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The use of propranolol in adult burn patients: Safety and outcome influence

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ABSTRACT

Objectives: This study investigated safety and effect of propranolol on adult patients with severe burn.
Methods: A prospective study was conducted on 124 severely adult burn patients who were randomly divided into propranolol and non-propranolol group. Propranolol was given by nasogastric tube to achieve the target of lowering 15–20% of initial heart rate.
Results: Average dose of propranolol was 1.9 ± 0.5 mg/kg/day ranging from 0.9 to 3.3 mg/kg/day and was not affected by burn extent and inhalation injury. Mean heart rate reduced by 21.2% during the 28 day period. Recorded adverse events included hypotension (11.9%), bradycardia (1.6%), hypoglycemia (17.7%) and total number of held events was 8 occurring in 7 (11.3%) patients. Serum levels of glucose, total protein, albumin, cholesterol and triglyceride at different times were not significantly different between the two groups. Significantly lower resting energy expenditure on the 7th and 14th day were seen in propranolol group ($p < 0.05$). After 3 weeks, liver size in the propranolol group did not change significantly from admission, while in the non-propranolol group, liver size increased significantly ($p < 0.05$). The complete healing time of partial-thickness burns and donor sites were significantly shorter in propranolol group ($p < 0.01$). Duration of ventilation, length of stay in intensive care unit and in hospital, number of operations, rate of multiple organ failure, and death were not different between the two groups ($p > 0.05$).
Conclusion: For severely burned adults, propranolol was safe and effective on reducing energy expenditure, limited hepatomegaly, and accelerated partial burn wound and donor site closure, but does not affect length of stay in ICU, hospitalization, complication ormortality rate.

1. Introduction

Despite significant progress in the therapeutic strategy such as improvement in resuscitation, infection control, early enteral nutrition, early excision and skin graft, complication and mortality rates of severe burn patients are still high, especially in developing countries. One of the important "keys" contribute to this situation is hypermetabolic response [1,2].

The hypermetabolic response begins within the first 48 –72 h after the burn and is considered to be greatest compared to any other type of injury or surgery. Prolonged and severe

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hypermetabolism will lead to loss of lean body mass, wasting, increased risk of infection, immunodeficiency, osteoporosis, prolonged wound healing and recovered time, increased complication and mortality [3–5].

Since first report by Herndon and colleagues in 1986, propranolol has been widely used in pediatric burns with safety and positive impact on outcomes, especially limiting hypermetabolic response, accelerating wound healing process [6,7]. However, for patients with adult burns, the use of propranolol is still limited with inconsistent results and concerned side effects [8,9].

In this study, we assessed the safety, the dose to achieve the hemodynamic goal, and outcome influence of oral propranolol in adult patients with severe burns.

2. Material and methods

A prospective study was conducted on 124 severely adult burn patients admitted to Burn intensive care unit (ICU), National Burn Hospital from August 2016 to August 2018. Selected criteia for patients included age from 16 to 60 years old, admitted to hospital during 72 h after burn, burn extent ≥20% total body surface area (TBSA); without any concomitant trauma or comorbidity. Eligible patients were randomly divided into propranolol and non-propranolol group with 62 patients of each. Randomisation was done as followed: the first selected patient was in propranolol group, then the second selected patient was in non-propranolol group. This order was kept until 62nd patient in each group (Fig. 1).

All patients in this study received the same management regime including fluid resuscitation with Parkland formula. Enteral feeding was applied within 24 h of admission. Burn extent and depth were clinically determined on admission by experience burn surgeon. For fullthickness burns, early excision and grafting with auto and allo-skin grafts were performed. For partial wounds, daily dressing change was performed and the healing status was assessed by attending physician.

Propranolol was given by nasogastric tube with an initial dose of 20 mg three times daily (every 8 h) from day three after burn. The dose of propranolol was adjusted every 8 h to achieve a goal of 15–20% reduction in initial heart rate (HR). If the HR did not drop to the target, the next dose would be 40 mg and then back to 20 mg for the next dose as usual. Hemodynamic parameters including HR and blood pressure were monitored every hour in ICU and every 3 h in the wards. Hypotension and bradycardia were considered once mean arterial pressure (MAP) <60 mmHg or HR < 60 beats per minute (bpm) respectively. In such cases, the next dose of propranolol was withheld (considered as hold event) and only half of the initial dose of propranolol (10 mg) was given at the next time. Patients received propranolol until transferred to the rehabilitation unit or death.

Resting energy expenditure (REE) measurements were obtained on the 3rd, 7th, 14th, 21st and 28th day after burn using Carescape R860 ventilator, GE Health Care, USA. Accordingly, REE measurements were performed before 6 a. m. while the patients were sleeping and receiving continuous enteral feeding. Serum level of protein, albumin, glucose, cholesterol and triglyceride was measured on admission and on the 7th, 14th, 21st and 28th day after burn.

Liver size was measured by ultrasound using the 4D Logiq S7 (GE Health Care) echocardiogram conducted on admission and 21st day after burn on patients without deep burn injuries at upper abdominal area (34 patients of each group) as described by previous authors [10]. Accordingly, the patient was in the supine position, the 3.5 MHz probe was placed

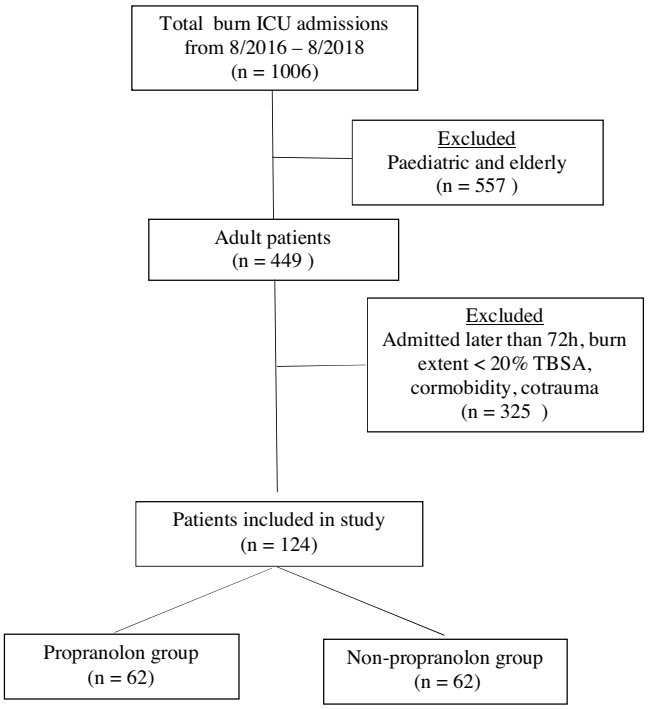

Fig. 1 – Flow diagram of patients included and excluded.

directly below the midline of the rib cage on the right upper quadrant in a vertical line running through the right nipple. Once image of the liver appears on the screen, scanning in a plane perpendicular to the base of the liver. The base of the liver and the free edge hepatic dome was marked on the screen and the distance between these two points was automatically measured.

Primary outcomes included dose of propranolol to achieve the target, used duration, changing of HR and MAP over time, adverse events including hypotension, bradycardia, bronchospasm, hypoglycemia, hold events in propranolol group.

Secondary outcomes included changing of REE, liver size, serum levels of protein, albumin, glucose, cholesterol and triglyceride along the time; volume of transfused blood and plasma; healing time for partial burn injury and donor site; number of surgical intervention; duration time of mechanical ventilation, length of stay in ICU and in hospital; rate of multiple organ failure (MOF) and mortality.

Collected data were presented as frequency counts and percentages. Continuous variables were displayed as mean and standard deviation (SD) when the value distribution was standard; otherwise the median with inter-quartile range (IQR: 25th–75th percentile) was presented. Chi-squared test was used to test for differences between frequencies. In a symmetrical distribution, t-test was used to compare the mean of a variables, and the Mann–Whitney U was used in case of comparing the medians. Stata software version 14.0 was used with p value <0.05 regarded as the significant level. This study was approved by the hospital's Committee for human research ethics with individual patient's or relatives' consent.

3. Results

Patient characteristics and burn features are shown in Table 1. There were no statistically significant differences between the two groups for age, burn extent, present of inhalation injury, and admission time. Propranolol was administered at an average dose of 1.9 ± 0.5 mg/kg/d, ranging from 0.8 mg/kg/d to 3.3 mg/kg/d to achieve hemodynamic goal. Maximum dose was 2 ± 0.6 mg/kg/d, ranging from 0.8 to 3.9 mg/kg/d. There was an insignificant difference of dose between subgroups of burn extent, inhalation injury (data not shown). The average duration of used propranolol was 25.8 ± 13.8 days, ranging from 4 to 58 days. Of the 62 patients receiving propranolol, following adverse events were noted: hypotension in 7 patients (11.9%), bradycardia in one patient (1.6%), and hypoglycemia in 11 patients (17.7%). The total 7number of hold events was 8 occurring in 7(11.3%) patients (Table 2).

As compared to non-propranolol group, significantly lower HR was recorded in propranolol group from third day after burn onward ($p < 0.001$). In addition, among propranolol group, along the time HR gradually reduced from 115 ± 16.4 bpm to 90.2 ± 11.5 bpm after 4 weeks ($p < 0.001$) with reduction rate of 21.2% in comparison with initial value (Table 3). During the first week of treatment, average MAP was significantly lower in propranolol group ($p < 0.05$) but still in normal physiological values (>65 mmHg). Serum levels of total protein, albumin, glucose, cholesterol and triglycerides changed over time but did not differ significantly between the two groups (Table 4).

Mean REE of patients in both groups increased and reached peak value at the 7th day after burn then gradually reduced but still kept higher as compared with basal level after 4 weeks. It is noted that significantly lower REE was seen in propranolol group on the 7th (2843.9 ± 509.2 Kcal/day vs. 3071.9 ± 534.4 Kcal/day; $p < 0.01$) and on the 14th day (2647.9 ± 484.4 Kcal/day vs. 2880.9 ± 581.3 Kcal/day; $p < 0.01$) comparing with that of non-propranolol group.

On admission, the liver sizes were not significantly different between the two groups ($p > 0.05$). After 3 weeks of burns, liver size was significantly greater in the non-propranolol group compared with that in the propranolol group (Table 5). In addition, in the propranolol group, liver size did not change significantly from admission, while in the non-propranolol group, liver size increased significantly ($p < 0.05$).

Regarding to wound healing, completed healing time of partial thickness burns was remarkably shorter in patient with propranolol ($p < 0.01$). Moreover, the healing time of donor site was also shorter in propranolol group (9.6 ± 1.3 vs. 12.8 ± 2.7 days; $p < 0.01$). Meanwhile, number of surgical intervention as well as volume of transfused red blood cells and plasma were not significantly different between patients with or without propranolol. Duration of ventilation, length of ICU and hospital stay, rate of MOF and death were also not remarkably different between two groups ($p > 0.05$).

4. Discussion

The hypermetabolic response after severe burn is considered as largest comparing to any diseases and trauma. Persistently increased HR, body temperature, cardiac output and resting energy expenditure as results of hypermetabolic state are

Table 1 – Patient demographic and burn features.

Parameter	Non-propranolol (n = 62)	Propranolol (n = 62)
Age (year)	35.2 ± 10.9	35.9 ± 9.4
Male/female	46/16	46/16
Burn size (% TBSA[a])	50.1 ± 17.4	50.1 ± 19.7
Deep burn area (% TBSA)	19.3 ± 16.3	19.4 ± 18.3
Admission time (h)	5 (3–9)	4 (3–7)
Inhalation injury, n (%)	8 (12.9)	6 (9.7)

[a] TBSA: total body surface area.

Table 2 – Propranolol dose, used duration and inversed events (n = 62).

Parameter	Value or mean	Range
Average dose, mg/kg/day	1.9 ± 0.5	0.8–3.3
Maximum dose	2 ± 0.6	0.8–3.9
Used duration, day	25.8 ± 13.8	4–58
Patients with hypotension, n (%)	7 (11.9)	
Patients with bradycardia, n (%)	1 (1.6)	
Patients with hypoglycemia (< 3.6 mmol/l), n (%)	11 (17.7)	
Patients with bronchospasm	0	
Patients with hold events, n (%)	7 (11.3)	
Total hold events, n	8	

Table 3 – Changes of hemodynamic parameters along the time.

Parameter	Time points	Non-propranolol	Propranolol
HR, bpm	3rd day	117.7 ± 12.9	115 ± 16.4
	7th day	118.1 ± 12.4	99.5 ± 17.1**
	14th day	112.7 ± 17.6	95.5 ± 16**
	21st day	104.2 ± 11.4	91.8 ± 14.6**
	28th day	101.4 ± 13.7	90.2 ± 11.5**
MAP, mmHg	3rd day	89.5 ± 7.9	86.7 ± 6.4*
	7th day	90.5 ± 13.1	86.1 ± 6.1*
	14th day	87.1. ± 7.5	85.9 ± 5.5
	21st day	87.5 ± 5.2	86 ± 5.3
	28th day	87.8 ± 4	86 ± 3.9

* $p < 0.05$.
** $p < 0.01$.

Table 4 – Change of some metabolic criteria along the time.

Criteria	Subgroup	Admission	7th day	14th day	21st day	28th day
Glucose, mmol/l	Non-propranolol	7.5 ± 2.1	8.4 ± 3.5	7.9 ± 3.1	7.3 ± 2.2	7.5 ± 2.1
	Propranolol	7.9 ± 3.6	8.2 ± 2.7	7.9 ± 3.1	7.4 ± 3.3	6.9 ± 2.6
Protein, g/l	Non-propranolol	48.4 ± 7.5	55.5 ± 7.4	60.4 ± 8.8	62.4 ± 7.6	62.9 ± 7.2
	Propranolol	50.9 ± 8.4	57.8 ± 8.7	61 ± 9.1	62.5 ± 10.1	65.7 ± 6.9
Albumin, g/l	Non-propranolol	26.5 ± 6.2	29.8 ± 5.8	29 ± 4.8	30.5 ± 5.7	30.6 ± 5
	Propranolol	26.5 ± 6.5	28 ± 4.7	28.9 ± 5.6	28.7 ± 5.5	30.2 ± 4.3
Cholesterol, mmol/l	Non-propranolol	4 ± 1.1	3.2 ± 0.9	3.2 ± 0.9	3.8 ± 1.2	3.9 ± 1.4
	Propranolol	4.4 ± 1.4	3.5 ± 1	3.3 ± 1.2	3.8 ± 1.3	4.2 ± 1.2
Triglyceride, mmol/l	Non-propranolol	1.9 ± 1.3	2.2 ± 1.4	2.5 ± 1.6	2 ± 1	2 ± 1
	Propranolol	1.9 ± 1.4	2.4 ± 1.7	2.2 ± 1.5	2 ± 0.9	2 ± 1

commonly seen in severe burn patients. In addition, hyperglycemia, proteolysis, lipolysis, reduction in muscle mass and body weight with worse outcome are also noted in severe burn patients [11,12]. Even the mechanism of hypermetabolic response is not fully understood, studies showed significant increase in level of serum catecholamine, cortisol, glucagon and dopamine. Moreover, increased secretion pro-inflammatory cytokine and mediators such us interleukin 1β, Interleukin 6, TNFα has been also determined among severely burn patients [13,14].

As a non-specific beta blocker often indicated for cardiac patients, propranolol is capable of attenuating serum catecholamine which has been proved to raise up to 10–20 times after extensive burn [15,16]. In 1986, this medication was first used to treat hypermetabolic state in pediatric burn patients. Along the time, further impact of propranolol on severely burn patients has been investigated. Propranolol can reduce peripheral lipolysis and increase protein synthesis by promoting better protein kinetics in the skeletal muscle with an improved net protein balance. In severely burn children, propranolol at dose of 4 mg/kg/d reduced the cardiac physiology, limited hepatomegaly with positive outcomes in pediatric burn patients [17–19].

Regarding to the use of propranolol in adult burn patients, numerous studies have been conducted [20,21]. Like the use of propranolol in children, hemodynamic target with reducing HR to 15–20% of initial value was set up for most current studies. It is noted that, to achieve the target, the dose and regime of propranolol administration were variety between studies. The does was 1 mg/kg/d with maximum dose of 1.98 mg/kg/d given in six divided doses by Mohammadi et al. [22]. It was 0.46 mg/kg/d (ranging from 0.1 to 3.8 mg/kg/d) with

Table 5 – Outcome measurement.

Parameter	Subgroup	Non-propranolol	Propranolol
REE, Kcal/day	3rd day	2431.9 ± 502.2	2428.8 ± 529.8
	7th day	3071.9 ± 534.4	2843.9 ± 509.2**
	14th day	2880.9 ± 581.3	2647.9 ± 484.4**
	21st day	2581.8 ± 430.5	2522.1 ± 496.2
	28th day	2618 ± 513.5	2567.4 ± 468.2
Right liver size, mm, n = 34	3rd day	134.9 ± 13.8	137.3 ± 12.2
	21st day	144.4 ± 10.9	139.4 ± 9.1*
Left liver size, mm, n = 34	3rd day	73.6 ± 7.7	76 ± 7.2
	21st day	82 ± 6.8	78.2 ± 6.8*
Completed healing, day	Superficial burn	9.4 ± 1.5	9.1 ± 1.6
	Superficial dermal burn	16 ± 2.2	14.7 ± 2.8*
	Deep dermal burn	25.10 ± 5.18	22.4 ± 5.2*
	Donor site	12.8 ± 2.7	9.6 ± 1.3**
Surgical intervention, n	For 10% deep burn	1.6 ± 1.5	1.3 ± 1.5
	Overall	2.2 ± 2	2.3 ± 2.3
Volume of transfused blood and plasma, ml		5800.8 ± 565	4545.2 ± 428.4
Duration, day	Ventilation	99.2 ± 166.4	71.8 ± 132.3
	ICU stay	18.9 ± 11.1	17.9 ± 12.3
	Hospital stay	35.1 ± 17.1	35 ± 19.9
MOF, n (%)		10(16.1)	13(21)
Death, n (%)		11 (17.7)	12 (19.4)

* $p < 0.05$.
** $p < 0.01$.

maximum dose of 0.61 mg/kg/d given in four divided dose to reduce 25% of HR after 28 days of treatment in the retrospective study by Brown et al. [8]. Meanwhile in study by Ali et al., patient received an average propranolol dose of 3.3 ± 3.0 mg/kg/d [23]. In recent study, we found that with the average dose was 1.9 ± 0.5 mg/kg/d real reduction of HR was 21.6% as compared to initial value. It is also interesting to note that, the dose of propranolol in our study was also not affected by burn extent and present of inhalation injury.

One of most concerning issues for using propranolol in adult burn patients is adverse effect which is less reported in pediatric burn patients [24,25]. Propranolol has been used for a long time for cardiac patients and common reported side effects include hypotension, bradycardia, hypoglycemia, bronchospasm, and ischemia. In addition, propranolol can cause life-threatening reactions such as pulmonary edema, shock and complete heart block. Brown et al. reported high rate of hypotension (72%) and bradycardia (15%) and hold event (32%) when propranolol was used in adult burn patients [8]. However, in other study, Ali et al. indicated that the incidence of hypotension, bradycardia, ischemia were not significant higher in propranolol group comparing to that in the control group [26]. In current study, we also noted a low rate of hypotension (11.9%) and bradycardia (1.6%) in the propranolol group. The reason for different results between studies could be variety on sample size, dose regime and variety of burn severity among studies.

During acute phase, the REE of severely burn patients could significantly increase up to 200% and then decreased over time but remained at high levels for two years after the burn and the use of propranolol can limit this tendency [27]. In pediatric burns, studies showed that both short and long-term propranolol treatment significantly reduced REE [24,28]. Breitenstein reported that in adult burn patients, propranolol infusion reduced the resting metabolic rate by 135% and this figure was 129% in case of oral administration [29]. In our study, significantly lower REE was noted in the propranolol group on 7th and 14th day after burn compared with that in the group not taking propranolol as well as baseline value.

Severe burns cause disorders of many organs including the liver. Some studies suggested that an increase in liver size after a severe burn is due to an increase in the amount of triglycerides in the liver and due to post-burn liver edema [30,31]. Works of Jeschke and coworkers showed that liver size increased, peaked at 2 weeks after burn (220%) and remained at high levels until discharge. Liver size and weight increased by 126% ± 19% at the second week after burns and prolong to 12 months after burns with increased from 40% to 50% compared with estimated weight [10].

Propranolol reduces peripheral lipid breakdown and free fatty acid release through action on the specific adrenergic receptors which have responsibility for regulating lipolysis response to burns [18,32]. Numerous studies clinically proved that propranolol admission can limit hepatomegaly in burn patients. Barrow and colleagues found that liver size increased two folds in 80% of patients who did not take propranolol, while 86% of patients taking propranolol showed decreased or no changes liver size [33]. In our study, after three week of treatment, in the propranolol group, liver size did not change significantly from admission, while in the non-propranolol group, liver size increased significantly.

Currently reported that propranolol accelerated burn wound healing, reduced skin graft number, required less blood transfusion and length of hospital stay [19,23,34,35]. In our study, completely healing time for dermal burn and donor site were significantly shorter than in propranolol group but

we did not find remarkable difference of length of stay in ICU and in hospital, volume of transfused blood and plasma between two groups. As other studies on adult burn patients, we did not find significant differences of MOF as well as mortality rate between patients with or without taking propranolol.

This study also had some limitations including small sample size with large range in burn extent and fullthickness burn area even baseline parameter was insignificant between two group. In addition, in our study, only acute phase of burn was included. Further studies need to be carried out with larger sample size, longer duration of used propranolol, on adult burn patients with co-trauma or concomitant diseases as well as on elderly group.

5. Conclusion

We have shown that using propranolol for adult burn patients could be safe, can significantly reduce resting energy expenditure, limit increased liver size, accelerate wound healing for donor sites and partial thickness burn injuries but do not influence duration of ventilation, length of stay in ICU and hospital as well as MOF and mortality rate. Further studies need to be conducted to determine further effect of propranolol in adult burn patients.

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None.

Conflict of interest

No conflicts of interest in term of financial and personal relationship with others could be declared to this study.

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