (18)	77.3±20.5 vs 104±52	p=0.29	NS

(μIU/ml)				
Insulin dose (units/hour)	Hart et al (2002) (16)	1.0±0.8 vs 1.5±1.5	NS	NS
Serum TNF (pg/ml)	Jeschke et al (2007) (20)	Significant decrease at one time point	p<0.05	Propranolol
Serum IL-1 β (pg/ml)	Jeschke et al (2007) (20)	Significant decrease at one time point	p<0.05	Propranolol
Serum IL-6 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-6 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-8 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-10 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum monocyte chemoattractant protein-1 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum macrophage inflammatory protein 1- β (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Healing Time (days)	Mohammadi et al. (2009) (22)	21.52 vs 16.13±7.4	p<0.004	Propranolol
Time ready for graft (days)	Mohammadi et al. (2009) (22)	33.46±9.17 vs 28.23±8.43	p=0.007	Propranolol
Area needed skin graft (%TBSA)	Mohammadi et al. (2009) (22)	18.72 vs 13.75	p=0.006	Propranolol
Hospital stay period (days)	Mohammadi et al. (2009) (22)	30.95±8.44 vs 24.41±8.11	p=0.004	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Mean Arterial Blood Pressure (mm Hg)	Herndon et al. (2001) (18)	81±3 vs 74±4	p=0.7	NS
	Herndon et al. (2012) (19)	78±8 vs 73±8 (two weeks)	p=0.01	Control
		79±8 vs 74±8 (four weeks)	p=0.01	Control
		81±9 vs 77±9 (6 months)	NS	NS
		78±8 vs 77±8 (12 months)	NS	NS
Sepsis (Incidence)	Hart et al. (2002) (16)	4/19 (21.05%) vs 1/12 (8.33%)	NS	NS
	Herndon et al. (2001) (18)	3/12 (25%) vs 4/13 (30.7%)	p=1.0	NS
	Jeschke et al. (2007) (20)	14/143 (9.79%) vs 7/102 (6.86%)	NS	NS
	Mohammadi et al. (2009) (22)	12/42 (28.57%) vs 9/37 (24.32%)	p=0.18	NS
Mortality (Incidence)	Herndon et al. (2012) (19)	6/89 (6.74%) vs 4/90 (4.44%)	p=0.72	NS
	Jeschke et al. (2007) (20)	14/143 (9.79%) vs 7/102 (6.86%)	NS	NS
	Mohammadi et al. (2009) (22)	12/42 (28.57%) vs 9/37 (24.32%)	p=0.92	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Clinical Consequences (Description)	Barrow et al. (2006) (15)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS
	Hart et al. (2002) (16)	No clinically relevant hypotension or bronchospasm	NS	NS
	Herndon et al. (2001) (18)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS
	Herndon et al. (2003) (17)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Monoamine Oxidase-A Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	0.58±0.31 vs 1.91±0.21	p<0.05	Propranolol
Osteopontin Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	2.33±0.09 vs 0.65±0.02	p<0.05	Control
IGF-1 Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	1.1±0.28 vs 0.91±0.019	NS	NS
HSP70 Gene Expression (mRNA/β-actin ratio)	Herndon et al. (2003) (17)	0.54±0.01 VS 1.21±0.06	p<0.05	Propranolol

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Serum IL-6 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-6 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-8 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
Serum IL-10 (pg/ml)	Jeschke et al (2007) (20)	No significant difference between groups	NS	NS
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Area needed skin graft (%TBSA)	Mohammadi et al. (2009) (22)	18.72 vs 13.75	p=0.006	Propranolol
Hospital stay period (days)	Mohammadi et al. (2009) (22)	30.95±8.44 vs 24.41±8.11	p=0.004	Propranolol

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Mean Arterial Blood Pressure (mm Hg)	Herndon et al. (2001) (18)	81±3 vs 74±4	p=0.7	NS
	Herndon et al. (2012) (19)	78±8 vs 73±8 (two weeks)	p=0.01	Control
		79±8 vs 74±8 (four weeks)	p=0.01	Control
		81±9 vs 77±9 (6 months)	NS	NS
		78±8 vs 77±8 (12 months)	NS	NS
Sepsis (Incidence)	Hart et al. (2002) (16)	4/19 (21.05%) vs 1/12 (8.33%)	NS	NS
	Herndon et al. (2001) (18)	3/12 (25%) vs 4/13 (30.7%)	p=1.0	NS
	Jeschke et al. (2007) (20)	14/143 (9.79%) vs 7/102 (6.86%)	NS	NS
	Mohammadi et al. (2009) (22)	12/42 (28.57%) vs 9/37 (24.32%)	p=0.18	NS
Mortality (Incidence)	Herndon et al. (2012) (19)	6/89 (6.74%) vs 4/90 (4.44%)	p=0.72	NS
	Jeschke et al. (2007) (20)	14/143 (9.79%) vs 7/102 (6.86%)	NS	NS
	Mohammadi et al. (2009) (22)	12/42 (28.57%) vs 9/37 (24.32%)	p=0.92	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Clinical Consequences (Description)	Barrow et al. (2006) (15)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS
	Hart et al. (2002) (16)	No clinically relevant hypotension or bronchospasm	NS	NS
	Herndon et al. (2001) (18)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS
	Herndon et al. (2003) (17)	Neither requirement of MV (except for brief perioperative periods) nor pneumonia in both control and propranolol groups	NS	NS

OUTCOME	AUTHORS	RESULTS	SIGNIFICANCE	FAVORS
Monoamine Oxidase-A Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	0.58±0.31 vs 1.91±0.21	p<0.05	Propranolol
Osteopontin Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	2.33±0.09 vs 0.65±0.02	p<0.05	Control
IGF-1 Gene Expression (mRNA/β-actin ratio)	Barrow et al. (2006) (15)	1.1±0.28 vs 0.91±0.019	NS	NS
HSP70 Gene Expression (mRNA/β-actin ratio)	Herndon et al. (2003) (17)	0.54±0.01 VS 1.21±0.06	p<0.05	Propranolol

SDC 1. The efficacy and safety of adrenergic blockade post burn injury: systematic review protocol

Registered at PROSPERO CRD 42014015115

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INTRODUCTION

Rationale, research question and objective

Burns are a common type of traumatic injuries requiring nearly eleven million medical attentions throughout the world in 2004 (1). Although mortality has been decreased over the last decades (2), studies have been demonstrated that hypermetabolic response following severe burns still cause several detrimental effects twelve months (3) and even three years (4) after injury. Mediated by raised catecholamines concentration (5), this chronic impairment is a major problem characterized by increased metabolic rate (6), increased heart rate and cardiac stress (7), increased oxygen consumption (8), changes in body composition (3), and higher muscle (3) and bone (6) catabolism. Variable incidence of sepsis (9) and mortality (2) have been also reported in burned patients.

As catecholamines are primary mediators of the hypermetabolic response post burns (5), adrenergic blockade has been extensively used to attenuate catecholamine-induced changes after severe thermal injuries (5, 7, 10-22).

However, there has not been a systematic evaluation of benefits associated with propranolol use and safety of such therapeutic intervention. Therefore, the purpose of the systematic review proposed is to assess the quality of evidence supporting the efficacy and safety of use of adrenergic blockade on adult and children affected by burn injuries.

METHODS

Eligibility

A population, intervention, comparison and outcomes (PICO) approach was created to develop an inclusion/exclusion criteria. In summary, PICO's approach will be considered as follows:

- Population: adults or children in any phase of burn injury. Animal model experiments and studies based in patients with toxic epidermal necrolysis syndrome will be excluded.
- Intervention: Beta Blockers in general or propranolol as specific drug. Adrenergic blockade should be used as the exclusive intervention and consequently, studies reporting combined intervention will be excluded.
- Comparison: no comparison will be made with any other treatment.
- Outcomes: any relevant endpoint showing changes in efficacy and safety after intervention will be considered to include.

Study design: We will select systematic reviews, randomized controlled trials and non-randomized controlled trials as designs to be included in this study. Consequently, we will exclude any study with retrospective deign, non-controlled trials (including studies using historical controls) and narrative reviews.

Language: Eligibility will be restricted to articles published in English, French and Spanish.

Time: studies published from database inception to December 2014 will be considered.

Sources: Searching will be restricted to electronic databases and manual search from references of selected articles. We will search on Medline via OVID, Pubmed, CINAHL, Cochrane Library, Embase and Web of Science.

Search strategy

A search strategy was created and tested. For Population, the term "burns" (truncation) OR burns (MeSH) OR "thermal injury" OR "burn injury" will be used as broad as possible for each database. For Intervention, the terms "Beta Blockers" (truncation) OR "Adrenergic Beta-Antagonists" (truncation) OR "Adrenergic Beta-Antagonists" (MeSH) OR "Propranolol" (truncation) will be used for each database.

Searching will be performed using the following combination (when possible)

a) Keywords for population combined by "OR" command: "burns" (truncation) OR burns (MeSH) OR "thermal injury" OR "burn injury"
b) Keywords for intervention combined by "OR" command: "Beta Blockers" (truncation) OR "Adrenergic Beta-Antagonists" (truncation) OR "Adrenergic Beta-Antagonists" (MeSH) OR "Propranolol" (truncation)
c) Results for Population keywords and Intervention keywords will be combined using the "AND" command.

Keywords will be searched in a broadly approach, but to focus the searching process, four limits will be used:

a. As interest is focused in Clinical Trials, limitation to studies performed in Humans will be used according to possibilities offered for each database.
b. As quality of studies need to be controlled, limitation to type of study will be used selecting "Meta-Analysis", "Systematic Review", "Randomized Controlled Trials", "Controlled Clinical Trials" and "Reviews" as a limitation criteria.
c. Publication date from inception to 2014/12/31
d. Language limited to English, French and Spanish.

Selection Process: The EndNote™ X7 reference manager software (Thomson Reuters, Toronto ON, Canada) will be used for import references, discard duplicates and manage the references obtained in each stage of the selection process.

Two reviewers (OF and JP) will conduct independently, a title and abstract screening for eligibility. After abstract screening, selected studies will be retrieved for a second-stage manuscript full-text review and application of inclusion criteria. Divergences will be resolved by discussion and a third reviewer. A data collection sheet will be constructed, tested and refined. Information will be extracted of each included study retrieving data regarding a) characteristics of participants (age, total body surface area (%TBSA) affected by burns, time from injury, third degree burn percentage, gender, etc); b) intervention (drug, dose, duration, frequency, administration via) and c) Outcomes measures and results. If necessary, authors will be contacted via email to ask for further information.

Risk of bias analysis

To appraise the risk of bias on selected reports, two reviewers (OF, JP) working independently, will use a modified and updated version of the method for assessing the quality of Randomized Controlled Trials published by Chalmers et al. (1981)(23).

Data Analysis

A quantitative approach will be used to analyse the data at a group level, if there were a sufficient number of trials with homogenous outcomes. To compare results between trials, for continuous outcomes the unbiased effect size estimators (Hedges g) with 95% confidence intervals will be calculated, using Comprehensive Meta-analysis™ software. Dichotomous outcomes will be expressed as risk ratios with 95% confidence intervals. The data will be pooled using the fixed effects model, however when heterogeneity was statistically significant (Q statistic $p<0.01$), the data will be re-analysed using the random effects model.

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SDC 2. PRISMA 2009 Checklist. Efficacy and safety of adrenergic blockade post-burns.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1,2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2, 3, SDC 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3, 4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3, 4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4, 5, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5, SDC 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-12, Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15, 16

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

SDC 3. Search Strategy

The efficacy and safety of adrenergic blockade post burn injury: A systematic review and meta-analysis

Search strategy: PubMed

1. burns*
2. burns [MeSH Terms]
3. "thermal injury"
4. "burn injury"
5. #1 OR #2 OR #3 OR #4
6. beta blockers*
7. adrenergic beta-antagonists
8. adrenergic beta-antagonists [MeSH Terms]
9. propranolol*
10. #6 OR #7 OR #8 OR #9
11. #5 AND #10
12. (#5 AND #10) Filters: Controlled Clinical Trials; Meta-analysis; Randomized Controlled Trial; Review; Systematic Review
13. (#12) Filters: Humans
14. (#13) Filters: publication date to 2014/12/31
15. (#14) Filters: English; French; Spanish

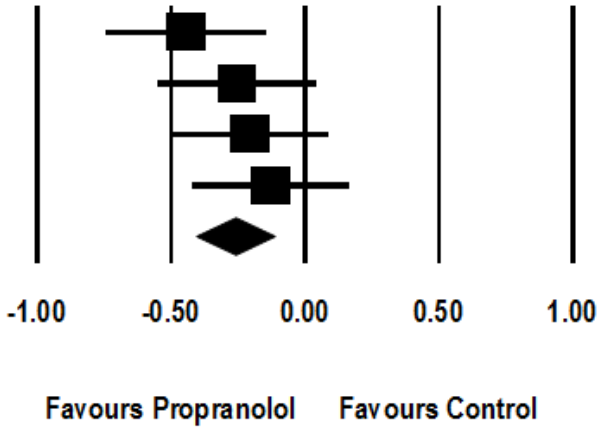
SDC 4. Risk of Bias in individual selected studies

AUTHORS / ITEMS	SDRL	RSG	AC	BPatients	Placebo	BPersonnel	ENES	ASA	COD	CNSR
Akcay,M et al (2005)(14)	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
Barrow, RE et al. (2006)(15)	YES	YES	NO	NO	YES	NO	NO	YES	NO	YES
Hart, DW et al. (2002)(16)	YES	YES	NO	NO	NO	NO	NO	YES	NO	YES
Herndon, DN et al. (2001)(18)	YES	YES	NO	NO	NO	NO	NO	YES	NO	YES
Herndon, DN et al. (2003)(17)	YES	YES	NO	NO	YES	NO	NO	YES	NO	NO
Herndon, DN et al. (2012)(19)	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES
Jeschke, MG et al. (2007)(20)	YES	YES	NO	NO	YES	NO	NO	YES	NO	YES
Mohammadi, A et al. (2009)(22)	YES	YES	NO	YES	YES	YES	NO	YES	YES	YES
Morio, B et al. (2002)(23)	NO	YES	NO	NO	NO	NO	NO	YES	NO	YES
Williams, FN et al. (2011)(21)	YES	YES	NO	NO	NO	NO	NO	YES	NO	YES
SUMMARY (Overall Percentage)	80%	90%	0%	10%	40%	10%	0%	90%	30%	90%

SDRL=Selection Description and Reject Log; RSG=Random Sequence Generation; AC=Allocation Concealment; Bpatients=Blinding of Patients; Placebo: Use of Placebo in Controls; Bpersonnel=Blinding of Personnel; ENES=Estimation of numbers, endpoints, significance; ASA=Appropriate Statistical Analysis; COD=Complete Outcome Data; CNSR=Complete Non-Selective Reporting.

SDC 5. Heart Rate (% predicted). Change over 12 months' time period.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Herndon et al 2012 (2 weeks) (19)	-0.445	0.151	0.023	-0.740	-0.149	-2.950	0.003
Herndon et al 2012 (4 weeks) (19)	-0.255	0.149	0.022	-0.548	0.038	-1.708	0.088
Herndon et al. 2012 (6 months) (19)	-0.206	0.149	0.022	-0.498	0.087	-1.378	0.168
Herndon et al. 2012 (12 months) (19)	-0.129	0.149	0.022	-0.421	0.163	-0.868	0.385
	-0.258	0.075	0.006	-0.404	-0.111	-3.446	0.001



SDC 6. Insulin Resistance. Changes over 2 weeks' time period.