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The Clinical Impacts of Using Propranolol as Anti-Catabolic Agent in Hospitalized Malnourished Patients

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Abstract

Objective: The prevalence of malnutrition among hospitalized patients is high. The degree of catabolism may be a determinant element in regard to clinical outcomes of critically ill patients. The hypermetabolic status is primarily mediated by catecholamine signaling through the beta-adrenergic receptors in which Propranolol can mitigate this hyperdynamic and hypermetabolic status through its non-selective adrenergic antagonist. The aim of this study is to evaluate the clinical impacts of using Propranolol as anticatabolic agent in adjunctive to enteral nutrition provision.

Methods: A retrospective analysis will be conducted in our institution between April 2017 and April 2019. Discharged or dead patients were excluded if failed to complete at least 1 week after hospital admission. All patients' continuous variables were analyzed using Independent Samples and One-Sample T-test while categorical data were expressed as numbers with percentages by using Chi Square test.

Results: The mean age of our 188 studied malnourished hospitalized patients was 58.94±10.37 years in which 131 patients (69.7%) of the eligible sample were males and 57 patients (30.3%) were females. Malnourished hospitalized patients who were administered Propranolol tab 40 mg three times daily (TID) as an anti-catabolic agent (Group I) had significantly higher average albumin level (ALB_{avg}) than malnourished hospitalized patients who were not administered Propranolol (Group II) (3.49±0.02 g/dl vs 3.25±0.06 g/dl) with Mean difference±SEM of +0.24±0.01 g/dl.

Conclusion: Significant higher ALB_{avg} accompanied with lower blood urea nitrogen (BUN) in Group I compared with Group II may indicate for Propranolol anti-catabolic effect which may have a positive major and minor clinical impacts in malnourished critically ill patients.

Keywords: Anticatabolic agents, Hypoalbumenia, Malnourished hospital patients, Propranolol.

Introduction

In a severe illness setting, basal metabolic rate (BMR) is usually elevated [1] and resting energy expenditure (REE) is increased by up to 100%.[2] In hospitalized individuals, inflammation and immobility are the most relevant mechanisms altering protein metabolism which, as reported by studies, is characterized by high-protein breakdown and low-protein synthesis as a result of complex interactions between the neurohormones and several inflammatory mediators released from the cells,

i.e. free radicals, cytokines, and prostaglandins.[2,3] Hypermetabolism and enhanced catabolism represent an attempt by the body to aid in the healing process, by allowing provision of amino acids and energy, mainly to the liver, in order to maintain gluconeogenesis and synthesis of acute-phase proteins needed for tissue repair and immunological response.[3,4] Although initially beneficial, prolonged adaptive metabolic response can lead to adverse outcomes such as the loss of total body protein mass[5] through muscle breakdown and results in a reduction in lean body mass (LBM)[6], leading to rapid malnutrition and persistent weakness.[3,7] The prevalence of malnutrition among hospitalized patients is as high as 50%.[7] The degree of catabolism may be a determinant element in regard to clinical outcomes of critically ill patients with an increased risk of morbidity, mortality, and longer hospital length of stay (LOS).[3,4]

Although appropriate nutrition can limit protein catabolism, it does not stop the loss of protein mass occurring in acute severe illness.[5] The hypermetabolic status is primarily mediated by catecholamines.[8] Propagation of catecholamine signaling is mainly through the beta-adrenergic receptors.[9] Propranolol, a nonselective beta-adrenergic receptor antagonist, holds promise for the mitigation of catecholamines' actions and thus, significantly reducing the hyperdynamic and hypermetabolic state. Administration of Propranolol for 2 weeks to decrease heart rate by 15% augments net protein balance in muscle by enhancing the availability of free amino acids for muscle protein synthesis, it also decreases the loss in LBM and lowers resting energy expenditure.[10] The role of Propranolol has been extensively studied in specific groups of population with proven efficacy in burned, septic and trauma patients[10,11-13], but there are only a few studies to show the effect of adjunctive Propranolol therapy in malnourished hospitalized adults who are already on enteral nutrition feeding (ENF). The aim of this study is to evaluate the clinical impacts of using propranolol as anticatabolic agent in malnourished hypoalbumenic critically ill patients in adjunctive to enteral nutrition provision regarding average albumin level (ALB_{avg}), average c-reactive protein to ALB ratio ($CRP:ALB_{avg}$), percentage changes in blood urea nitrogen (%ΔBUN), hemodynamics differences, and major clinical outcomes of hospital length of stay (LOS) and overall 28-day hospital mortality.

Material and Methods

This is a single-center observational retrospective study conducted in the departments of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. In this study, 188 malnourished hospitalized patients who were already on ENF were included. A flow chart of patients' selection and data collection processes is fully illustrated in Figure 1.

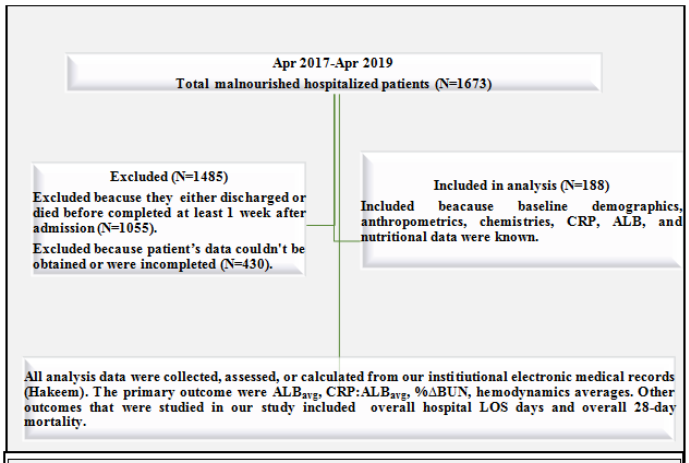

Fig 1. Flow chart of malnourished patient's selection and data collection process.

Apr: April. CRP: C-reactive protein

ALB: Albumin.

All patients' continuous variables were analyzed using independent samples T-test and expressed as Mean±SD for Group I and Group II, and as Mean difference±SEM between Group I and Group II. One sample T-test was

used to express the variables as Mean±SD for total malnourished hospitalized patients. Total patients, Group I, and Group II groups' categorical data was expressed as numbers with percentages by using Chi Square test. Statistical analysis was performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA), and P-values ≤0.05 were considered to be statistically significant.

Results

The mean age of our 188 studied malnourished hospitalized patients was 58.94±10.37 years in which 131 patients (69.7%) of the eligible sample were males and 57 patients (30.3%) were females. Malnourished hospitalized patients who were administered Propranolol tab 40 mg three times daily (TID) as an anti-catabolic agent (Group I) had significantly higher ALB_{avg} than malnourished hospitalized patients who were not administered Propranolol (Group II) (3.49±0.02 g/dl vs 3.25±0.06 g/dl) with Mean difference±SEM of +0.24±0.01 g/dl. Though there were insignificant differences between the two groups regarding CRP_{avg}, the $CRP:ALB_{avg}$ was significantly lower in Group I compared with Group II (7.25±1.51 vs 7.66±1.57) with Mean difference±SEM of -0.41±0.04. All nutritional indices of TCI_{avg}, PD_{avg}, and $H.ALB_{avg}$ were significantly lower in Group I compared with Group II (1122.6±210.9 Cal/day, 4.21±0.60 g/100 Cal, and 19.67±1.80 g/day vs 1291.6±243.6 Cal/day, 4.42±0.93 g/100 Cal, and 21.23±3.61 g/day) with Mean differences±SEMs of -168.9±33.3 Cal/day, -0.21±0.11 g/100 Cal, and -1.57±0.42 g/day, respectively. Group I had significantly lower BUN_1 and %ΔBUN than in Group II (14.09±1.89 mg/dl and 16.66%±33.07% vs 20.64±3.14 mg/dl and 40.06%±54.73%) with Mean differences±SEMs of -6.55±0.38 mg/dl and -23.40%±6.65%, respectively. All tested hemodynamics of SBP_{avg}, DBP_{avg}, MAP_{avg}, and HR_{avg} were significantly lower in Group I than in Group II (105.45±10.07 mmHg, 64.52±7.49 mmHg, 78.39±9.40 mmHg, and 75.64±9.94 bpm vs 110.24±9.92 mmHg, 71.14±5.81 mmHg, 85.30±8.21 mmHg, and 79.92±10.85 bpm) with Mean differences±SEMs of -4.79±1.46 mmHg, -6.63±0.98 mmHg, -6.91±1.29 mmHg, and -4.29±1.52 bpm, respectively. Regarding major clinical outcomes of LOS and mortality, patients in Group I had significantly lower hospital LOS and overall 28-day mortality than in patients of Group II (11.73±3.15 days and 10 (10.99%) vs 14.09±5.76 days and 26 (26.80%), respectively) with hospital LOS Mean difference±SEM of -2.37±0.68 days. The demographics, anthropometrics, nutritional indices, hemodynamics, and major clinical outcomes of all, Group I, and Group II hypoalbumenic malnourished hospitalized patients are fully presented in Table 1.

Discussion

This study demonstrates that non-selective beta-blockade with propranolol improves survival in malnourished hospitalized patients without evidence of clinically significant hemodynamic compromise. Furthermore, for the first time the anti-catabolic effect of Propranolol and its effectiveness on the general population of malnourished hospitalized patients who received ENF were studied, without limiting the study to a specific group of hospitalized patients. The measured overall anthropometrics of our malnourished hospitalized subjects of study were 74.05±10.23 kg and 25.90±3.97 kg/m^2 for actual body weight (ABW) and body mass index (BMI), respectively. There is an established correlation between CRP level, which is a positive acute phase reactant, and ALB. Both Inflammation and malnutrition reduce ALB concentration by decreasing its rate of synthesis, while inflammation alone is associated with a higher fractional catabolic rate (FCR) and, when extreme, increased escape of albumin from the intravascular compartment, while the

rate of synthesis of ALB is inversely related to the CRP.[14]

Moreover, many studies stated that Albumin remains a useful tool in evaluating nutrition and predicting the patient's risk for morbidity.[15] Therefore, these two markers were used to give an indication about the anti-catabolic effect of Propranolol. In our study, the difference in CRP levels between the two groups was statistically insignificant, while the differences in ALB levels and CRP: ALB ratio were significant, (3.49±0.02 g/dl vs 3.25±0.06 g/dl) and (7.25±1.51 vs 7.66±1.57) with Mean difference±SEM of (+0.24±0.01 g/dl) and (-0.41±0.04), respectively. Our explanation for the significant differences in ALB levels is the anti-catabolic effect of Propranolol. Confirmed by the lower %ΔBUN in Group I (the intervention group) compared with Group II, (16.66%±33.07%) vs (40.06%±54.73%), respectively. Hemodynamic differences between the two groups were statistically significant due to the anti-adrenergic effects of Propranolol, but were clinically acceptable, with SBP_{avg}, DBP_{avg}, MAP_{avg}, and HR_{avg} were significantly lower in Group I. Hospital LOS and overall 28-day mortality among patients were significantly lower in Group I than in Group II (11.73±3.15 days and 10 (10.99%) vs 14.09±5.76 days and 26 (26.80%), respectively) with hospital LOS Mean difference±SEM of -2.37±0.68 days. These major clinical outcomes are consistent with the outcomes of other previous studies.[3,4]

In summary, significant higher ALB_{avg} accompanied with lower blood urea nitrogen (BUN) in Group I compared with Group II may indicate for Propranolol anti-catabolic effect which may have a positive major and minor clinical impacts in malnourished critically ill patients. This study is limited by its retrospective design, using single-center data. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders.

Table 1. The demographics, anthropometrics, nutritional indices, hemodynamics, and major clinical outcomes of all, Group I, and Group II malnourished hospitalized patients.

Variable		Total (N=188)	Propranolol (Group I, N=91) Mean±SD	Non-Propranolol (Group II, N=97) Mean±SD	Mean difference±SEM	P-Value
Age (Yrs)		58.94±10.37	59.82±10.22	58.11±10.50	1.71±1.51	0.259 (NS)
Gender	Female	57 (30.3%)	27 (29.7%)	30 (30.9%)		0.489 (NS)
	Male	131 (69.7%)	64 (70.3%)	67 (69.1%)		
BW (Kg)		74.05±10.23	76.52±10.51	71.73±9.45	4.79±1.46	0.001 (S)
BMI (Kg/m^2)		25.90±3.97	26.97±3.91	24.89±3.79	2.08±0.56	0.000 (S)
CRP_{avg} (mg/dl)		25.11±4.67	25.30±5.05	24.91±4.53	0.39±0.61	0.091 (NS)
$H.ALB_{avg}$ (g/day)		20.48±2.98	19.67±1.80	21.23±3.61	-1.57±0.42	0.000 (S)

TCI_{avg} (Cal/kg/day)	17.63±3.12	16.20±2.63	18.96±2.96	-2.76±0.41	0.000 (S)
TCI_{avg} (Cal/day)	1209.8±242.9	1122.6±210.9	1291.6±243.6	-168.9±33.3	0.000 (S)
PD_{avg} (g/100 Cal)	4.32±0.79	4.21±0.60	4.42±0.93	-0.21±0.11	0.031 (S)
ALB_{avg} (g/dl)	3.37±0.05	3.49±0.02	3.25±0.06	0.24±0.01	0.000 (S)
CRP:ALB_{avg} (X:1)	7.45±1.54	7.25±1.51	7.66±1.57	-0.41±0.04	0.000 (S)
BUN_0	14.87±5.27	12.90±3.89	16.71±5.74	-3.81±0.72	0.000 (S)
BUN_1	17.47±4.19	14.09±1.89	20.64±3.14	-6.55±0.38	0.000 (S)
%ΔBUN	28.73%±46.92%	16.66%±33.07%	40.06%±54.73%	-23.40%±6.65%	0.001 (S)
SBP_{avg}	107.77±10.26	105.45±10.07	110.24±9.92	-4.79±1.46	0.001 (S)
DBP_{avg}	67.72±7.49	64.52±7.49	71.14±5.81	-6.63±0.98	0.000 (S)
MAP_{avg}	81.73±9.47	78.39±9.40	85.30±8.21	-6.91±1.29	0.000 (S)
HR_{avg}	77.85±10.61	75.64±9.94	79.92±10.85	-4.29±1.52	0.005 (S)
Hospital LOS	12.91±4.45	11.73±3.15	14.09±5.76	-2.37±0.68	0.000 (S)
Overall 28-day Survival	152 (80.85%)	81 (89.01%)	71 (73.19%)		0.000 (S)
Overall 28-day Mortality	36 (19.15%)	10 (10.99%)	26 (26.80%)		

Values are presented as Mean±SD by using independent T-test and one sample T-test or as number (%)by using Chi-square test.

Group I: Malnourished hospitalized patients who were administered Propranolol tab 40 mg TID as an anti-catabolic agent.

Group I: Malnourished hospitalized patients who weren't administered Propranolol tab.

Yrs: Years.

Kg: Kilogram.

BW: Actual body weight.

BMI: Body mass index.

S: Significant (P-Value <0.05).

NS: Nonsignificant (P-Value >0.05).

N: Number of study's patients.

0: Baseline before the intervention was commenced.

1: 1 week after the intervention was commenced.

Avg: Average value of the tested variable over 1 week.

BUN: Blood urea nitrogen.

CRP: C-reactive protein.

CRP:ALB ratio: C-reactive protein to albumin

TCR: Total calories requirement. PD: Protein density. Δ: Changes occurred after an intervention. ALB: Albumin level. H.ALB: Human albumin 20%.	level ratio. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MAP: Mean arterial pressure. HR: Heart rate. Bpm: Beat per minute. LOS: Length of stay.

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