Safety and Efficacy of Multi-chamber Bag Parenteral Nutrition

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Research Article

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Abstract

Background There is a significant degree of debate regarding the use of standardized parenteral solutions. Multi-chamber bag parenteral nutrition (MCB-PN) showed advantages over compounded PN in previous literature. Meanwhile, some literature has shown the limitations in use of MCB-PN. This study was conducted to evaluate the nutritional efficacy and safety of commercially available MCB-PN.

Methods All adult hospitalized patients who have been on MCB-PN for at least seven consecutive days at King Faisal Specialist Hospital & Research Center in Riyadh from January 2015 until December 2019 were included. Laboratory parameters were evaluated before PN started, which was used as a baseline, and every seven days while on PN. Primary outcomes were the percentage of patients who achieved calculated target calories and protein and the percentage of patients who developed electrolyte abnormalities. The secondary outcome was a percentage of adverse drug reactions during the treatment period.

Results Two hundred and thirty-one patients met the inclusion criteria. Among the included subjects, 101 (44%) achieved target calories; 29 (12.6%) were underweight; 40 (17.3%) were normal weight; 18 (7.8%) were overweight; and 14 (6.1%) were in obese subgroups, with *p*-value 0.145. Sixty-eight (29.6%) achieved the target protein dose; 26 (11.3%) were underweight; 33 (14.3%) were normal weight; five (2.2%) were overweight; and four (1.7%) were in obese subgroups, with *p*-value < 0.01. One hundred and ninety-one (83.4%) developed electrolyte imbalances; 39 (16.9%) were underweight; 87 (37.7%) were normal weight; 34 (14.7%) were overweight; and 34 (14.7%) were in obese subgroups, with *p*-value 0.085, during the treatment period. A small percentage of ADRs and metabolic abnormalities were reported during the treatment period.

Conclusion Among patients receiving MCB-PN, only 44% achieved the caloric target, and 29.6% achieved the target protein dose with fewer percentages of ADRs.

Introduction

Parenteral nutrition preparations are considered a high-alert medication according to ISMP Medication Safety Self-Assessment® for High-Alert Medications. The chances for errors, contamination, and complications related to PN therapy are high. Standardization is a suggested strategy to ensure patient safety associated with PN therapy. As mentioned in the 2007 American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), position statement on PN standardization, a standardized, commercial PN product available from a manufacturer requires limited compounding.[1–2]

Ready-made PN formulations are prepared in single-container or multi-chamber bags, usually cited as “premixed” despite the fact that they need mixing in the pharmacy before administration. Ready-made formulations have been marketed as safer and more efficient delivery systems for nutrients compared with traditional formulations compounded manually or by automated compounder machines.[3] The

acids in one chamber and dextrose in the other chamber.

Bags with and without added electrolytes in final volumes of 1 L and 2 L have been available in markets over past years.[1] The lipid can be given through a Y-connector inserted in the IV catheter. While three-chamber bags contain the same elements of the two-chamber bags, the third chamber contains lipids.[1] Multichambered PN with compounded formulations are an available formulation choice for hospitalized patients to best meet an institution's patient needs.[3] The benefits of using the ready-made parenteral solutions compared to the customized solutions include reduced medication error throughout the whole preparation process, reduced incidents of bloodstream infections (BSIs), and possible lower cost.[4–5] To accommodate particular patient demands for electrolytes, vitamins, and minerals, these positive impacts must be weighed against the need for individual adaptation.[6]

The ready-made parenteral solutions are made with a fixed number of calories and electrolytes designed to fit the majority of the population. Thus, there are major limitations, including that ready-made solutions cannot be used in populations requiring higher protein requirements (e.g., obese, underweight, and CRRT patients), a possible inability to maintain electrolyte balances in patients who require higher or lower requirements (e.g., HF patients, CKD or AKI, and post bone marrow transplant), and difficulty achieving target calories/day while maintaining the patient's hydration status.[7] In conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism, and sepsis, SmofKabiven should be prescribed with caution.[8] SmofKabiven® is a premixed PN available on the market. Approved by the FDA in August 2014 to be used in patients 2 years and older, SmofKabiven® is the first premixed PN added to King Faisal Specialist Hospital's formulary in 2015. SmofKabiven is a three-chamber container available in different pack sizes: 960 ml, 1080 ml, 1200 ml, 1320 ml, 1440 ml, 1560 ml, 1680 ml, 1800 ml, and 1920 ml. Each bag contains amino acids (3.2 g/100 mL), dextrose anhydrous (7.1 g/100 mL), and lipids (2.8 g/100 mL) with electrolytes. Each component is located in a separate chamber. These components must be mixed before administration and should be administered via a central line, as the maximum allowed peripheral osmolarity is 900 mOsmol/L for adults.[7–8] Contraindications for use, as defined by the manufacturer, are hypersensitivity to fish-, egg-, soya-, or peanut protein or corn (maize) and corn products or to any of the active substances or excipients; severe hyperlipidemia; severe liver insufficiency; severe blood coagulation disorders; congenital errors of amino acid metabolism; severe renal insufficiency without access to hemofiltration or dialysis; unstable conditions (such as extreme post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis, severe sepsis, hypotonic dehydration and hyperosmolar coma); uncontrolled hyperglycemia; and elevated serum levels of any of the included electrolytes. In addition, the manufacturer includes uncontrolled hyperglycaemia contraindications to infusion therapy, such as acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency. Previous literature compared the use of compounded monobags with industrially manufactured three-chamber bags. MCB-PN had proven benefits compared to customized PN in terms of reduced cost and reduced risk of BSIs. This study was conducted to evaluate the nutritional efficacy and safety of MCB-PN. In terms of efficacy, the percentage of patients who achieved calculated target calories and protein and the percentage of patients who developed

electrolyte imbalances were evaluated. In terms of safety, the incidence of BSI and MCB-associated complications developed during the treatment period were evaluated.

Methods

The study was a retrospective chart review, approved by the local institutional review board (IRB). We included all adult hospitalized patients who had been on MCB- PN consecutively for at least 7 days at King Faisal Specialist Hospital & Research Center in Riyadh (KFSHRC-R) from January 2015 until December 2019. We excluded patients who received MCB-PN for less than 7 days. The following was collected for this study. In terms of efficacy, we evaluated the percentage of patients who achieved calculated target calories and protein and the percentage of patients who developed electrolyte abnormalities. In terms of safety, we evaluated the incidence of central line-associated bloodstream infections (CLABSIs) and MCB-associated complications developed during the treatment period. The data collection sheet was formulated by using the REDCAP system for entering and analyzing valuables (please refer to appendix A). Total calories, total macronutrients g/day (proteins, dextrose, and fat), electrolyte contents, and the volume provided from SmofKabiven® are available in the product information reference (please refer to appendix B). Laboratory parameters were determined and used as a baseline before the PN started and at day 7 after starting PN, including hematological parameters (hemoglobin, red blood cell count, white blood cell count, platelet count, percentage of granulocyte, and hematocrit), parameters of blood coagulation function (prothrombin time and activated partial thromboplastin time), liver function parameters (alanine aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, total bilirubin, and serum albumin), blood chemistry and electrolytes (triglycerides, total cholesterol, blood glucose, serum urea nitrogen, creatinine, sodium, potassium, chloride, and phosphate), and C-reactive protein (CRP) and prealbumin (as a short-term marker for nutrition status). The changes in prealbumin levels between POD 1 (i.e., before administration of PN) and POD 7 (i.e., after administration of PN for 7 consecutive days) were reviewed using the hospital electronic healthcare record (EMR) system (ICIS). The institutional review board (IRB) of hospital institution approved the study, before data collection started. The study was performed in compliance with all ethical principles of King Faisal Specialist Hospital & Research Center.

Statistical Analysis

Baseline and demographic characteristics were summarized using descriptive statistics (means, standard deviations) for continuous variables, such as age, and percentages for categorical variables, such as race and ethnicity. Data were entered in the REDCAP system. Data were presented as means ± SD. Statistical significance was set at $p < 0.05$. The results are presented in percentages and tables by the REDCAP system. A chi-square test was done for post hoc analysis.

Results

Study Population

Results are stated descriptively as means (95% confidence intervals) and proportions. Of the 660 hospitalized patients on MCB-PN from January 2015 until December 2019, 231 patients met the inclusion criteria. Among the 231 patients, 51.5% were males, and 48.5% were females. Furthermore, 21.6% were underweight (BMI less than 18.5); 44.6% were normal weight (BMI 18.5 to 24.9); 18.6% were overweight (BMI 25 to 29.9); and 15.1% were obese (BMI 30 or more) (Table 1–3). Eligible patients weighed between 18 and 125 kg and had nutrition requirements between 1500–2000 kcal/d. Patients who received MCB-PN for less than 7 days were excluded. Of the patients, 77.9% were admitted electively for surgery; 45.5% were for hyperthermic intraperitoneal chemotherapy (HIPEC); 4.44% were for partial or total gastrectomy; 6.66% were for bowel resection; 2.8% were for a Whipple procedure; and 40.6% were for other procedures. Furthermore, 35.9% were admitted with a chief complaint of GI symptoms; 2.2% were admitted for nutritional support; and 14.3% were admitted for other reasons. Table 3 presents the indications for use of MCB-PN: 70.1% for post-operative nutritional support, 6% for GI symptoms, 4% for inflammatory bowel disease, 2% for bowel obstruction or ischemia, 7.2% for lower gastrointestinal tract perforation or leak, 2.8% for high output fistula (more than 500 ml/day), 0.4% for short bowel syndrome with sever malabsorption, 0.4% for gastrointestinal bleeding, 1.3% for sever oral mucositis after chemotherapy, and 5.9% for other reasons. Patients received PN via central veins. The average infusion rate was approximately 65 mL/hr, and the average duration was approximately 16 days.

Primary outcomes

Among the included subjects, 101 patients (44%) achieved target calories; 29 (12.6%) were underweight; 40 (17.3%) were normal weight; 18 (7.8%) were overweight; and 14 (6.1%) were in obese subgroups (*p*-value 0.145). Sixty-eight patients (29.6%) achieved the target protein dose; 26 (11.3%) were underweight; 33 (14.3%) were normal weight; five (2.2%) were overweight; and four (1.7%) were in obese subgroups (*p*-value < 0.01). Of the patients, 191 (83.4%) developed electrolyte imbalances; 39 (16.9%) were underweight; 87 (37.7%) were normal weight; 34 (14.7%) were overweight; and 34 (14.7%) were in obese subgroups during the treatment period (*p*-value 0.085). Electrolyte imbalances developed during treatment: 59.2% hypokalemia, 14.7% hyperkalemia, 42.9% hyponatremia, 3.7% hypernatremia, 53.4% hypophosphatemia, 18.3% hyperphosphatemia, 38.2% hypomagnesemia, 3.1% hypermagnesemia, 3.1% hypocalcemia, and 0.5% hypercalce

Electrolyte Replacement

mia.

Bolus doses

During the treatment period, one to five boluses were given of 32.5% potassium chloride, 45.0% phosphate, 34.2% magnesium sulfate, and 6.9% calcium gluconate. Five to 10 boluses were given of 6.1% potassium chloride, 6.5% phosphate, 6.1% magnesium sulfate, and 0.0% calcium gluconate. Ten to 15 boluses were given of 1.3% potassium chloride, 6.5% phosphate, 0.9% magnesium sulfate, and 0.0% calcium gluconate. Fifteen to 20 boluses were given of 0.4% potassium chloride, 0.4% phosphate, 0.9%

magnesium sulfate, and 0.0% calcium gluconate. Twenty to 25 boluses were given of 0.4% potassium chloride, 0.0% phosphate, 0.0% magnesium sulfate, and 0.0% calcium gluconate.

Maintenance electrolytes infusion

During the treatment period, 43.3% were on potassium chloride infusion; 2.2% were on phosphate infusion; 14.7% were on magnesium sulfate infusion; and 0.4% were on calcium gluconate, with MCB-PN and close monitoring of electrolyte serum levels daily.

Secondary outcomes

There was no documented incidence of CLABSI. However, 7.8% of study subjects developed hyperglycemia; 2.2% developed hypoglycemia; 10.4% developed liver injury; 1.3% developed hypertriglyceridemia; 3.0% developed fluid overload; and 1.3% developed refeeding syndrome. After stopping MCB-PN, 74.5% of the population started an oral diet; 1.7% shifted to enteral feeding; 0.9% died; 22.5% shifted to customized PN; and 1.3% developed SmofKabiven®-associated complications (i.e., liver injury, hypertriglyceridemia, and hyperkalemia). During the treatment period, 22.5% of the population shifted from MCB-PN to customized PN for the following reasons: 71.1% due to electrolyte imbalances, 23.1% due to not achieving their nutritional targets in term of calories and protein, 3.8% due to AKI, 9.6% due to fluid overload, and 3.8% due to other reasons.

Discussion

Standardization is suggested to ensure patient safety associated with PN therapy.[1–2] Published literature has demonstrated the advantages of standardized formulations in hospitalized individuals who received parenteral therapy.[1–2] Literature comparing the standardized and customized PN is limited, not commonly of good quality, and comes from Europe.[1,13–19] Almost all of these studies have shown that MCB-PN is less pricey than customized nutrition is. However, MCB-PN has been shown to have higher costs or equivalent costs.[14–20] By analyzing the data, there are several confounding factors and variables to consider, including compounding hours, the organization's policies, compounding machine costs, type of premix (whether three-chambered or two-chambered bags with additional intravenous lipid emulsion), administration tube costs, nurse time, staff salaries for pharmacy and nursing, and outside added electrolyte boluses when using premixed PN.[1,21] A prospective open-label randomized control trial of 100 patients comparing MCB-PN to customized PN was published in *Advances in Pharmacology and Pharmacy*. In this study, MCB-PN was not superior to customized PN formulas in terms of safety and efficacy, but it was a less expensive formula.[2,7] Fewer adverse drug reactions and metabolic disturbances were shown in patients who received premixed PN than those in patients receiving tailored PN.[2,7] In an EPICOS study, an international, multicenter, prospective, open-label, controlled trial studied the impact of PN delivery systems on the incidence of BSIs in critically ill patients. They suggested that the use of MCB-PN

could be considered a nutritional support option with fewer incidences of BSIs compared to a customized one in five Chinese hospitals compared MCB-PN to

customized PN formulations. Among 240 patients, prealbumin levels rose dramatically

in the study population by 2.70 ± 5.69 mg/dL ($P < .001$). The preparation time decreased dramatically by almost 8 minutes in the study population ($P < .001$), and no significant differences in safety parameters were defined in their study in terms of adverse reactions and 30-day mortality.[10]

In our study, we aimed to study standardized PN formulation regarding the efficacy of nutrition support and safety in hospitalized patients. Among patients receiving MCB-PN, only 44% achieved target calories, and 29.6% achieved the target protein dose. Overweight and obese patients may be at higher risk of not achieving target protein requirements while on MCB-PN. A smaller percentage of patients experienced adverse drug reactions and metabolic abnormalities during the treatment period. Individualized nutritional assessment and evaluation before starting MCB-PN are warranted to ensure appropriate use of PN formulas. Compared to previous published studies, our study included more patients in different hospital settings, a longer PN intervention ($\geq$ 7 days), and an ad hoc analysis to examine the primary outcomes in all patients with different BMIs.

Limitations

In evaluating the results of this analysis, some limitations should be noted. First, the unavailability of an indirect calorimetry device and the use of estimated equations (e.g., Harris–Benedict equations and Mifflin) may not give a patient's accurate nutritional requirements and targets. Second, efficacy was determined by achieving the target calories and protein specified by an assigned clinical pharmacist every day. Although these factors are significant, they are not the only indicators of effectiveness in terms of support for nutrition. Third, confounding variables were not controlled because the nature of our study was retrospective. Finally, this study is a single arm; we did not compare the findings of the study with standard therapies.

Conclusion

In conclusion, among patients receiving MCB-PN, patients with BMI more than 30 kg/m^2 are less likely to achieve the recommended target protein requirements (p-value < 0.05). Less than 60% of all included patients with different BMIs achieved target caloric requirements. Electrolyte abnormalities remained high in all included patients while on MCB-PN.

Declarations

Funding (information that explains whether and by whom the research was supported)

no funding support was provided.

Conflicts of interest/Competing interests (include appropriate disclosures)

Non.

Ethics approval (include appropriate approvals or waivers)

this study was approved by king faisal specialist hospital's research & ethical center.

Consent to participate (include appropriate statements)

not applicable

Consent for publication (include appropriate statements)

The primary author, Muna Islami, declares the following on behalf on me and co-authors:

- Neither the paper nor portions of it have been previously published (except as an abstract has been presented as poster in ASPEN21),
- The manuscript has not been proposed for publication in another journal and it will not be published anywhere until the editorial process at SN COMPREHENSIVE CLINICAL MEDICINE is completed

Availability of data and material (data transparency)

All data and records generated throughout the course of the study will be kept confidential in alignment with King Faisal Specialist Hospital and Research center (KFSHRC) Policies and the Primary investigators and co-investigators will be the only ones to have access to the study data and records for the purposes of conducting the study. All data will be stored and built using a study data management systems, (RedCap,), the data stored in REDCap's back end database, the software application employs multiple methods to protect against users who may try to identify and exploit any security vulnerabilities in the system. Data will be only accessed and used by investigators during study period.

Code availability (software application or custom code)

All data will be stored and built using a study data management systems, (RedCap,).

Authors' contributions

Author	Title	Work contribution
Muna Islami	Primary author and corresponding author	Writing proposal form Submitting for IRB approval Writing data collection sheet Data collection Writing manuscript Submit for publication
Mohammad Alsharhan	Co-author	Generate research idea Review proposal form and editing. Reviewing an editing data collection sheet Supervising data collection phase Review manuscript Mentor and program director
Areej A. Alfattani	Co-author	Writing the statical analysis Statical analysis Data coding
Haya K. Almeshari	Co-author	Review proposal form and editing. Reviewing an editing data collection sheet.
Manar S. Alawwad	Co-author	Reviewing an editing data collection sheet.

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Tables

Table 1: Composition of SmofKabiven®

Volume (ml)	**960**	**1080**	**1200**	**1320**	**1440**	**1560**	**1680**	**1800**	**1920**
Amino Acids (gm)	48.73	54.82	60.91	67.01	73.1	79.19	85.28	91.37	97.46
Lipids (gm)	36.55	41.12	45.68	50.25	54.82	59.39	63.96	68.53	73.09
Dextrose (gm)	121.82	137	152.28	167.51	182.74	197.96	213.19	228.42	243.65
Calories (kcal)	**974.3**	**1096.2**	**1217.9**	**1340.07**	**1364.4**	**1583.7**	**1705.7**	**1827.37**	**1946.1**
Na+ mmol	38.98	43.86	48.73	53.6	58.48	63.35	68.22	73.1	77.97
K+ mmol	29.24	32.89	36.55	40.2	43.86	47.51	51.17	54.82	58.48
Ca++ mmol	2.44	2.74	3.05	3.35	3.65	3.96	4.26	4.57	4.87
Mg++ mmol	4.87	5.48	6.09	6.7	7.31	7.92	8.53	9.14	9.75
SO4-- mmol	4.87	5.48	7.09	6.7	7.31	7.92	8.53	9.14	9.75
PO4-- mmol	12.18	13.71	15.23	16.75	18.27	19.8	21.32	22.84	24.37
Acetate- mmol	101.85	114.58	127.31	140.04	152.77	165.5	178.23	190.86	203.7
Cl- mmol	34.11	38.38	42.64	46.9	51.17	55.43	59.7	63.96	68.22
Zinc mmol	0.038	0.043	0.05	0.05	0.06	0.06	0.07	0.07	0.08
Rate	**40 ml/hr**	**45 ml/hr**	**50 ml/hr**	**55 ml/hr**	**60 ml/hr**	**65 ml/hr**	**70 ml/hr**	**75 ml/hr**	**80 ml/hr**
Additives addition									
Trace elements	6 ml/1970 ml								
Multivitamin	10 ml/1970 ml								
Selenium	40 mcg/1970 ml								

Table 2. Characteristics of Study Population.

Item	n=231
Age, mean ± SD, y	53.7 ± 17.19
Male/female, No.	119/112
Height, mean ± SD, cm	161.97 ± 9.97
Weight, mean ± SD, kg	62.08 ± 17.18
BMI , mean ± SD, kg/m^2	23.67 ± 6.37
BMI < 18.5, No	50
BMI 18.5 - 24.9, No	103
BMI 25 - 29.9, No	43
BMI 30, No	35
Medication history, no/yes, No.	16/215
Cardiovascular diseases, No	40
Diabetes, No	38
Kidney disease, not on IHD, No	3
Kideny disease on IHD, No	1
Hepatic disease, No	0
Other diseases, No	133
Admitted electively for surgery, No	180
GI surgeries, No	107
Other procedures, No	73
Admitted for nutritional support, No	5
Admitted GI symptoms, No	13
Admitted for others, No	33
Treatment period, mean ± SD, d	16 ± 16.7

GI = Gastrointestinal, BMI= Body Mass Index, IHD= Intermittent Hemodialysis

Table 3. Patient's Nutritional Facts.

Item	n=231
BEE , mean ± SD, kcal/d	2614.63 ± 346. 71
BEE 1.3 , mean± SD, kcal/d	3393.61 ± 450.12
BEE 1.5, mean ± SD, kcal/d	161.97 ± 9.97
PN indications	
Post operative nutritional support, No	162
GI symotms, No	45
Poor oral intake, No	35
IBD, No	27
Bowel obstruction or ischemia, No	19
GI perforation or leak, No	7
High output fistula (> 500 ml/day), No	4
SBS with sever malabsoprtion, No	1
GI bleeding, No	1
Sever oral mucositis after chemotherapy, No	3
Others, No	37

BEE=Basal Energy Expenditure, PN= Parenteral Nutrition, GI= Gastrointestinal, IBD= Inflammatory Bowel Diseases, SBS= Short Bowel Syndrome

Table 4. Secondary Outcomes (n=231)

Item	n (%)
Central Line Associated Blood Streem Infection (CLABSI)	0 (0)
Acute Kidney Injury (AKI)	2 (0.86)
Hyperglycemia	18 (7.79)
Hypoglycemia	5 (2.16)
Parenteral Nutrition Associated Liver Disease	24 (10.39)
Hypertriglyceridemia	3 (1.29)
Refeeding Syndrome	3 (1.29)

Table 5. Post Hoc Analysis (n=231)

	Underweight n=50 (%)	Normal weight n=103 (%)	Overweight n=43 (%)	Obese n=35 (%)	*P-value*
calories	29 (58)	40 (38.83)	18 (41.86)	14 (40)	0.145
ed protein achieved	26 (52)	33 (32)	5 (11.62)	4 (11.43)	<0.05
lyte's ıalities	39 (78)	87 (84.47)	34 (79)	34 (97.14)	0.084

Figures

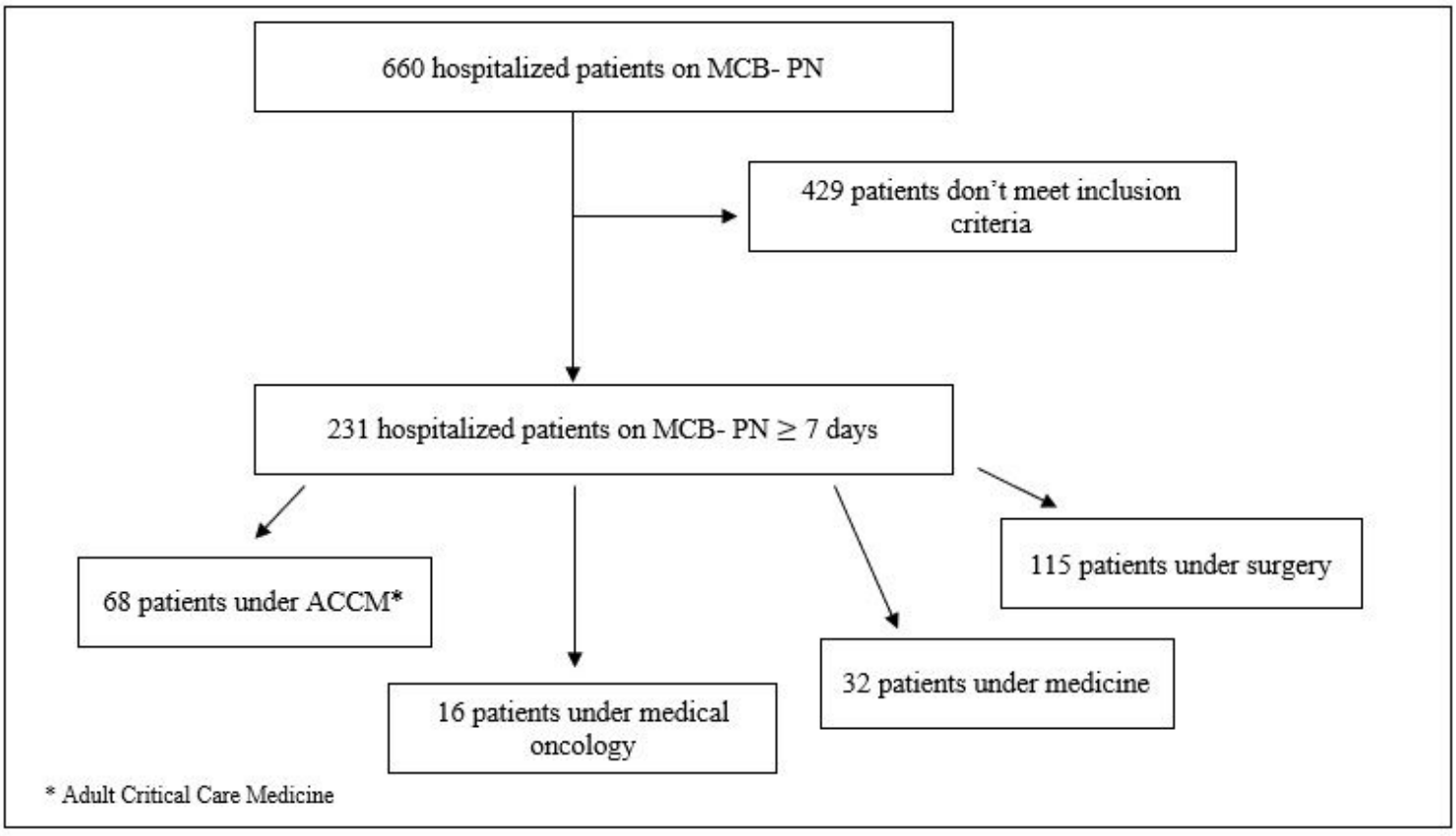

Figure 1

Participant flowchart

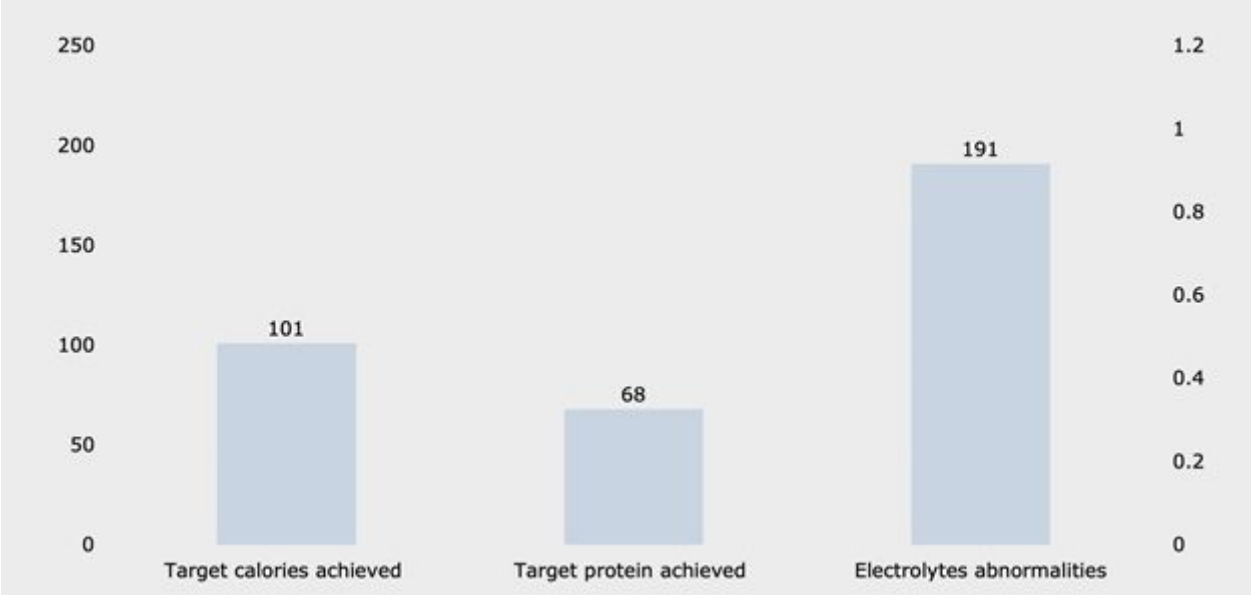

Figure 2

Primary Outcomes n = 231