Effects of Propranolol and Exercise Training in Children with Severe Burns

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Objectives To investigate whether propranolol administration blocks the benefits induced by exercise training in severely burned children.

Study design Children aged 7-18 years (n = 58) with burns covering ≥30% of the total body surface area were enrolled in this randomized trial during their acute hospital admission. Twenty-seven patients were randomized to receive propranolol, whereas 31 served as untreated controls. Both groups participated in 12 weeks of in-hospital resistance and aerobic exercise training. Muscle strength, lean body mass, and peak oxygen consumption (VO_2 peak) were measured before and after exercise training. Paired and unpaired Student t tests were used for within and between group comparisons, and χ^2 tests for nominal data.

Results Age, length of hospitalization, and total body surface area burned were similar between groups. In both groups, muscle strength, lean body mass, and VO_2 peak were significantly greater after exercise training than at baseline. The percent change in VO_2 peak was significantly greater in the propranolol group than in the control group ($P < .05$).

Conclusions Exercise-induced enhancements in muscle mass, strength, and VO_2 peak are not impaired by propranolol. Moreover, propranolol improves the aerobic response to exercise in massively burned children. *(J Pediatr 2013;162:799-803)*.

Burn injury induces a massive increase in catecholamines, resulting in impaired immune function, increased heart rate, lipolysis, and persistent skeletal muscle catabolism as well as stress caused by surgical interventions, tubing, and prolonged bed rest, all of which are normally part of burn care.[1,2] The response to burn injury can persist for over 12 months post-burn, hampering the long-term recovery of burned victims.[3] We have previously demonstrated that participation in exercise activities has beneficial effects in the rehabilitation of burned children. Improvements in the range of joint movement,[4] lean body mass (LBM), muscle strength, aerobic capacity, and average muscle power are seen in burned children after completion of 12 weeks of exercise training.[5-7] However, exercise does not reduce metabolic rate in burned children.[8] Administration of the β-adrenergic blocker, propranolol, following severe burns has been shown to attenuate the hypermetabolic response that typically accompanies burns and to exert anti-catabolic effects. However, previous studies have linked β-blockers to the impairment of exercise training benefits in non-burned populations.[9-13] The aim of this study was to evaluate the effect of combining propranolol with a 12-week aerobic and resistance exercise training program in massively burned pediatric patients.

Methods

From January 2000-May 2011, 246 children were enrolled in a double-blinded trial during acute admission to Shriners Hospitals for Children (Galveston, Texas). Inclusion criteria were age 7-18 years, electrical or flame burns covering ≥30% of the total body surface area (TBSA), and participation in the exercise program within 6 months post-burn. Exclusion criteria included receipt of study drugs other than propranolol, and presence of psychological disorders, quadriplegia, or certain behavior or cognitive disorders (eg, aggressive behavior, impulsivity, dementia) that may prevent adequate participation in exercise activities. Twenty-nine patients were randomized to receive the oral non-selective β-adrenergic blocker, propranolol plus exercise (PROPEX), and 33 patients served as untreated controls, exercise only (EX). Patients were randomized by research nurses according to a randomization schedule generated by our statistician. This study was part of a large

EX	Exercise only
LBM	Lean body mass
PKT	Peak torque
PROPEX	Propranolol plus exercise
TBSA	Total body surface area
VO_2	Oxygen consumption
VO_2 peak	Peak oxygen consumption

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clinical trial (www.ClinicalTrials.gov: NCT00675714) evaluating the outcomes of burn survivors receiving therapeutic agents such as oxandrolone, propranolol, insulin, and the combination of oxandrolone and propranolol.

All patients received standard burn care during hospitalization at Shriners Hospitals for Children.[14,15] At discharge, patients were assigned by research personnel to participate in the exercise training program, with agreement of the attending physician (**Figure 1**; available at www.jpeds.com).

In the PROPEX group, propranolol dosage was titrated to decrease the resting heart rate by 15%-20% from the patient's admission value (dose range, 4 to 8 mg/kg/d), starting within 48 hours of admission and continuing until the end of the exercise training. Patients in the EX group received standard burn care only. Both groups participated in an exercise program, starting within 6 months post-burn. The exercise program consisted of 12 weeks of in-hospital, supervised resistance and aerobic exercise routines. After discharge, patients underwent body composition assessments and baseline testing (start of exercise training). Thereafter, both groups began participating in the exercise program. At the completion of the program, patients were reassessed for results comparisons.

Before enrollment in the study, informed written consent was obtained from a legal guardian by the research nurse. Children older than 7 years assented to participate. This study was approved by the Institutional Review Board of the University of Texas Medical Branch (Galveston, Texas).

During the acute stay, parents or legal guardians were instructed in the proper use of the study drug by the research nurse. At each hospital visit, participants were interviewed by the research staff to evaluate long-term compliance and to answer questions related to adverse reactions and missed drugs. Participants were blinded to drug. The attending physician administering study drug was not blinded to drug but did not intervene in data input or analyses; those involved in data analyses were blinded during the study and data analyses via de-identified data.

The individualized exercise training routine was supervised to confirm the frequency, intensity, duration, and participation of the patients. Patients were regularly monitored; routines were reviewed and adapted to meet specific patient requirements as needed.

Exercise Training Program

The exercise program consisted of supervised and individualized in-hospital aerobic and resistance exercise training, which was carried out 5 days per week for 12 weeks in accordance with guidelines set by the American College of Sports Medicine and the American Academy of Pediatrics.[16,17] Our exercise program is regularly offered for continuity of care while the children remain as outpatients in temporary housing facilities assigned by our institution. Resistance exercises included bench press, shoulder press, leg press, leg extension, biceps curl, triceps curl, leg curl, and toe rises. Exercises were performed 3 times per week starting at 60% of the previously determined individual 3 repetition maximum load, with 3 sets of 8-12 repetitions being performed at each exercise session. Aerobic exercises included treadmill, bicycle ergometer, arm ergometer, elliptical, and rowing machine. Participants exercised at 60%-85% of their previously determined individual peak oxygen consumption (VO_2 peak).

Strength Measurements. Isokinetic testing of the patient's dominant leg extensors was performed at an angular velocity of 150°/s using the Biodex System-3 dynamometer (Biodex Medical System, Shirley, New York) before and at the end of the 12-week exercise program. The patient performed a warm-up session of 3 submaximal repetitions without load. The patient was then asked to perform 10 voluntary maximal full-leg extensions and full-leg flexions, which were followed by 3 minutes of rest. The test was then repeated. The Biodex software system calculated and provided the peak torque (PKT) measurement corrected for gravitational movements of the lower leg and the lever arm. The highest measurement of the two trials was selected.

LBM. Total body LBM was measured by dual energy X-ray absorptiometry (QDR-4500W Hologic; Waltham, Massachusetts) using pediatric software, according to the manufacturer's instructions.[18,19] The system was calibrated daily against a spinal phantom in the anteroposterior, lateral, and single-beam modes. Individual pixels were calibrated against a tissue bar phantom.

VO_2 Peak. Cardiorespiratory fitness was assessed using a standardized treadmill exercise test (modified Bruce Protocol). Patients wore a nose clip (sometimes a mask) and breathed room air through a 2-way valve system where, breath-by-breath, inspired and expired gases, flow, and volume were analyzed. Concomitantly, patients began to walk on a treadmill at a speed of 1.7 miles/h at zero grade of elevation. Each stage consisted of 3-minute intervals in which the speed and treadmill incline gradually increased. Oxygen consumption (VO_2) was measured and analyzed using the Medgraphics CardiO2 combined VO_2/electrocardiogaphy exercise system exercise system (St. Paul, Minnesota).[20] Heart rate was continuously monitored using the Polar T-31 Coded Transmitter (Lake Success, New York) and a signal extraction pulse oximeter (Masimo, Irvine, California). The test was considered complete when the respiratory exchange ratio was $\geq$1.10 and the peak volitional effort was achieved.

Statistical Analyses

Data analysis was performed as an intent-to-treat analysis. Student paired t tests were used for within-group comparisons of before and after values. Unpaired t tests were used for between-group comparisons. χ^2 Statistics were used for nominal data. Data were expressed as means ± SD. Significance was set at $P < .05$.

Results

Between January 2000 and May 2011, 62 children were enrolled in this study and randomized to the PROPEX group