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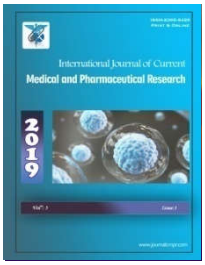

THE CLINICAL IMPACTS OF NON NUTRITIONAL CALORIES ON THE RISK OF HYPERCAPNIA AND VENTILATOR FREE DAYS IN CRITICALLY ILL PATIENTS WHO ARE TAKING ENTERAL NUTRITION

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ABSTRACT

Objectives: Most critically ill patients take dextrose saline which yields 3.4 Cal/g. Also, some ICU patients take propofol as sedative agents which yield 1.1 Cal/ml. Both dextrose and propofol can be significant sources of non-nutritional calorie (NNC). NNC may cause hypercapnia which can delay the weaning from ventilator and increase risk of multi-drug resistant (MDR) bacteria. The aim of this study is to evaluate the clinical impacts of NNCs) in mechanically ventilated critically ill patients who are also taking enteral nutrition.

Materials and Methods: We performed a retrospective analysis of patients admitted to the adult ICU.Collected data were analyzed by one-way ANOVA test followed by Tukey Kramer Post Hoc test to determine the mean differences of significant dependent variables between the Eucapnic (Group I), mild hypercapnic (Group II), moderate hypercapnic (Group III), and severe hypercapnic (Group IV). Risk of NNC associated hypercapnia were analyzed by chi square test.

Results: The mean overall age was 57.88±9.01 years, and 85 subjects (72.0%) were male. The overall risk of NNC associated hypercapnia was 74.58% (88 patients). Risk of mild hypercapnia (27.12%) was significantly higher in our study than either moderate hypercapnia (24.58%) or severe hypercapnia (22.88%).

Conclusion: NNCs may increase the risk of hypercapnia and subsequently ventilator weaning difficulties if g Carb: g Lipid ratio or %Carb Cal_TCI are also increased especially if the TCI exceeds TCR. As the PaCO2 level is increased, the weaning from ventilator and VFD chances are decreased and subsequently the risk of MDR bacteria of Acinetobacter, Pseudomonas, and Enterobacteriaceae are increased.

INTRODUCTION

Most critically ill patients take maintenance IV fluids of dextrose with or without saline regardless of saline concentration. Each gram of dextrose monohydtae yields 3.4 Cal. Also, some of mechanically ventilated critically ill patients take propofol as sedative agent after anlagosedative opioids. Each ml of propofol yields 1.1 Cal. Both dextrose and propofol can be significant sources of NNCs in ICU patients. NNCs may cause overfeeding associated hypercapnia (defined as PaCO2>45 mmHg when RQ>1) which occurs when total caloric inputs (TCIs) exceeds caloric expenditure. Caloric inputs may be nutritional and non-nutritional. NNC may increase the risk of hypercapnia and many other complications if it is not assessed as part of TCI when calculating patient's TCR. Hyperglycemia and insulin resistant, non-alcoholic fatty liver diseases (NAFLDs) and other liver disorders, infectious morbidities, ventilator weaning difficulties and subsequently lower VFDs, longer ICU LOS, and increased overall mortality are the most important complications of NNC associated overfeeding and hypercapnia in mechanically ventilated critically ill patients.[1-4]The aim of this study is to evaluate the clinical impacts of NNCs from maintenance dextrose fluids and propofol sedative agent on the risk of hypercapnia occurrence and subsequently on VFDs in mechanically ventilated critically ill patients who are taking enteral nutrition.

MATERIALS AND METHODS

We conducted a single-center observational retrospective study in a mixed surgical-medical adult ICU of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan to assess the risk of NNCs associated hypercapnia in four stratified groups based on $PaCO_2$ level as fully described in Table 1. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included a cohort of critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards

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with any medical or surgical problem. Flow chart of critically ill patient's selection and data collectionprocess is fully illustrated in Figure 1.

Table 1 Studied critically ill patients group's description

Group #	Group I	Group II	Group III	Group IV
Description	Eucapnic Critically ill patients with PaCO2 level of 35-45 mmHg	Mild hypercapnic Critically ill patients with PaCO2 level of 45.1-50 mmHg	Moderate hypercapnic Critically ill patients with PaCO2 level of 50.1-60mmHg	Severe hypercapnic Critically ill patients with PaCO2 level of > 60 mmHg

The collected data of each desired outcome in Group I-IV were analyzed using one-way ANOVA test to compare the mean value of dependent variables among groups followed by Tukey Kramer Post Hoc test to determine the mean differences of significant dependent variables between each group of the four tested groups. In case of gender (male or female), risk of NNC associated hypercapnia, level of hypercapnia, and level of calorie input were presented as number (percentage) using chi square analysis. Statisticalanalyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

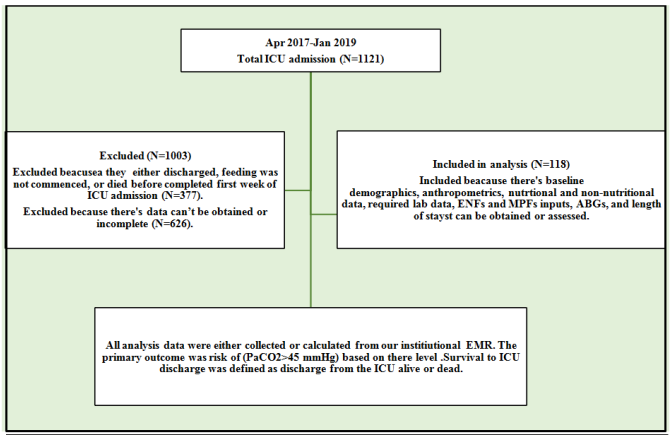

Fig 1 Flow chart of critically ill patient's selection and data collection process. Jan: January. ABGs: Air blood gases. MF: Maintenance fluid. Apr: April. ICU: Intensive Care Unit. ENF: Enteral nutritional formula.

RESULTS

The mean overall age was 57.88±9.01 years, and 85 subjects (72.0%) were male. The overall risk of NNC associated hypercapnia was 74.58% (88 patients). Risk of mild hypercapnia(27.12%) was significantly higher in our study than either moderate hypercapnia (24.58%) or severe hypercapnia (22.88%). ∑NNC was significantly highest in Group IV (442.1±15.6 Cal/day) followed by Group III, Group II, and Group I (364.5±93.8 Cal/day,292.9±95.6 Cal/day, and 252.7±57.2 Cal/day, respectively) with highest significant mean differences between Group I and IV (-189.39±19.73 Cal/day).% Glu $_{IV}$ Cal_NNC was significantly highest in Group IV (19.6%±1.4%) followed by Group III, Group II, and Group I (15.6%±5.3%,11.1%±5.4%, and 10.5%±3.9%, respectively) with highest significant mean differences between Group I and IV (-9.1%±1.2%). Both the % Carb Cal_TCI and g Carb: g Lipid ratio were significantly highest in Group IV (58.3%±2.6% and 5.45±0.18, respectively) followed by Group III, Group II, and Group I (51.1%±4.2% and 4.23±0.61, 47.9%±4.1% and 3.77±0.31, 44.9%±4.7% and 3.15±0.26, respectively) with highest significant mean differences between Group I and IV (-13.4%±1.1% and -2.29±0.10, respectively). VFDs was significantly highest in Group I (3.83±1.93 days) followed by Group II, Group III, and Group IV (3.31±2.40 days, 1.379±2.11 days, and 0.00±0.00 days, respectively) with highest significant mean differences also between Group I and IV (3.83±0.50 days). .Demographics, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarized in Table 2 and Table 3.

DISCUSSION

The present study included mechanically ventilated critically ill patients who were taking nutritional caloric sources from enteral nutrition formulas (ENFs) and non-nutritional caloric sources from dextrose IV with or without sedative propofol IV. Although the %NNC_TCI may exceed 1/5 of TCI (up to 23.6%±1.6% in our study), the pearson correlation between PaCO2 and %NNC_TCI is significant but lower than the two stronger affecting variables (%Carb Cal_TCI and g Carb: g Lipid ratio). Carbohydrate has the highest RQ value in compared with the two macro-nutrients yielding energy (Protein and lipid). RQ is 1 for carbohydrate while it is 0.8 for protein and 0.7 for lipid. In other word, balance diet has RQ value between 0.8-0.9 which is roughly equivalent to the acceptable macro-nutrient distribution ranges of 10-20%, 20-30%, and 40-60% for protein, lipid, and carbohydrate, respectively. So that, as RQ value is increased the risk of hypercapnia is increased and the relationships between hypercapnia and RQ, TCI, TCR, %Carb_TCI, g Carb: g Lipid ratio, and % NNC_TCI are complex. However, when nutritional support is advancing to achieve TCR, the risk of overfeeding may increase when also NNCs are provided to ICU patients. As long as the TCI is below the TCR, (%TC goal <100%) the risk of NNCs on hypercapnia is low as compared to the stronger effectors (g Carb: g Lipid ratio and % Carb Cal_TCI).Risk of hypercapnia was significantly highest correlated with g Carb: g Lipid ratio (R= 0.897) followed by %Carb Cal-TCI (R=0.82) and %NNC-TCI (R=0.56) as fully described in Table 4. The grams of carbohydrate in g Carb: g Lipid ratio and the calories of carbohydrate in %Carb Cal_TCI are from both nutritional and non-nutritional sources which is directly related to %TCI_TCR. As the $PaCO_2$ level is increased, the weaning from ventilator and VFD chances are decreased and subsequently the risk of MDR bacteria of Acinetobacter, Pseudomonas, and Enterobacteriaceae are increased.

In summary, our study demonstrate that NNCs may increase the risk of hypercapnia and subsequently ventilator weaning difficulties if g Carb: g Lipid ratio or %Carb Cal_TCI are also increased especially if the TCI exceeds TCR or TC Goal is above 100%. As this intake can be marked in critically ill patients, close monitoring is warranted when administering large maintenance fluids or high-dose propofol in pharmacological induced coma to prevent overfeeding, particularly when nutritional support is reaching pre-set energy targets.This study is limited by its retrospective design, using single-center data, including only septic ICU patients. 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 2 Demographics, anthropometrics, and follow-up comparison data of the study's critically ill patients.

Variables	Total (N=118)	Eucapnia	Hypercapnia (N=45)			P-Value
		Group I (N=30)	Group II (N=32)	Group III (N=29)	Group IV (N=27)	
Age (Yrs)	57.88±9.01	57.33±8.28	55.69±10.34	55.97±9.04	63.15±5.84	0.005 (S)
BW_0 (Kg)	68.76±8.99	71.76±6.44	69.27±8.59	72.66±10.86	60.66±2.52	0.000 (S)
BMI_0 (Kg/m²)	23.51±3.73	24.30±2.89	23.49±2.89	25.97±4.59	20.00±0.73	0.000 (S)
Sex Male	85 (72.0%)	21 (70.0%)	23 (71.9%)	14 (48.3%)	27 (100%)	0.000 (S)
Female	33 (28.0%)	9 (30.0%)	9 (28.1%)	15 (51.7%)	0 (0.0%)	
PaCO2 (mmHg)	51.01±8.31	42.01±2.09	47.20±1.39	52.52±2.26	63.91±3.35	0.000 (S)
Eucapnia (35-45 mmHg)			30 (25.42%)			0.000 (S)
Mild Hypercapnia (45.1-50 mmHg)			32 (27.12%)			
Moderate Hypercapnia (50.1-60 mmHg)			29 (24.58%)			
Severe Hypercapnia (>60 mmHg)			27 (22.88%)			
VFDs ($Day_{(s)}$)	2.21±2.41	3.83±1.93	3.31±2.40	1.379±2.11	0.00±0.00	0.000 (S)
TCI (Cal/Kg/day)	28.39±5.87	26.07±7.27	30.40±6.38	28.57±5.68	28.42±1.22	0.035(NS)
Low level Cal (<25 Cal/kg/day)	27 (22.9%)	15 (50.0%)	5 (15.6%)	7 (24.1%)	0 (0.0%)	
Moderate level Cal (25-30 Cal/kg/day)	55 (46.6%)	7 (23.3%)	11 (34.4%)	10 (34.5%)	27 (100%)	0.000 (S)
High level Cal (>30 Cal/kg/day)	36 (30.5%)	8 (26.7%)	16 (50.0%)	12 (41.4%)	0 (0.0%)	
TCI (Cal/day)	1916.5±426.5	1803.4±536.5	2072.2±503.8	1892.2±339.3	1883.6±156.2	0.083 (NS)
TCR (Cal/day)	2175.8±392.9	2056.5±461.7	2256.9±459.1	2149.3±296.7	2240.8±284.9	0.171 (NS)
% TC Goal	87.6%±6.8%	86.5%±7.9%	91.1%±6.6%	87.7%±6.3%	84.5%±4.3%	0.001 (S)
∑NNC (Cal/day)	334.4±102.3	252.7±57.2	292.9±95.6	364.5±93.8	442.1±15.6	0.000 (S)
%NNC_TCI	18.2%±6.1%	15.1%±4.9%	14.9%±6.2%	19.8%±5.7%	23.6%±1.6%	0.000 (S)
g Glu_{IV} (g/day)	76.16±30.13	51.94±16.62	64.07±28.08	84.75±27.24	108.20±5.61	0.000 (S)
NNC_Glu_{IV} (Cal/day)	258.9±102.4	176.6±56.5	217.8±95.5	288.1±92.6	367.9±19.1	0.000 (S)
% Glu_{IV} Cal_NNC	13.9%±5.7%	10.5%±3.9%	11.1%±5.4%	15.6%±5.3%	19.6%±1.4%	0.000 (S)
g $Lipid_{Propofol}$ (g/day)	6.89±0.49	7.04±0.45	6.76±0.59	6.89±0.45	6.90±0.41	0.159 (NS)
NNC_ $Lipid_{Propofol}$ (Cal/day)	75.80±5.36	77.39±4.97	74.31±6.44	75.71±4.92	75.89±4.52	0.160 (NS)
% $Lipid_{Propofol}$ Cal_NNC	4.20%±1.21%	4.72%±1.54%	3.90%±1.45%	4.15%±0.94%	4.04%±0.13%	0.042 (S)
NC (Cal/day)	1581.7±430.7	1549.4±538.2	1780.1±493.9	1528.4±343.1	1439.8±142.7	0.014 (S)
%NC_TCI	81.8%±6.1%	84.8%±5.0%	85.0%±6.3%	80.3%±5.6%	76.3%±1.6%	0.000 (S)
NC_Carb (Cal/day)	694.1±161.4	615.4±169.5	758.2±180.9	668.8±134.2	732.7±111.2	0.002 (S)
% Carb Cal_NC	44.6%±5.7%	40.8%±4.2%	43.4%±5.1%	44.3%±5.1%	50.7%±3.3%	0.000 (S)
NC_ Lipid (Cal/day)	485.5±126.3	513.9±143.9	538.5±136.8	470.7±102.9	407.1±63.0	0.000 (S)
% LipidCal_NC	31.1%±4.1%	33.9%±2.9%	30.8%±3.6%	31.4%±5.2%	28.2%±1.9%	0.000 (S)
∑Carb Input (g/day)	249.69±48.85	205.79±44.95	253.62±44.89	251.95±30.59	291.38±31.98	0.000 (S)
Carb Cal (Cal/day)	953.1±185.8	792.0±176.7	976.0±175.2	956.9±117.9	1100.6±125.3	0.000 (S)
%Carb Cal_TCI	50.4%±6.3%	44.9%±4.7%	47.9%±4.1%	51.1%±4.2%	58.3%±2.6%	0.000 (S)
∑Lipid Input (g/day)	62.37±13.88	65.71±15.61	68.09±14.87	60.72±11.44	53.67±7.50	0.000 (S)
Lipid Cal (Cal/day)	591.4±140.5	612.8±133.8	546.5±102.9	482.9±67.6	561.3±124.9	0.000 (S)
%Lipid Cal_TCI	29.6%±4.1%	33.4%±2.8%	29.9%±2.8%	29.2%±4.4%	25.5%±1.5%	0.000 (S)
g NPR (X: 1)	4.11±0.91	3.15±0.26	3.77±0.31	4.23±0.61	5.45±0.18	0.000 (S)

Values are presented as mean±standard deviation by using ANOVA test or number (%) by using Chi square test (significance level at p-value< 0.05).

ICU: Intensive care unit. BW_0: Actual body weight at admission. g NPR: g Carb: g Lipid ratio.
S: Significant (P-Value <0.05). BMI_0: Body mass index at admission. Cal: Kcal or calorie.
NS: Nonsignificant (P-Value >0.05). TCI: Total calorie input. NC: Nutritional calorie.
N: Number of study's critically ill patients. NNC: Non-nutritional calorie. Carb: Carbohydrate.
VFDs: Ventilation free days. Glu: Glucose. Group III: Moderate hypercapnic ICU patients.
Group I: Eucapnic ICU patients. Group II: Mild hypercapnic ICU patients. Group IV: Severe hypercapnic ICU patients.

Table 3 Multiple comparison of the significant dependent variables between the four tested groups

Dependent Variable	Group I vs II	Group I vs III	Group I vs IV	Group II vs III	Group II vs IV	Group III vs IV
	Mean diff ±SEM (Sig)	Mean diff ±SEM (Sig)	Mean diff ±SEM (Sig)	Mean diff ±SEM (Sig)	Mean diff ±SEM (Sig)	Mean diff ±SEM (Sig)
Age (Yrs)	1.65±2.19 (NS)	1.37±2.25 (NS)	-5.82±2.29 (NS)	-0.28±2.21 (NS)	-7.46±2.25 (S)	-7.18±2.31 (S)
BW_0 (Kg)	2.48±1.99 (NS)	-0.89±2.03 (NS)	11.10±2.07 (S)	-3.38±2.00 (NS)	8.62±2.04 (S)	11.99±2.09 (S)
BMI_0 (Kg/m²)	0.81±0.79 (NS)	-1.67±0.81 (NS)	4.29±0.83 (S)	-2.48±0.79 (S)	3.49±0.81 (S)	5.97±0.83 (S)
PaCO2 (mmHg)	-5.19±0.59 (S)	-10.51±0.61 (S)	-21.90±0.62 (S)	-5.32±0.59 (S)	-16.71±0.61 (S)	-11.39±0.63 (S)
VFDs ($Day_{(s)}$)	0.52±0.48 (NS)	2.45±0.49 (S)	3.83±0.50 (S)	1.93±0.49 (S)	3.31±0.49 (S)	1.38±0.51 (S)
∑NNC (Cal/day)	-40.28±18.90 (NS)	-111.8±19.4 (S)	-189.39±19.73 (S)	-71.47±19.07 (S)	-149.1±19.4 (S)	-77.7±19.9 (S)
%NNC_TCI	0.14%±1.28% (NS)	-4.7%±1.3% (S)	-8.5%±1.3% (S)	-4.8%±1.3% (S)	-8.6%±1.3% (S)	-3.8%±1.3% (S)
g Glu_{IV} (g/day)	-12.13±5.53 (NS)	-32.81±5.67 (S)	-56.26±5.78 (S)	-20.673±5.58 (S)	-44.13±5.69 (S)	-23.46±5.82 (S)
NNC_Glu_{IV} (Cal/day)	-41.26±18.81 (NS)	-111.6±19.3 (S)	-191.29±19.64 (S)	-70.29±18.98 (S)	-150.0±19.4 (S)	-79.75±19.79 (S)
% Glu_{IV} Cal_NNC	-0.54%±1.12% (NS)	-5.1%±1.1% (S)	-9.1%±1.2% (S)	-4.5%±1.1% (S)	-8.6%±1.2% (S)	-4.0%±1.2% (S)
% Lipid Cal_NNC	0.82%±0.29% (S)	0.6%±0.3% (NS)	0.7%±0.3% (NS)	-0.3%±0.3%(NS)	-0.1%±0.3%(NS)	0.1%±0.3% (NS)
NC (Cal/day)	-230.7±105.9 (NS)	21.0±108.5 (NS)	109.5±110.5 (NS)	251.7±106.8(NS)	340.2±108.9 (S)	88.5±111.4 (NS)
%NC_TCI	-0.27%±1.28% (NS)	4.5%±1.3% (S)	8.4%±1.3% (S)	4.8%±1.3% (S)	8.7%±1.3% (S)	3.9%±1.4% (S)
NC_Carb (Cal/day)	-142.76±38.92 (S)	-53.4±39.9 (NS)	-117.3±40.6 (S)	89.4±39.3(NS)	25.5±40.0 (NS)	-63.9±40.9 (NS)
% Carb Cal_NC	-2.59%±1.15% (NS)	-3.5%±1.2% (S)	-9.9%±1.2% (S)	-0.9%±1.2%(NS)	-7.3%±1.2% (S)	-6.4%±1.2% (S)
NC_ Lipid (Cal/day)	-24.55±29.92 (NS)	43.22±30.66 (NS)	106.86±31.23 (S)	67.8±30.2 (NS)	131.4±30.8 (S)	63.6±31.5(NS)
% LipidCal_NC	3.2%±0.9% (S)	2.6%±0.9% (S)	5.8%±0.9% (S)	-0.6%0.9% (NS)	2.6%± 0.9% (S)	3.2%±0.9% (S)
∑Carb Input (g/day)	-47.82±9.92 (S)	-46.16±10.17 (S)	-85.58±10.36 (S)	1.66±10.01 (NS)	-37.76±10.21 (S)	-39.42±10.44 (S)
Carb Cal (Cal/day)	-184.01±38.78 (S)	-164.5±39.7 (S)	-308.58±40.48 (S)	19.1±39.1 (NS)	-124.57±39.88 (S)	-143.6±40.8 (S)
%Carb Cal_TCI	-3.0%±1.0%(S)	-6.2%±1.0% (S)	-13.4%±1.1% (S)	-3.2%±1.0% (S)	-10.4%±1.1% (S)	-7.2%±1.1% (S)
∑Lipid Input (g/day)	-2.38±3.29 (NS)	4.99±3.37 (NS)	12.04±3.43 (S)	7.37±3.31 (NS)	14.42±3.38 (S)	7.05±3.46 (NS)
Lipid Cal (Cal/day)	-21.46±29.57 (NS)	44.91±30.29 (NS)	108.36±30.86 (S)	66.4±29.8 (NS)	129.8±30.4 (S)	63.45±31.11 (NS)
%Lipid Cal_TCI	3.5%±0.8% (S)	4.2%±0.8% (S)	7.9%±0.8% (S)	0.7%±0.8% (NS)	4.4%±0.8% (S)	3.7%±0.8% (S)
g NPR (X: 1)	-0.62±0.09 (S)	-1.07±0.09 (S)	-2.29±0.10 (S)	-0.46±0.09 (S)	-1.68±0.09 (S)	-1.22±0.10 (S)

Data are presented as Mean difference ±Standard error of mean and are analyzed by using Tukey Kramer post-hoc multiple comparison analysis (significance level at p-value< 0.05).

ICU: Intensive care unit. BW_0: Actual body weight at admission. g NPR: g Carb: g Lipid ratio.
S: Significant (P-Value <0.05). BMI_0: Body mass index at admission. IV: Intravenously.
NS: Nonsignificant (P-Value >0.05). TCI: Total calorie input. Cal: Kcal or calorie.
N: Number of study's critically ill patients. NNC: Non-nutritional calorie. NC: Nutritional calorie.
VFDs: Ventilation free days. Glu: Glucose. Carb: Carbohydrate.
Group I: Eucapnic ICU patients. Group II: Mild hypercapnic ICU patients. Group III: Moderate hypercapnic ICU patients.
Group IV: Severe hypercapnic ICU patients.

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