



REVIEW

Systematic review of the effect of propranolol on hypermetabolism in burn injuries[☆]



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KEYWORDS

Burns/metabolism;
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Abstract

Background: The use of propranolol has been proposed to reduce the hypermetabolic response of patients with burn injuries.

Objectives: To review the studies published up to December 2013 on the effects of propranolol in burn patients.

Methods: A PubMed search was conducted using the terms “burns”, “thermal injury”, “beta-blocker” and “propranolol”, with the filters “human” and “English” and “Spanish”. A total of 42 citations were retrieved, 15 of which were randomized clinical trials. The main results are summarized.

Main results: Propranolol at doses adjusted to decrease the heart rate by 20% of the baseline value (4–6 mg/kg/day p.o.) reduces suprphysiological thermogenesis, cardiac work, resting energy expenditure and peripheral lipolysis. It likewise increases the efficiency of muscular protein synthesis and reduces central mass accretion. Most studies have been conducted in pediatric burn patients.

Conclusions: Propranolol reduces the hypermetabolic response in pediatric burn patients. More studies on its effects in adult burn patients are needed.

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PALABRAS CLAVE

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terapéutico

Revisión sistemática del efecto del propranolol sobre el hipermetabolismo del quemado

Resumen

Antecedentes: El uso de propranolol se ha propuesto para atenuar la respuesta hipermetabólica del paciente quemado.

Objetivos: Revisar los estudios publicados hasta diciembre de 2013 que analizan los efectos del propranolol en el paciente quemado.

Métodos: Se aplicaron los términos «burns», «thermal injury», «betablocker» y «propranolol», con los filtros «human» y «English» y «Spanish» en el buscador Pubmed. Se identificaron 42 artículos de los que 15 eran ensayos clínicos aleatorizados. Se resumen los resultados principales de estos artículos.

Resultados principales: El propranolol ajustado para lograr una frecuencia cardiaca un 20% menor a la basal (4–6 mg/kg/día por vía enteral) disminuye la termogénesis suprafisiológica, el trabajo cardiaco, el gasto energético en reposo y la lipólisis periférica. Aumenta la eficiencia de la síntesis proteica muscular y disminuye la acreción de masa central. La mayor parte de estudios han sido realizados en niños.

Conclusiones: El propranolol atenúa la respuesta hipermetabólica del paciente quemado pediátrico. Son necesarios más estudios sobre su efecto en la población adulta.

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Introduction

Severe burns are the type of injury exhibiting the greatest degree of hypermetabolism in humans. In severe burn patients the energy expenditure can be up to twice as high as the estimated resting energy expenditure.^{1,2}

Such hypermetabolism is accompanied by increased muscle metabolism,^{2–4} in an attempt to provide the body with the nutrients required by the high energy demands. This situation has a negative impact upon organ's and system's function and structure, including skeletal muscle, skin, the immune system, and membrane transport. As a result, hypermetabolism can lead to multiorgan dysfunction and even death.⁵

The metabolic and inflammatory changes persist up to three years after injury.⁶ The duration and magnitude of the hypermetabolic response are major determinants of burn patient morbidity.⁷ The prolonged catabolic response conditions body changes such as loss of muscle mass and bone mineral content that slow patient recovery and reincorporation to daily life.^{6,8,9}

An increase in non-protein energy supply does not reduce the loss of lean body mass. Overfed patients tend to store the extra calories in the form of fat, without modifying lean mass catabolism.^{10,11}

Different drugs for reducing catabolism or improving burn patient anabolism have been investigated in recent years. Their use would allow the provision of fewer calories, reducing the risks associated to overfeeding (liver steatosis, accumulation of peripheral adipose tissue and increased production of CO₂).¹²

The most important drugs used in this respect include anabolic hormones (growth hormone, insulin, IGF-1, combinations of IGF-1 and IGFBP-3, oxandrolone and testosterone) and anticatabolic agents such as adrenergic antagonists (propranolol or metoprolol)¹³ (Table 1).

The use of propranolol has been proposed in burn patients for different reasons. On one hand, endogenous catecholamines are primary mediators of the hypermetabolic response,^{2,14} and blocking their action logically can be expected to reduce this response at least in part. On the other hand, propranolol improves recycling of the intracellular free amino acids, thus increasing the efficiency of protein synthesis in muscle,¹⁵ reducing peripheral lipolysis¹⁶ and increasing liver free fatty acid secretion efficiency.¹³

The present study offers a review of the studies that analyze the effects of the administration of propranolol in both pediatric and adult burn patients.

Materials and methods

The articles considered in this review were identified based on a PubMed search. The key words "propranolol", "beta-blocker", "burns" and "thermal injury" were used in combination ("propranolol" + "thermal injury"; "beta-blocker" + "thermal injury"; "propranolol" + "burns"; "beta-blocker" + "burns") to retrieve the relevant

Table 1 Drugs that attenuate the hypermetabolic response in burn patients.

Anabolic agents	Anticatabolic drugs
Growth hormone	Beta-blockers
Insulin	
Metformin	
IGF-1	
Combinations of IGF-1 and IGFBP-3	
Oxandrolone	
Testosterone	

Table 2 Randomized clinical trials.

Authors	Place of study	Study objectives	Patients	Propranolol dose and route	Findings
Herndon et al. (1994) ¹⁶	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To assess the effect of β_1 block upon the cardiovascular system and lipid and protein kinetics in burn patients - To show that the metabolic effects of catecholamines in burn patients are mediated by β_2 receptors 	16 pediatric patients and adolescents (>40% BBS) <ul style="list-style-type: none"> - 8 receive metoprolol - 8 receive propranolol 	Propranolol 2 mg/kg/day i.v., every 8 h, during 5 days. Dose later adjusted for HR 20% less than basal	<ul style="list-style-type: none"> - No significant difference between REE of day 1 and day 5 - Both drugs: decrease in HR and HR-pressure product ($p < 0.05$) - Propranolol reduces lipolysis; metoprolol does not ($p < 0.05$) - Neither propranolol nor metoprolol alter protein kinetics
Aarsland et al. (1996) ²⁸	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To assess the effect of propranolol upon peripheral lipolysis in pediatric burn patients receiving treatment with rhGH - To determine whether there are alterations in VLDL-bound triglyceride secretion rate 	Cross-over clinical trial in 6 children (third-degree burns >30% BBS) <ul style="list-style-type: none"> - 6 patients receive treatment with rhGH and with rhGH + propranolol - 6 controls 	6 days of combined treatment with rhGH (0.2 mg/kg/day s.c.) and propranolol (2 mg/kg/day i.v.). Dose later adjusted for HR 20% less than basal	<ul style="list-style-type: none"> - rhGH increases release of FFAs in pediatric major burn patients - Propranolol reduces release of FFAs, but maintains VLDL-bound TG secretion rate (greater efficiency of FFA conversion to VLDL-bound TGs and release from liver) ($p < 0.05$) - No significant difference in REE
Herndon et al. (2001) ¹⁵	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To assess the effect of propranolol upon REE and muscle catabolism in severe burn patients 	25 pediatric patients and adolescents (>40% BBS) <ul style="list-style-type: none"> - 13 receive propranolol - 12 controls 	After second surgery: propranolol 0.33 mg/kg/4 h through NGT. Dose later adjusted for HR 20% less than basal. Maintained at least 14 days	Propranolol reduces REE (-422 ± 197 kcal/day after 2 weeks [$p = 0.001$]) and lean mass catabolism in pediatric severe burn patients (net muscle protein balance 82% greater than basal ($p = 0.002$) versus 27% less in control group (n.s.))
Hart et al. (2002) ²⁰	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To determine whether combination treatment with GH + propranolol exerts additive effects upon the reduction of burn-induced catabolism 	56 pediatric patients and adolescents (>40% BBS) <ul style="list-style-type: none"> - n = 12: rhGH - n = 12: propranolol - n = 12: rhGH + propranolol - n = 20: controls 	Propranolol 0.33 mg/kg/4 h p.o. Dose later adjusted for HR 20–25% less than basal. Maintained at least 10 days rhGH 0.2 mg/kg/day s.c.	<ul style="list-style-type: none"> - Propranolol: accelerates protein synthesis in early hypercatabolic period in pediatric major burn patients, and reduces REE ($p < 0.05$) - rhGH exerts no additive effect upon muscle protein accretion or REE

Table 2 (Continued)

Authors	Place of study	Study objectives	Patients	Propranolol dose and route	Findings
Morio et al. (2002) ³⁶	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To quantify components of the splanchnic metabolism of FAs and VLDL-TGs in order to understand the mechanisms underlying fatty liver development in severe burn patients - To determine whether propranolol can reduce the accumulation of FAs in the liver, over the short and long term 	8 adult and pediatric patients (BBS>55%) <ul style="list-style-type: none"> - All 8 receive propranolol i.v. in the first study and serve as their own controls - 4: propranolol 3 weeks - 4: controls 	Propranolol i.v. (bolus: 1.5 mg/kg and then perfusion 0.04 μ mol/kg/min) Propranolol p.o. 2 mg/kg/day every 4 h during 3 weeks. Dose later adjusted for HR 25% less than basal	<ul style="list-style-type: none"> - Liver fat is stored in burn patients with diet rich in CHs, due to low FA oxidation rate and secretion in form of VLDL-TGs - Propranolol: reduces availability of FAs and liver storage of TGs ($p < 0.05$). - The effect of propranolol persists after 3 weeks of treatment - Balance between protein synthesis and protein catabolism: <ul style="list-style-type: none"> - 14.3 ± 12.9 nmol/min/100 ml in controls; - $+69.3 \pm 34.9$ nmol/min/100 ml in propranolol group ($p < 0.012$) - Increase of 9 genes implicated in muscle metabolism and decrease of 5 genes implicated in gluconeogenesis and insulin resistance in the propranolol group - Propranolol prevents or attenuates the increase in weight and liver size in pediatric major burn patients ($p < 0.001$) - Propranolol reduces the expression of genes related to lipid metabolism in adipose tissue
Herndon et al. (2003) ²²	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To assess the effect of propranolol upon protein metabolism of pediatric burn patients - To define the genetic and phenotypic events associated to beta-adrenergic block 	37 pediatric patients and adolescents (BBS >40%) <ul style="list-style-type: none"> - 14 receive propranolol - 23 controls 	After second surgery, propranolol 0.3–1 mg/kg/4–6 h through NGT. Dose later adjusted for HR 10–15% less than basal	<ul style="list-style-type: none"> - Increase of 9 genes implicated in muscle metabolism and decrease of 5 genes implicated in gluconeogenesis and insulin resistance in the propranolol group - Propranolol prevents or attenuates the increase in weight and liver size in pediatric major burn patients ($p < 0.001$) - Propranolol reduces the expression of genes related to lipid metabolism in adipose tissue
Barrow et al. (2006) ²³	Shriners Burns Institute (USA)	<ul style="list-style-type: none"> - To determine whether propranolol can be beneficial in pediatric major burn patients by attenuating peripheral lipolysis, portal blood flow and hepatomegalia 	98 pediatric patients and adolescents (BBS>40%) <ul style="list-style-type: none"> - 44 receive propranolol - 54 receive placebo 	After second surgery, propranolol 0.3–1 mg/kg/4–6 h through NGT adjusted for HR 12–15% less than basal. Maintained until healing of 95% of the surface	<ul style="list-style-type: none"> - Propranolol prevents or attenuates the increase in weight and liver size in pediatric major burn patients ($p < 0.001$) - Propranolol reduces the expression of genes related to lipid metabolism in adipose tissue

Table 2 (Continued)

Authors	Place of study	Study objectives	Patients	Propranolol dose and route	Findings
Jeschke et al. (2007) ²⁹	Shriners Burns Institute (USA)	- To determine the effect of propranolol upon infections, sepsis and inflammation in severe burn patients	245 pediatric patients and adolescents (BBS >40%) - 102 receive propranolol - 143 controls	Propranolol 0.5–1.5 mg/kg/6 h enteral route started after 7 days. Intent-to-treat: all administered for at least 3 days	- No significant difference between groups in terms of mortality (6% controls, 5% treated), incidence of infections (30% controls, 21% propranolol) or sepsis (10% controls, 7% propranolol) - Propranolol: decrease in REE, TNF- α and IL-1 β ($p < 0.05$)
Jeschke et al. (2008) ⁴⁶	Shriners Burns Institute (USA)	- To determine whether combined treatment with rhGH + propranolol improves hypermetabolism, the hepatic acute phase response, and the inflammatory response in severe burn patients, without adverse effects	30 pediatric patients and adolescents (BBS >40%) - n = 15: propranolol + rhGH - n = 15: controls	Treatment started on day 7–10 of admission with rhGH (0.2 mg/kg/day s.c.) and propranolol (0.5 mg/kg/4 h, adjusted for HR 10–15% less than basal). Treatment maintained for 25 days	- REE $-5 \pm 8\%$ of predicted value in treated versus $35 \pm 20\%$ in controls ($p < 0.05$) Treated group ($p < 0.05$): - Decrease in C-reactive protein, cortisone, GPT, GOT, FFAs, IL-6, IL-8 and MIP-1 - Increase in IGF-I, IGFBP-3, GH, prealbumin and IL-7 - Without side effects of rhGH alone
Mohammadi et al. (2009) ³⁹	Shiraz Burn Research Center (Iran)	- To determine whether propranolol shortens healing time in burn patients	79 patients (16–60 years; 20–50% BBS) - 37 receive propranolol - 42 controls	Treatment started on day 4 of admission with propranolol 1 mg/kg/day every 4 h enteral route, adjusting for HR 20% less than basal (maximum 1.98 mg/kg/day)	Treated group: - Shorter superficial burn epithelization time (16.13 ± 7.4 versus 21.52 ± 7.94 days; $p < 0.004$) - Shorter graft bed preparation time in deep burns (28.23 ± 8.43 versus 33.46 ± 9.17 days; $p < 0.007$) and greater reduction of size of burn area for grafting (treated: mean BBS 31.42% - require grafting 13.75%; controls: mean BBS 33.61% - require grafting 18.72% [$p < 0.006$]) - Shorter stay (24.41 ± 8.11 versus 30.95 ± 8.44 days, $p < 0.05$) - No significant difference in mortality or sepsis

Table 2 (Continued)

Authors	Place of study	Study objectives	Patients	Propranolol dose and route	Findings
Williams et al. (2011) ²⁷	Shriners Burns Institute (USA)	– To determine the propranolol dose that reduces HR by 15% with respect to HR upon admission and improves cardiac function	340 pediatric patients and adolescents (>30% BBS) – 125 with propranolol (n = 80 BBS 30–60%; n = 33 BBS 60–80%; n = 12 BBS >80%) – 215 controls (n = 139 BBS 30–60%; n = 58 BBS 60–80%; n = 18 BBS > 80%)	From 24 to 72 h until end of admission, propranolol every 6 h via enteral route. Start with 1 mg/kg/day. Dose later adjusted for HR 15–20% less than basal	– Propranolol at dose of 1 mg/kg/day reduces HR 15% with respect to basal. The dose must increase to 4 mg/kg/day the first 10 days in order to maintain the effect (4–6 mg/kg/day in the BBS 60–80% group) – Effective plasma concentration in pediatric burn patients within 30 min (50 ng/ml). Half-life: 4 h – M2b: predominate in non-treated pediatric burn patients – Patients with propranolol: no predominance of M2b ($p < 0.001$)
Kobayashi (2011) ⁵¹	Shriners Burns Institute (USA)	– To determine whether propranolol reduces M2b monocytes in peripheral blood	– First part: 22 pediatric patients (BBS>30%) and 6 healthy volunteers – Second part: randomization to two groups of 15 patients (8 receive propranolol and 7 placebo)	Propranolol 4 mg/kg/day enteral route during 7–17 days, starting 2–5 days after injury	– Burn patients showed activation of PARP – Propranolol: suppresses activation of PARP in the muscle biopsies of the patients ($p < 0.05$)
Olah et al. (2011) ²¹	Shriners Burns Institute (USA)	– To assess the activation of PARP in burn patients and the effect of propranolol upon such activation	– First part: 16 vastus lateralis muscle biopsies in different burn stages versus 3 cleft palate/lip biopsies in controls – Second part: 21 patients (0–17 years, BBS>40%) – 9 receive propranolol – 12 do not receive propranolol	Propranolol 4 mg/kg/day enteral route from admission and during 10 ± 1 months	– Burn patients showed activation of PARP – Propranolol: suppresses activation of PARP in the muscle biopsies of the patients ($p < 0.05$)
Herndon et al. (2012) ¹⁸	Shriners Burns Institute (USA)	– To determine whether the long-term administration of propranolol improves cardiac function, REE and body composition	179 pediatric patients and adolescents (BBS>30%) – 90 receive propranolol – 89 controls	Propranolol started 3 ± 2 days after admission, at dose required to reduce HR 15% (mean dose 4 mg/kg/day p.o.)	– Low mortality in both groups (5 controls, 4 treated), without significant differences. All deaths due to sepsis – Propranolol: few adverse effects (0 hypotension, 2 bradycardia, 1 hypoglycemia, 1 cardiac arrhythmia, 2 respiratory problems) – Propranolol reduces HR and cardiac work. The drug reduces central body mass and trunk fat, improves lean body mass and bone mineral density ($p < 0.001$ – 0.02)

Table 2 (Continued)

Authors	Place of study	Study objectives	Patients	Propranolol dose and route	Findings
Porro et al. (2013) ¹²	Shriners Burns Institute (USA)	- To assess the effect of aerobic and resistance exercise during 12 weeks together with propranolol treatment in pediatric major burn patients	46 pediatric patients and adolescents (7–18 years, BBS > 30%) - n = 27: propranolol + exercise - n = 31: only exercise	Propranolol adjusting to reduce HR by 15–20% versus basal (4–8 mg/kg/day p.o.). Start in first 48 h of admission and maintained until end of physical training (within 6 months after injury)	- 50% increase in muscle strength after training in all children - Increase in peak O ₂ consumption greater in patients with propranolol (36% versus 22%; p < 0.05)

FAs, fatty acids; FFAs, free fatty acids; CO, cardiac output; REE, resting energy expenditure; CHs, carbohydrates; i.v., intravenous; MIP, macrophage inflammatory protein; n.s., non-significant; MBP, mean blood pressure; PARP, poly-(ADP-ribose) polymerase; rhGH, recombinant human growth hormone; s.c., subcutaneous; BBS, burned body surface; NGT, nasogastric tube; TGs, triglycerides; p.o., oral route.

publications. We selected studies in humans published in English and Spanish up to December 2013.

Results

The search without filters identified 131 articles. After applying the filters referred to language (English and Spanish) and studies in humans, and eliminating duplicated articles and studies in which "burns" was the name of an author, as well as publications not referred to treatment with beta-blockers in burn patients, the total number of articles was reduced to 42.

A total of 15 randomized clinical trials were identified (Table 2). The rest of the articles (n=27) were non-randomized clinical trials or studies in which randomization was not specified, cohort studies, review articles, editorials and letters to the editor.

We also retrieved 7 studies in animals designed to investigate the mechanism of action of propranolol and to evaluate possible alterations in its absorption. These articles were identified from the references cited in the articles found in our PubMed search.

Justification of the use of beta-blockers in burn patients

Endogenous catecholamines are primary mediators in the hypermetabolic response observed in burn patients.^{2,14} This systemic response is characterized by hyperdynamic circulation, increased basal energy expenditure, and increased muscle protein catabolism. Blocking of the beta-adrenergic stimulus reduces supraphysiological thermogenesis,¹⁷ cardiac work and resting energy expenditure (REE)¹⁸ (Table 3).

Beta-blockers moreover reduce peripheral lipolysis through β_2 -receptor block,¹⁶ and increase liver efficiency in secreting free fatty acids. Propranolol also has an effect upon lean body mass. On one hand, it improves recycling of the intracellular free amino acids, thus increasing the efficiency of protein synthesis in muscle. These intracellular amino acids derived from protein catabolism are again incorporated to proteins without leaving the muscle cell. On the other hand, propranolol also stimulates the expression of genes involved in muscle metabolism and reduces the activation of genes involved in gluconeogenesis, thereby resulting in a decrease in net catabolism.¹³

For these reasons the use of propranolol has been suggested in burn patients. Although most of the existing studies have been carried out in pediatric patients, with confirmation of its beneficial effects, it must be mentioned that the differences in beta-blocker prescription practice among different centers attending pediatric burn patients indicate that this drug has not yet been accepted as standard treatment in the pediatric population.¹⁹ The scant information on the effects of the drug in adult burn patients underscores the need for further studies in this population group.

Table 3 Effects of propranolol in burn patients.

Physiopathology and particularities of burn patients	Effects of propranolol in burn patients or animal burn models
Primary mediators of hypermetabolic response: catecholamines	Non-selective β -adrenergic receptor block
Hyperdynamic circulation and increased cardiac output	Decreases heart rate and cardiac work
Increased basal energy expenditure	Reduces supraphysiological thermogenesis and resting energy expenditure
Increased muscle protein catabolism	Favors recycling of intracellular free amino acids in muscle Stimulates the expression of genes implicated in muscle metabolism and reduces the activation of genes implicated in gluconeogenesis, with reduction of net catabolism
Increased peripheral lipolysis	Reduces peripheral lipolysis
Fat accumulation in liver	Increases efficiency of liver free fatty acid secretion Reduces mesenteric blood flow
Need for healing of burns and graft donor zones	Increased fractional protein synthesis in wound Increased efficacy in use of amino acids from wound catabolism for synthesizing new proteins Increased protein accumulation and free amino acid concentrations in the wound Improved healing and epithelization
In sepsis, increased monocytosis with suppression of inflammatory response of monocytes	Reduction of monocytosis induced by sepsis in burns, increase in percentage of inflammatory monocytes, granulocytosis and production of TNF- α
Predominance of type M2 monocytes, with lesser antibacterial capacity	Increase in type M1 monocytes, with possibly greater resistance to certain infections (<i>S. aureus</i> , <i>E. faecalis</i>)

Mechanism of action of propranolol

The cellular mechanisms by which propranolol accelerates muscle protein synthesis are not clear. However, it has been seen that β_1 -agonists such as clenbuterol also promote muscle anabolism.²⁰ In this section we offer a summarized description of the most recent studies on the effects of propranolol at molecular and genetic expression levels.

The activation of poly-(ADP-ribose) polymerase (PARP) promotes cell energy collapse and cell necrosis, and possibly contributes to the inflammatory responses and cell dysfunction seen in burn patients. Peak activation is observed in the third week after burn injury, and in some cases activation persists even one year later. Muscle biopsy studies have shown PARP activation to occur mainly in the vascular endothelial cells and in some mononuclear cells. However, the muscle biopsies of pediatric patients treated with propranolol show marked suppression of PARP activation. Possibly some of the clinical benefits of propranolol in burn patients are related to this suppressive effect upon PARP activation—increasing the net protein balance and reducing lean mass catabolism by preventing skeletal muscle necrosis following severe burns.²¹

It has been seen that pediatric burn patients subjected to treatment with propranolol exhibit increased expression of the genes implicated in muscle metabolism (such as heat shock protein 70 [HSP70] or dynein), and decreased expression of fructose-1,6-biphosphatase, an important enzyme involved in gluconeogenesis and insulin resistance, as well as of VEGF and other genes. This increase in the expression of genes implicated in muscle metabolism is well correlated to the increase in net protein balance measured by isotopic

studies with phenylalanine.²² The administration of propranolol also reduces the expression of genes related to lipid metabolism in adipose tissue.²³

In murine models it has been observed that burns, through catecholamine release, induce stress response on the part of the endoplasmic reticulum (ER). This response in turn leads to the activation of c-Jun N-terminal (JNK) kinase, the suppression of insulin receptor signaling via phosphorylation of insulin receptor substrate 1 (IRS-1) and subsequent insulin resistance.²⁴ The administration of propranolol attenuates the ER stress response and the activation of JNK. This implies increased insulin sensitivity, as has been determined by activation of the hepatic phosphatidylinositol 3-kinase/Akt signaling cascade via the phosphorylation of IRS-1. Propranolol therefore has the potential to suppress the hypermetabolic response, preventing hepatic ER stress and increasing insulin sensitivity.²⁵

Another model in rats has shown that burns result in cardiomyocyte activation of mitogen-activated protein kinase (p38 MAPK) and JNK, and translocation of nuclear factor (NF)- κ B. These molecules are important in transduction of the signals that induce the biosynthesis of inflammatory cytokines. MAPK participates in cardiomyocyte secretion of TNF- α , which increases the risk of cardiac dysfunction and promotes the nuclear translocation of NF- κ B, and consequently the transcription of genes. Alpha-agonists also increase the activity of p38 MAPK and JNK. However, beta-agonists have no effect in this animal model. Alpha-antagonists inhibit the burn-mediated activation of p38 MAPK and JNK, and the translocation of NF- κ B, though these phenomena are curiously also inhibited by beta-blockers. This may be due to propranolol-mediated

inhibition of the phospholipase D pathway, which activates MAPK.²⁶

Dosing of propranolol

When used at adequate doses, propranolol is effective in reducing the resting heart rate (HR) by 15–20% of the HR recorded upon admission. However, neither the propranolol dose needed to achieve this decrease in HR nor the pharmacokinetics of the drug in the burn population is precisely known.²⁷

Some studies in pediatric patients have used initial doses of 2 mg/kg/day (0.33 mg/kg/4 h or 0.5–1.5 mg/kg/6 h), followed by increments until achieving a decrease in HR of 20% with respect to the basal HR^{28,29}—with mean doses of 6.3 mg/kg/day at the end of hospital stay.¹⁵ In a randomized prospective trial in children, Williams et al. determined the dose per kg body weight of oral propranolol required to achieve adequate attenuation of cardiac work. They also studied the kinetics of the drug. Propranolol dosing was started as 1 mg/kg/day via the enteral route (every 6 h), and was adjusted to reduce the HR by 15–20%. The treatment was started once the patients were stabilized with fluids, about 24–72 h after admission. The initial dose of 1 mg/kg/day was enough to lower the HR by 10–15%, but had to be increased to 4 mg/kg/day in order to achieve and maintain a HR decrease of 15%. There were no differences in dose requirement according to patient's age or gender. However, on comparing the patients according to burned body surface, those patients with 60–80% burns required doses of between 4 and 6 mg/kg/day, while those with burns affecting less than 60% or more than 80% of the body surface required a dose of 4 mg/kg/day. The effective therapeutic propranolol concentration was 50 ng/ml. The peak drug levels were reached 30 min to 1 h after administration in pediatric burn patients, with trough levels within 1–2 h. The half-life of the drug was 4–6 h. Patients with burns affecting 80–100% of the body surface showed much greater dose variability than the patients with less extensive injuries. A number of factors probably influence such variability, since these patients are in a more critical condition, with greater resuscitation and surgery times that cause delays in the propranolol dose increments. Regarding the pharmacokinetics of the drug, pediatric burn patients usually do not reach adequate drug levels, and require dose escalation either because of tachyphylaxis or due to a maintained hypermetabolic response flow phase. Furthermore, these patients present such intense hypermetabolism that they reach peak levels earlier than expected. In such situations dosing with shorter intervals may be required. The principal metabolite, 4-hydroxypropranolol, is also active and may be more potent than propranolol. This would explain the decrease in HR even with low plasma propranolol concentrations.²⁷ Herndon et al. proposed the use of doses in excess of 4 mg/kg/day, since they produce few adverse effects and a high HR persists.¹⁸ Adults receive a standard dose of 20 mg every 6 h, with increments as required, though dosing studies have not been made in this population.²⁷

Regarding the administration route, Neudeck et al. conducted a study in rats with burns affecting 30% of the body surface. Although the burns resulted in a decrease

in the functional intestinal mucosal surface and a drop in glycoprotein-P content, no alteration in propranolol absorption was observed. This may be because propranolol is very lipophilic and is consequently easily absorbed. Moreover, a potential decrease in propranolol absorption could be countered by a lesser efflux of the drug, due to the lower glycoprotein-P content.³⁰

Clinical effects of propranolol in burn patients

In 1974, Wilmore demonstrated that catecholamine levels were increased after thermal injury, and that beta-adrenergic block decreased the metabolic rate, HR, ventilation/min and free fatty acids in burn patients.¹⁴ In 1987, Wolfe et al. described an increase in substrate (futile) cycles in burn patients, and showed that treatment with propranolol reduces triglyceride-free fatty acid substrate cycles.³¹ Furthermore, on measuring the rate of appearance of glycerol and palmitate, these authors showed that propranolol also reduces lipolysis in burn patients.³² One year later, Herndon et al. published a study in which adrenergic block was seen to reduce myocardial work in burn patients, maintaining adequate cardiac output and oxygen transport.¹⁷ Over the following years it was shown that propranolol reduces the myocardial oxygen demands in burn patients, without affecting oxygen delivery or body oxygen consumption,³³ or patient's capacity to increase energy expenditure in cold environments.³⁴ The number of publications has continued to grow, particularly those of the Galveston group, in relation to the use of this drug in burn patients. In this regard, in 2001 the mentioned group demonstrated that propranolol reduces muscle protein catabolism in pediatric burn patients.¹⁵ Further studies have been made on the effects of propranolol in burn patients; indeed, the drug is becoming increasingly popular in this patient population. The results of these studies are summarized below.

In pediatric burn patients, treatment with propranolol results in decreased cardiac work from the second week of treatment, and this decrease is sustained over time.^{18,27,35} Furthermore, the treated patients have a greater measured stroke volume.²⁷ Likewise, the decrease in HR persists one year after burn injury if treatment with propranolol is continued. A decrease in heart rate-pressure product of approximately 15% also persists 6 months after injury.¹⁸

Propranolol also improves skeletal muscle protein kinetics in children, exerting an anabolic effect upon muscle.¹⁵ The drug improves the efficiency of protein synthesis, with a lesser loss of lean body mass or the preservation of lean mass.^{15,18,22} As has been commented, propranolol induces an increase in the intracellular recycling of free amino acids, i.e., intracellular free amino acids resulting from protein catabolism are reincorporated again to proteins without leaving the muscle cell.¹⁵

Pediatric patients treated with propranolol for one year experience less accretion of central mass (organs and mesenteric fat) and of central fatty tissue. This is because propranolol reduces the central fat deposits, and is consistent with the findings (described further below) indicating that propranolol reduces mesenteric blood flow and peripheral lipolysis. Furthermore, the treated patients exhibit a greater increase in peripheral lean mass after 6 months of

treatment. A minor percentage of the patients lose more than 5% of their bone mineral content and total body mass, compared with untreated patients. Increased bone resistance can also indirectly contribute to improve lean body mass.¹⁸

Propranolol likewise reduces resting energy expenditure (REE) in pediatric patients,^{15,18,29} though the respiratory ratio experiences no significant variations.¹⁵ If the treatment is maintained, the decrease in REE is also more pronounced between two weeks and 6 months after burn injury when compared with untreated patients.¹⁸

However, propranolol does not appear to have an effect upon the inflammatory reaction in burn patients. During acute hospital admission, only minor differences have been observed between patients with and without propranolol treatment. Jeschke et al. found no differences in the expression of IL-6, IL-8, IL-10, MCP-1 or MIP-1 β . Differences were recorded at a single timepoint in relation to the concentrations of TNF- α and IL-1 β , which were seen to be lower in the treated group.²⁹

Likewise, no differences have been found between children with and without propranolol treatment in terms of mortality, the duration of hospital stay or multiorgan failure.²⁹ In any case, detecting differences in mortality in pediatric burn patients would require the conduction of multicenter studies with many patients, since the mortality rate in this population group is 4–6%.²⁹

The net fat balance through the liver is conditioned to the uptake of fatty acids from plasma, the intrahepatic oxidation of fatty acids, and the release of triglycerides bound to very low density lipoproteins (VLDL).^{28,36} Propranolol reduces the availability of free fatty acids for the liver. By reducing the release of fatty acids from the periphery in burn patients (peripheral lipolysis)^{16,28} and reducing splanchnic blood flow, the liver receives a lesser supply of fatty acids.³⁶ Furthermore, the drug increases the efficiency of free fatty acid conversion to VLDL-bound triglycerides and their release from the liver.²⁸ Thus, in burn patients propranolol has the beneficial effect of reducing liver fat accumulation—a frequent problem in patients of this kind.^{23,28,36}

Studies have also been made of the effect of propranolol upon wound healing. Zhang et al. investigated the effect of the administration of the drug upon healing of the partial thickness donor zones in rabbits. In the propranolol group the fractional protein synthesis rate in the wound was found to be greater, with a correlation between the protein synthesis rate and the percentage decrease in HR. In addition, propranolol increased the efficacy of amino acid utilization in wound catabolism for the synthesis of new proteins. The protein depositing rate and the concentrations of free essential amino acids were also greater in the propranolol group. Wound DNA synthesis, the expression of beta-adrenergic receptors, and the expression or activation of signaling cascade targets were not different between the treated and non-treated rabbits. However, the authors indicated that infusion of the drug can result in faster transition from shock condition to flow phase.³⁷

Romana-Souza et al. studied the effect of propranolol (6 mg/kg/day p.o.) in a model of scalding third-degree burns affecting 10% of the total body surface in Wistar rats. Wound healing was found to be better in the

treated group, which exhibited a lesser wound area after 63 days of treatment. This group also showed a decrease in local inflammatory response (with lesser inflammatory infiltration), improved contraction of the wound, greater reepithelization, cell proliferation, granulation tissue formation, collagen accumulation, myofibroblast density, and nitrite and metalloproteinase-2 levels, together with a lesser vessel density. Treatment with propranolol appeared to stimulate the development of less vascularized and more organized collagenous granulation tissue. The authors suggested that many of these effects were attributable to nitric oxide synthesis stimulated by propranolol.³⁸

Mohammadi et al. conducted a randomized, double-blind clinical trial in adult burn patients with or without propranolol treatment. In their series the patients were treated with delayed graft covering until the appearance of clean granulation tissue. The patients started treatment with propranolol at a dose of 1 mg/kg/day p.o., followed by gradual elevation to 1.98 mg/kg/day, adjusting the dose in order to lower the HR by 20% of the basal HR in each patient. The authors evaluated the time from admission to epithelization or preparation for skin grafting, as clinical indicators of burn healing time. The patients in the propranolol treatment group showed faster epithelization and a shorter time to graft bed suitability. Furthermore, the administration of propranolol reduced the size of the burn surface finally requiring grafting, as well as the duration of hospital stay.³⁹

Beta-blockers prevent memory reconsolidation, and have been administered to patients exposed to traumatic effects in order to prevent post-traumatic stress syndrome. However, the studies in this regard among children and adults have not shown beta-blocker administration to reduce the incidence of post-traumatic stress syndrome or acute distress disorders.^{40,41}

Some studies have related beta-blockers to worsening of the benefits of training in non-burn patient populations. No such effect has been observed in pediatric burn patients, however. Porro et al. evaluated the effects of a 12-week aerobic exercise and resistance program in children over 7 years of age with burns affecting more than 30% of the total body surface and treated or not treated with propranolol. The authors recorded an increase in muscle resistance (by 50%), lean body mass and peak VO₂ (oxygen consumption) in both groups when compared with children not enrolled in the exercise program. The group treated with propranolol moreover showed greater peak VO₂, possibly as a result of slower capillary blood flow in the muscle, thereby allowing for greater tissue oxygen extraction.⁴²

There are few studies on the effects of propranolol in adult burn patients. Arbabi et al. published a retrospective study comparing the prognosis of adult burn patients treated with beta-blockers from before admission and with continued treatment during admission versus non-treated burn patients matched for percentage burn surface area and age. The authors identified a total of 21 patients treated with beta-blockers for different reasons (arterial hypertension in 20 cases and migraine in one patient), and included 42 controls. Most of the patients received treatment with β_1 -antagonists, including metoprolol, esmolol and atenolol. Two patients were treated with labetalol and one with propranolol. Although the patients receiving treatment had a higher prevalence of heart disease

and arterial hypertension, they showed lesser mortality (5% versus 13%), shorter healing times, and a tendency toward shorter stay in hospital and in Intensive Care.⁴³ The improvement in mortality may have been due in part to the cardioprotective effect of the beta-blockers. The authors suggested that a randomized prospective study is needed in order to confirm these findings.⁴³

The investigators of the abovementioned study furthermore propose the use of selective β_1 -antagonists such as metoprolol, because they could be used in patients with inhalation syndrome, with a lesser risk of bronchospasm.⁴³ Caution in this respect is required, however, since an increase in mortality has been observed among patients with arteriosclerosis treated with metoprolol during non-cardiac surgery.⁴⁴ However, the Herndon group recommends the use of propranolol instead of other more selective beta-blockers, since the effect upon lipid metabolism is mediated by β_2 -receptor block.^{16,45}

Effects of jointly administered propranolol and growth hormone (rhGH)

Combined treatment with propranolol and growth hormone (rhGH) has been studied in three clinical trials in children. The first study was a crossover clinical trial in 6 patients administered rhGH and the combination of rhGH and propranolol, during 6 days. As has been commented above, propranolol was seen to decrease peripheral lipolysis and maintained the VLDL-bound triglyceride secretion rate.²⁸

The second clinical trial found no differences between the net protein balance and REE over the short term with the combination treatment or with propranolol alone. This lack of effect of growth hormone is in contraposition to the observations of previous studies, though the authors speculated that it may have been due to the fact that the effects were measured over the short term (10 days). In this regard, the effects of growth hormone upon the increase in lean muscle mass in pediatric burn patients are seen when the hormone is administered over several months. Furthermore, it is possible that propranolol exerts a greater anabolic effect, or that there is an anabolic ceiling effect already reached when administering propranolol alone.²⁰

The most recent clinical trial showed the joint administration of rhGH and propranolol to attenuate the inflammatory cascade and therefore hypermetabolism during the acute phase in pediatric patients. In addition, it avoided the adverse effects of rhGH (hyperglycemia and free fatty acid elevation). The combination treatment reduced REE and HR, and preserved body mass by reducing the presence of inflammatory mediators such as TNF- α , IL-6, IL-8, MIP-1 β , PCR and cortisol, and increasing the levels of IL-7, which stimulates the proliferation of early and mature T cells and B cells. Likewise, the treatment increased total bone mineral density and liver and muscle protein synthesis, and decreased the transaminase (ALT and AST) concentrations.⁴⁶ However, the mentioned study did not compare the administration of these two drugs in combination versus propranolol alone. The comparisons were made with a group of controls receiving no drug treatment.

Side effects of propranolol in burn patients

The treatment of burn patients with propranolol at doses that lower the HR by 20% with respect to the HR upon admission appears to be safe.^{15,27,28,39} However, blood pressure monitoring of the treated patients is required.¹⁵

Few side effects were reported in the study published in 2012 by Herndon et al. on the effects of propranolol in 90 pediatric burn patients treated with the drug during one year. Overall, there were two episodes of bradycardia, one episode of hypoglycemia, one cardiac arrhythmia and two episodes of breathing problems. There were no cases of hypotension, however. Five deaths were documented in the control group (89 patients), versus four in the active treatment group. There were no significant differences between the two groups in terms of mortality, which was due to sepsis in all the cases.¹⁸

A case of colon pseudo-obstruction (Ogilvie syndrome) has been reported in a patient treated with oral propranolol. Conservative management resolved the problem successfully after suspending propranolol.⁴⁷

Murine studies have reported that non-selective beta-adrenergic block during episodes of septicemia increases mortality.⁴⁸ However, no differences have been observed in relation to episodes of infection or sepsis, or mortality, between patients with or without propranolol treatment.^{15,29,39} Moreover, sepsis is characterized by changes similar to those observed in burns, with the development of a catabolic state, increased lipid and glucose metabolism, changes in cardiac output, immune modulating effects, increased REE, hyperglycemia and a loss of muscle mass. The attenuation of this response is associated to lesser mortality. A key mediator of the response to sepsis is the rapid rise in catecholamine levels, with activation of the sympathetic autonomic nervous system. It therefore has been suggested that propranolol could be useful for modulating these responses to sepsis, including a decrease in energy expenditure, inversion of catabolism, reduction of lipolysis, restoration of blood glucose control, and attenuation of the immune suppression caused by catecholamine action.⁴⁹

Studies in murine models have shown that burn-related sepsis is characterized by sympathetic stimulation that leads to monocytosis, though it suppresses monocyte inflammatory response. Beta-adrenergic block reduces such monocytosis induced by sepsis in burn cases. Furthermore, it increases the percentage of inflammatory monocytes, granulocytosis and the production of TNF- α on the part of the circulating granulocytes.⁵⁰

Type M1 monocytes (producers of IL-12 but not IL-10) are important effector cells in the first line of antibacterial defense within the context of innate immune responses. However, this subtype is not a manifest in burn patients, which show a predominance of type M2 monocytes (producers of IL-10 but not IL-12), which in turn inhibits the conversion of resident monocytes to type M1 cells. Specifically, subtype M2b is seen to predominate. The type M2 cells appear after catecholamine binding to beta-receptors of the resident monocytes, and possess a lesser antibacterial capacity. Burn patients treated with propranolol show a greater conversion of resident monocytes to type M1 cells. Since the M1 subtype affords greater resistance to infections

produced by *Staphylococcus aureus* and to the translocation of *Enterococcus faecalis*, the susceptibility of severe burn patients to such infections could be influenced by treatment with propranolol.⁵¹

Conclusions

Most of the studies on the effects of propranolol in burn patients have been carried out in children, with very promising results. Given the enormous potential benefits for adult burn patients, further studies are needed on the effects and dosing protocols of propranolol in this particular population group.

Conflict of interest

The authors declare that they have received no financial support or grants for this study, and have no conflicts of interest.

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