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MODULATION OF HYPERMETABOLISM IN BURN PATIENTS BY ADMINISTRATION OF PROPRANOLOL IN FIRST TWO WEEKS AND ASSESSING ITS EFFECT BY USING CLINICAL AND BIOCHEMICAL PARAMETERS

General Surgery

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ABSTRACT

Introduction: india being a developing country has a high incidence of thermal burns. Severe burn injury is followed by a state of hypermetabolism, which causes increased cardiac workload and increased resting energy expenditure causing muscle wasting, leading to increased morbidity. The aim of this study is to test the effect of propranolol in modulating the state of hypermetabolism in the acute post burn phase using various clinical and laboratory parameters. **Patients and methods:** this is a prospective randomized control study which includes 84 patients of burns with total burn surface area 20-40% conducted at department of surgery ,ssg hospital, baroda over a period of 1.5 year. The patients were divided into test (propanolol) and control groups. Similar burn treatment was continued in both groups and change in the laboratory, and clinical parameters were noted. Results were compared within the groups using paired *t*-test and in between the groups using unpaired *t*-test. **Result:** this study shows a significant reduction of 25% in the heart rate and 26% in the sleeping pulse rate with 2 weeks of propranolol therapy ($p < 0.001$). There was a 3.33% increase in the weight along with 2.5% increase in mid-arm circumference. There was a 5.7% increase in total serum albumin concentration and c-reactive protein was found to be reduced by 8.2%. **Conclusion:** the results prove propranolol as an effective modulator of hypermetabolism by counteracting the effect of catecholamine, reducing infection and inflammation hence improving the overall outcome of severe burn patients.

KEYWORDS

Burn,propranolol,catecholamine,hypermetabolism.

INTRODUCTION

Burn injury is always associated with a state of hypermetabolism. Severe thermal burn, defined as burns involving over 30% of a patient's total body surface area (TBSA), is followed by a pronounced hypermetabolic response that may last up to 1-2 years postburn. Burn-induced stress response stimulates secretion of endogenous catecholamine, which are thought to be primary mediators of hypermetabolism after stress due to injury.[1],[2] During this time, the metabolic and energy requirements are vast, necessitating recruitment of proteins and amino acids to sustain healing and recovery. This, in turn, increases protein turnover and produces a negative nitrogen balance. The accompanying reductions in lean body mass (LBM) and bone density produce weakness and impair wound healing. [3] Successful blockade of beta-adrenergic stimulation and the effects of elevated levels of catecholamine after severe injury decrease cardiac work, tachycardia, metabolic rates, and thermogenesis. [6] Beta-antagonist treatment reduces the rate of cardiac complications and decreases mortality after severe trauma. [7] Propranolol increases LBM and decreases skeletal muscle wasting as proven by stable isotope and body composition studies. [1] Treatment, at a dose of 0.5-4 mg/kg/day to reduce heart rates 15-20% of admitting heart rates, did not effect inward transport of amino acids, but did effectively increase the efficiency of muscle protein synthesis. [1] It enhances the availability of free amino acids for muscle protein synthesis. [2]Drugs that block this catecholamine surge have been shown to be effective at countering catecholamine-induced sequelae after severe burns. [9] Propranolol, a nonspecific beta-1, beta-2-adrenergic receptor antagonist that has been studied extensively, holds promise for the reduction of the post burn hypermetabolic response.

AIMS AND OBJECTIVES OF THE STUDY

To study the effect of oral Propranolol in burn patients for first two weeks by assessing clinical and biochemical parameters.

PATIENTS AND METHODS

The study was conducted in Dept. of Surgery, Medical college, Baroda and SSG Hospital from July 2017 to December 2018.

INCLUSION CRITERIA-Admission within 3 days of burn,TBSA = 20-40%,Flame (gas) burns, Chemical burns, Kerosene burns

EXCLUSION CRITERIA-Electric burns, Pregnant females, Cardiac failure cases, Diabetic patients,<18 years age and >60 years age, Known case of hypertension on beta blocker therapy previously, Patients with side effects of beta blocker - Bradycardia, COPD, Partial or complete heart block, Peripheral vascular disease, Prinzmetal's angina , Patient taking following drugs - Digitalis, Verapamil, Anti diabetic drugs, Alpha agonist, NSAIDS, Cimetidine, Lidocaine, Chlorpromazine.

STUDY DESIGN-The study is a prospective randomized control trial study set up at SSG Hospital, Vadodara. Cases will be divided into two groups randomly by odd and even type of simple randomization.

SAMPLE SIZE-Total sample size 84 patients.

METHODOLOGY

The test group was given propranolol in a dose of 0.5-1.5 mg/kg body weight (achieving a reduction in the heart rate by 20%) per day (6-8 hourly) orally for 2 weeks along with the standard burn care and treatment while the control group was given only the standard burn care and treatment. Adequate analgesia, feeding and fluid therapy was given to all patients. All the patients were subjected to routine investigations such as complete blood count, serum electrolytes, serum albumin and serum CRP. Propranolol therapy was given to the patients for 14 days and the results were assessed on various clinical and laboratory parameters. The study was planned to stop if patients showed features of hypersensitivity, cardiac changes or increased morbidity.Following parameters were compared between two groups. Clinical Parameters were Temperature, Heart rate ,Sleeping heart rate, Blood Pressure, Mid arm circumference and weight. Biochemical Parameters were Serum albumin and Serum CRP. Oral temperature charting was done every day 6 hourly and the average temperature was noted. Results were compared between the two groups on 1st,7th and 14th day. Heart rate was recorded 4 hourly using monitor. Results were compared on 1st, 7th and 14th day. In the test group dose of propranolol was adjusted so as to bring down heart rate by 20%, which is within safe limits of propranolol use. Sleeping pulse rate was measured using the monitor while the patient fast asleep and results was compared on every 7th day. Blood pressure was measured everyday 6 hourly and the average was noted. Results were compared between the two groups on 1st, 7th and 14th day. Mid arm circumference was measured in centimeters using inch tape every 7th day. Point where the measurement was done was marked to reduce the errors. Weight of every patients was measured in kilograms on a weighing scale on 1st, 7th and 14th day. Serum albumin concentration was investigated on 1st, 7thand 14th day. Serum CRP was measured on 1st, 7thand 14thday.

RESULTS

Total 84 burn patients were studied to assess effect of propranolol at Medical college and SSG Hospital, Vadodara from July 2017 to December 2018.

Same numbers of patients were compared in both the groups with similar age and sex distribution, according to TBSA (total burn surface area) to improve the accuracy of results as per [Table 1].

Table 1-Patients characteristics				
Variable	Propranolol Group	Non propranolol Group	Male	Female
Age(years) 18 to 30 31 to 45 46 to 60	12 16 14	08 18 16	10 14 16	10 20 14
Etiology Flame Chemical Scald	20 10 12	22 08 12		
TBSA 21-30% 31-40%	24 18	24 18		
Admitted on PBD	0-2 days	0-2 days		

TBSA-Total burn surface area, PBD-Post burn day

Maximum number of patients were between 31 to 45 years of age group in this study.

PROPRANOLOL GROUP

	DAY 1	DAY 7	DAY 14	%
Temperature(*F)	99.5 * F	99* F	98 * F	1.5 % ↓
Pulse rate(/min)	126	110	94	25.4 % ↓
Sleeping Pulse rate(/min)	120	104	88	26.7 % ↓
Blood pressure (mmhg)	100/70	104/78	106/80	6% ↑(systolic) 14.2%↑(diastolic)
Mid arm circumference(cm)	25.4	25.6	26	2.36% ↑
Weight (kg)	60	60	62	3.33% ↑
S.Albumin	3.5	3.5	3.7	5.7% ↑
S.CRP	12.2	12	11.2	8.2% ↓

NON PROPRANOLOL GROUP

	Day 1	Day 7	Day 14	%
Temperature(*F)	100 * F	99.5* F	99 * F	1% ↓
Pulse rate (/min)	130	124	110	15.38 %↓
Sleeping Pulse rate (/min)	120	112	100	16.7%↓
Blood pressure (mmhg)	104/70	106/74	110/78	5.8%↑(systolic) 11.42%↑(diastolic)
Mid arm circumference (cm)	25	25	24	4 % ↓
Weight (kg)	61	60	59	3.27% ↓
S.Albumin	3.6	3.5	3.2	11.11 % ↓
S.CRP	14.2	15	16	12.7 % ↑

TEMPERATURE COMPARISON-The average temperature in the propranolol group was 99.5 ± 1*F on 1st day and 98 ± 0.5*F on day 14. Whereas in non propranolol group on day 1 it was 100 ± 0.8*F and 99 ± 0.7*F on day 14. So difference between two groups found to be statistically significant. (P<0.001)

HEART RATE COMPARISON-Heart rate was recorded 4 hourly using monitor. Results were compared on 1st , 7th and 14th day. Average Heart rate on day 1 in propranolol group was 126 ± 10 and 94 ±8 on day 14. In non propranolol group it was 130 ± 8 on day 1 and 110 ± 9 on day 14.So difference between two groups found to be statistically significant. (P<0.001).

SLEEPING PULSE RATE COMPARISON-Sleeping pulse rate was measured using the monitor while the patient was fast asleep and results were compared on every 7th day. The average sleeping pulse rate was 120 ± 9 on day 1 and 88 ± 6 on day 14, in the propranolol group while it was 120 ± 8 on day 1 and 100 ± 10 on day 14, in non propranolol group after 2 weeks. So difference between two groups found to be statistically significant. (P<0.001)

BLOOD PRESSURE COMPARISON-Average systolic blood pressure on day 1 was 100 mmhg and 106 mmhg on day 14 in propranolol group. Average diastolic blood pressure on day 1was 70 mmhg and 80 mmhg on day 14 in propranolol group.

Average systolic blood pressure in non propranolol group was 104 mmhg on day 1 and 110 mmhg on day 14. Average diastolic blood pressure was 70 mmhg on day 1 and 78 mmhg on day 14 in non propranolol group. So difference between two groups found to be statistically insignificant. (P>0.05)

MID ARM COMPARISON-Mid-arm circumference was measured in centimetres using inch tape every 7th day. Mean mid-arm circumference was 25.4 ± 2.7 cm in test group on day 1, which increased to 26 ± 3 cm on day 14 while in control group the average values were 25 ± 2.5 on day 1 and 24 ± 2.6 on day 14.So difference between two groups found to be statistically significant. (P<0.05)

WEIGHT COMPARISION -Weight of every patient was measured in kilograms on a digital weighing scale on the day of admission and on the 14th day. The mean values on day 1 in propranolol group were 60 ± 6 and on day 14 were 62 ± 8 while in the control group the mean values on day 1 were 61 ± 10 on day 1 whereas the were 59 ± 10 on day 14.So difference between two groups found to be statistically significant. (P<0.001)

SERUM ALBUMIN COMPARISION-Serum albumin concentration was investigated every 7th day and the mean values were 3.5 ± 0.40 on day 1 and 3.7 ± 0.3 on day 14 while in control group mean values were 3.6 ± 0.3 on day 1 and 3.2 ± 0.2 on day 14. So difference between two groups found to be statistically significant. (P<0.05)

SERUM CRP COMPARISION -CRP was measured every 7th day and mean values in test group on day 1 were 12.24 ± 0.8 and on day 14 the mean values were 11.4 ± 1 whereas in the control group the mean values on day 1 were 14.2 ± 1 on day 1 and 16 ± 1.2 on day 14.So difference between two groups found to be statistically significant. (P<0.05)

DISCUSSION

The hypermetabolic response is thought to be due to postburn elevation of endogenous catecholamines and cortisol. The loss of LBM can drive detrimental responses in burn. This study included patient with 20-40% TBSA compared to 25-40% TBSA in the study by Segu *et al*. more than 40% TBSA in the study by Herndon *et al*. and 20-60% in Lunawat *et al*. [1],[11],[12]

The dose of propranolol was adjusted to reduce the heart rate by 20% which was similar to the dose used in study by Lunawat *et al*, Segu *et al*. and Herndon *et al.* and Williams and 18% reduction in the study by Hart *et al*. in 2002. [11],[12],[17],[18] In our study 25% reduction in baseline heart rate was seen by the end of 14 days in patients receiving propranolol therapy while only 15% reduction was seen in control cases and tachycardia still persisted.

Body temperature after propranolol therapy was found to be near normal while patients were still febrile in the control group.

Results were assessed on clinical parameters which included heart rate, sleeping pulse rate, weight and mid-arm circumference. The results were almost similar to the study by Lunawat et al and Segu *et al*. [12] with a $P < 0.05$ and null hypothesis is rejected. [12]

A 3.3% increase in the weight of the patients receiving propranolol was noted while the weight of the control group was found to be reduced by 3.27%.This indirectly provides evidence to prove increase in weight and mid-arm circumference. Though the mid-arm circumference may not to an absolutely precise parameter to assess anabolism because the mid-arm circumference results vary in patients who have sustained burn injuries in their arm unilaterally or bilaterally.

In our study the serum albumin concentration in patients receiving propranolol was increased by 5.7% at the end of 2 weeks . Similarly in the study by Lunawat *et al*., the serum albumin concentration has increased by 5% at the end of 2 weeks of propranolol therapy while it was reduced to 22% in control group not receiving propranolol. [12]

The values of CRP after 2 weeks of propranolol therapy were found to be reduced by 8.2% while it was increased by 12.7% in the control group.In Lunawat et al. values of CRP after 2 weeks of propranolol therapy was found to be reduced by 10% while it was increased by 20% in the control group with P<0.001. Similar results have been demonstrated in the study by Segu *et al*. with a $P < 0.05$, these values suggest a decreasing titre of infection in the body with propranolol

therapy and hence improving immunity. [12] A study by Póvoa *et al*. suggests CRP to be a good marker for assessment of sepsis.

No adverse effects of propranolol were observed with the given doses and there was never a requirement to withdraw due to any untoward effects. [19]

CONCLUSION

The above results clearly show the effect of propranolol on reducing cardiac workload and reduction of catabolism. Improvement in albumin concentration, mid-arm circumference and body weight implies improvement in LBM.A severe burn injury is invariably followed by a state of hypermetabolism causing increased morbidity and mortality. They counteract the effect of catecholamines and thus reduce infection and inflammation, thus reducing morbidity and eventually improving the long-term outcome of burn patients. Beta blockers are safe and efficient drugs in burn management can be included in the basic burn treatment protocol.

LIMITATIONS OF STUDY

Long duration study is required to assess wound healing status and duration required for healing.

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