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Effects of Propranolol and Exercise Training in Children with Severe Burns

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Abstract

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 (TBSA) were enrolled in this randomized trial during their acute hospital admission. Twenty-seven patients were randomized to receive propranolol, whilst 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 aerobic capacity (VO₂ peak) were measured before and after exercise training. Paired and unpaired Student T-tests were used for within and between group comparisons, and Chi-squared tests for nominal data.

Results—Age, length of hospitalization, and TBSA burned were similar between groups. In both groups, muscle strength, lean body mass, and VO₂ peak were significantly greater after exercise training than at baseline. The percent change in VO₂ peak was significantly greater in the propranolol group than in the control group (P< 0.05).

Conclusions—Exercise-induced enhancements in muscle mass, strength, and VO₂ peak are not impaired by propranolol. Moreover, propranolol improves the aerobic response to exercise in massively burned children.

Keywords

Beta blocker; rehabilitation; aerobic capacity; muscle strength; hypermetabolic response; hypercatabolic response

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

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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 beta 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 beta 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 to May 2011, 246 children were enrolled in a double-blinded trial during acute admission to Shriners Hospitals for Children (Galveston, TX). Inclusion criteria included an age of 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 (*e.g.*, aggressive behavior, impulsivity, dementia) that may prevent adequate participation in exercise activities. Twenty-nine patients were randomized to receive the oral non-selective beta-adrenergic blocker, propranolol (PROPEX), and 33 patients served as untreated controls (EX). Patients were randomized by research nurses according to a randomization schedule generated by our statistician. This study was part of a large 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/day), 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 three times per week starting at 60% of the previously determined individual three repetition maximum load, with three 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 aerobic capacity (VO_2 peak).

Strength measurements—Isokinetic testing of the patient's dominant leg extensors was performed at an angular velocity of $150^\circ/\text{s}$ using the Biodex System-3 dynamometer (Biodex Medical System, Shirley, NY) before and at the end of the 12-week exercise program. The patient performed a warm up session of three submaximal repetitions without load. The patient was then asked to perform ten 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 moments of the lower leg and the lever arm. The highest measurement of the two trials was selected.

Lean Body Mass—Total body LBM was measured by dual energy x-ray absorptiometry (QDR-4500W Hologic, Waltham, MA) 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.

Peak oxygen consumption—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 two-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/hour at zero grade of elevation. Each stage consisted of 3-minute intervals in which the speed and treadmill incline gradually increased. Oxygen consumption was measured and analyzed using the Medgraphics Cardio2 combined VO_2/ECG exercise system (St. Paul, MN) (20). Heart rate was continuously monitored using the Polar T-31 Coded Transmitter (Lake Success, NY) and a signal extraction pulse oximeter (Masimo, Irvine, CA). The test was considered complete when the respiratory exchange ratio (R) was ≥ 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. Chi-squared statistics were used for nominal data. Data were expressed as means $\pm$ standard deviations. Significance was set at $P < 0.05$.

RESULTS

Between January 2000 and May 2011, 62 children were enrolled in this study and randomized to the propranolol or control group, with both groups participating in the exercise program. Twenty-seven propranolol-treated patients were compared with 31 controls. Nine patients (EX = 4 and PROPEX = 5) could not complete the 12 weeks of exercise and discontinued exercise training for reasons such as immigration status, parents needing to take care of other family members back home, and the aftermath of Hurricane Ike. Data from these patients were included in the intent-to-treat data analysis, as we did have pre-exercise data and data immediately before departing. Apart from these nine patients, two patients in the EX group and 2 patients in the PROPEX group were excluded from the analysis. In the EX group, one patient fell during the treadmill test, invalidating the test. The second patient was excluded due to a knee surgery, which was performed during the time that the exercise program was ongoing and limited the patient's performance during the assessment. In the PROPEX group, one patient was excluded because the patient received another drug, and the other was excluded because a DEXA scan report showed that a feeding tube was in place during the initial assessment (Figure 1). Patient characteristics are shown in Table I. The mean age was comparable in the EX group (13.1 ± 3.5 years) and the PROPEX group (13.7 ± 3.1 years). Similarly, no significant differences were detected between the groups in TBSA burned, percent of TBSA with 3rd-degree burns, time from burn to admission, and length of hospital stay. The number of patients with inhalation injury in each group was similar and did not statistically differ (58% in the control group vs. 56% in the propranolol treated group; $P = 0.85$).

An analysis of PKT, LBM, and VO_2 peak revealed that, in both groups, each of these variables was significantly greater at the end of the exercise program than at baseline. PKT was divided by body weight (kg) to correct for differences in weight. The percent change in corrected PKT from baseline to program completion was $59\% \pm 45\%$ in the EX group and $50\% \pm 48\%$ in the PROPEX group (Table II). Both groups also showed an increase in whole-body LBM (EX, $10\% \pm 9\%$ vs. PROPEX, $7\% \pm 6\%$) (Table II). A significant increase in the VO_2 peak was seen in the propranolol-treated group when compared with the control group (EX, $22\% \pm 14\%$ vs. PROPEX, $36\% \pm 27\%$) ($P = 0.028$) (Figure 2).

We have previously shown that the percent change in each of these variables is significantly lower in patients not participating in exercise training than in patients completing an exercise program (5, 6). A comparison of the percent change values obtained from the non-exercising patients in our previous study with values obtained in the EX and PROPEX groups showed that the percent change in PKT, LBM, and VO_2 peak was significantly higher in the EX and PROPEX groups (Fig 2). During the 12-week period, no adverse effects such as hypoglycemia or hypotension were found.

DISCUSSION

This study demonstrates that exercise training in combination with propranolol improves the physical function of burned children during the rehabilitation process. After completion of 12 weeks of exercise training, all children exhibited a 50% increase in muscle strength, an outcome that has been previously been reported in other pediatric patient populations (21–29). Further, strength gains observed in children in the control group were no different from those of children undergoing the same resistance training protocol while receiving propranolol. Finally, strength improvements were coupled with similar increases in LBM in the EX and PROPEX groups. Our results expand on the observation that exercise increases muscle strength in burned children (30–33) by showing that propranolol does not impede

exercise-induced increases in muscle strength. Indeed, PKT in propranolol-treated children was significantly higher after the 12-week exercise program than at baseline.

Limited literature is available regarding changes in LBM during administration of beta blockers in children. Specific to burns, propranolol has been shown to attenuate the hypermetabolic response by reducing myocardial workload, resting energy expenditure, and lipolysis as well as by reversing muscle protein catabolism (34–37). In 2001, Herndon et al studied 25 burned children and showed that propranolol administration during acute hospitalization significantly decreases heart rate and resting energy expenditure. More importantly, propranolol-treated patients exhibited an 82% increase in muscle protein net balance compared with the placebo group (34). However, these findings relate to the acute time period. Our results showed that a significant improvement in LBM occurred in both the EX and PROPEX group, with PROPEX failing to have an advantage over EX with regard to muscle mass accretion or attenuation of muscle wasting.

Propranolol has been shown to reduce physical endurance and maximal oxygen uptake in adults (9, 12, 13, 38, 39). These effects are associated with reduced oxygen transport (9), increased muscle fatigue (10), and reduced availability of energy substrate (12, 13, 40). In the presence of propranolol, the workload-VO₂ relationship is maintained during submaximal exercise, suggesting that oxygen delivery is increased under these conditions as an adaptive mechanism. However, this response to exercise is not sustained during maximal effort (41). This variability may be due to differences in the patient population and metabolic responses to both treatment and exercise activity.

Despite reports of reduced exercise performance following beta blockade, some studies suggest that beta blockade during exercise is safe and may be beneficial. For example, children with hypertrophic cardiomyopathy who are treated with beta blockers have an adequate blood pressure response and reduced variability during exercise, suggesting that exercise performance in these individuals is normal (42). Similarly, in patients with LQT1 syndrome, beta blockers have a protective effect during exercise, shortening the QT and T peak-to-end intervals (43). In the present study, VO₂ peak increased with exercise training. Moreover, the increment in VO₂ peak was significantly greater in the PROPEX group than in the EX group (EX, 22% vs. PROPEX, 36%). We speculate that this rise in oxygen consumption with propranolol administration could be due to a slower capillary blood flow in the muscle, allowing greater muscle oxygen extraction (44, 45).

Although beta blockade is linked to reduced exercise performance in other patient populations (9, 10, 40, 46), our data validates the safety profile of this therapeutic agent in children. In both the EX and PROPEX groups, significant improvements in muscle strength, LBM, and cardiopulmonary capacity were not accompanied by any evidence of adverse events during the study period (31).

Limitations of our study include the relatively small sample size. Over 80% of the patients admitted to our institution are Hispanics that reside outside of the United States. The ability of the patients and families to remain at our institution for 12 weeks after discharge is often affected by socio-economic problems such as financial limitations, immigration status, or the need to take care of other family members at home. Other limitations include the need for surgical interventions during the immediate long-term period, which limits the patient's ability to participate in early exercise training. Additional studies are needed to investigate the mechanism by which propranolol improves peak oxygen consumption during exercise in this patient population.

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ABBREVIATIONS

EX	exercise only group
LBM	lean body mass
PROPEX	propranolol plus exercise
PKT	peak torque
TBSA	total body surface area
VO₂ peak	peak oxygen uptake

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Figure 1.
Consort diagram.

Figure 2.

Comparison of muscle strength (PKT), lean body mass (LBM) and peak aerobic capacity (VO₂ peak) between non-exercising (No EX) patients, the exercise alone (EX) group and the propranolol plus exercise (PROPEX) group. * $P < 0.05$ vs. previously published data for non-exercising patients (5, 6); † $P < 0.05$ between PROPEX and EX groups. Data are means $\pm$ standard deviations.

Table 1

Patient characteristics

Characteristic	Exercise (<i>n</i> = 31)	Exercise + Propranolol (<i>n</i> = 27)	<i>P</i> Value
Age (years)	13.1 ± 3.5	13.7 ± 3.1	0.50
Sex (% Male)	74%	93%	0.06
Ethnicity			
Hispanic (%)	87%	93%	0.49
Burn to Admit (days)	12.0 ± 24.0	5.9 ± 11.8	0.34
TBSA Burned (%)	60% ± 14%	60% ± 18%	0.91
TBSA 3rd degree (%)	44% ± 23%	50% ± 22%	0.28
ICU Length of Stay (days)	35.5 ± 28.2	37.8 ± 22.3	0.72
ICU Length of Stay/TBSA burned	0.58 ± 0.40	0.62 ± 0.27	0.66

Values shown as means ± standard deviations. TBSA: total body surface area, ICU: intensive care unit.

Table 2

Comparison of lean body mass, muscle strength, and peak aerobic capacity in patients undergoing exercise with or without propranolol treatment

Measure	Exercise (n = 31)		Exercise + Propranolol (n = 27)		
	Pre	Post	Percent Change	Pre	Post
LBM (kg)	33.1 ± 12.7	36.4 ± 14.3 [†]	10% ± 9%	35.6 ± 10.1	38.4 ± 11.2 [†]
VO ₂ peak (ml/kg/min)	26.4 ± 5.5	31.1 ± 6.5 [†]	22% ± 14%	24.5 ± 5.8	31.7 ± 5.3 [†]
PKT/BW (N·m/kg)	85.7 ± 36.3	127.9 ± 45.3 [†]	59% ± 45%	92.9 ± 36.0	126.7 ± 36.1 [†]

Values shown as mean ± standard deviation.

[†] P < 0.05, pre vs. post exercise, within group.

^{††} P < 0.05, exercise vs. propranolol + exercise, between group.

LBM: lean body mass, VO₂ peak: peak aerobic capacity, PKT: peak torque, BW: body weight, N·m: Newton-meter.