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Effects of early enteral bovine colostrum supplementation on intestinal permeability in critically ill patients: A randomized, double-blind, placebo-controlled study

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ABSTRACT

Objectives: In this study we sought to investigate the effect of early enteral bovine colostrum supplementation on intestinal permeability in intensive care unit (ICU)–hospitalized patients.
Methods: A total of 70 ICU-hospitalized adult patients were randomly assigned to receive a bovine colostrum supplement or placebo according to the stratified blocked randomization by age and admission category. Plasma endotoxin and zonulin concentrations were measured on days 5 and 10 of intervention.
Results: Out of 70 participants, 32 patients in the colostrum group and 30 patients in the control group were included in the final analysis of the outcomes. Plasma endotoxin concentration decreased significantly in the colostrum group on the 10th day ($P < 0.05$). Furthermore, plasma levels of zonulin reduced in the colostrum group significantly compared with the placebo group ($P < 0.001$).The incidence of diarrhea was significantly lower in the colostrum group than in the control group ($P = 0.02$).
Conclusions: Our results provide evidence that bovine colostrum supplementation may have beneficial effects on intestinal permeability and gastrointestinal complications in ICU-hospitalized patients. Further studies are needed to investigate the exact mechanism of action of these effects.

Introduction

The gastrointestinal (GI) epithelium functions as an immunologic barrier against luminal penetration by toxins, allergens, and pathogens [1]. This barrier function can be impaired by physical stress as a result of critical illness [2]. Moreover, the disruption of the specialized junctional complexes, called tight junctions, plays a crucial role in bacterial translocation and nosocomial infections [1]. These infections are commonly reported in the intensive care unit (ICU) and seem to be related to a gut-barrier malfunction in critically ill patients [2]. The overall function of transport through the intestinal epithelial paracellular route was assessed by non-invasive techniques including fractional urinary excretion of orally ingested probes, circulating the antiflagellin and antilipopolysaccharide immunoglobulins, and circulating the zonulin level [3].

Colostrum is the initial milk produced by the mammary glands of mammals during the first few postpartum days. This liquid is particularly rich in biologically active growth factors such as growth hormone, insulin growth–like factors, epidermal growth factors, transforming growth factor β, and platelet-derived growth factor. In addition, it contains immunoglobulins, antimicrobial peptides, and macro- and micronutrients [4]. Colostrum bovinum has been found to successfully protect or repair the intestinal barrier in both human and animal studies and is useful for the treatment of a wide variety of GI conditions, including inflammatory bowel disease, severe physical activity, non-steroidal antiinflammatory drug–induced gut injury, and chemotherapy-induced mucositis [5]. This efficacy of bovine colostrum in reducing the intestinal

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permeability may be attributed to a direct effect on maintenance of tight junctions in epithelial cells [6]. However, it has to be noted that the results from different studies are not always consistent and need further clarification. Despite the studies conducted on this subject, our current understanding of the impact of colostrum on intestinal permeability in critically ill patients is still limited.

We hypothesized that coadministration of early enteral formula with bovine colostrum would stimulate gut function and decrease intestinal permeability in critically ill patients. Therefore, to evaluate this hypothesis, a double-blind, randomized, placebo-controlled clinical trial was established to determine effects of early enteral bovine colostrum supplementation on intestinal permeability in ICU-hospitalized patients.

Materials and methods

Recruitment and eligibility screening

Critically ill patients were identified and recruited between June 2017 and March 2018 from the general ICU of a university hospital in Tehran, Iran. Because we did not find a study related to our objective, a true power calculation was not applicable. Thus we conducted a small pilot study to get the estimates needed to do a proper sample size calculation. Eligible patients or their legal representatives were informed about the study procedures by intensivists, specialists in critical care medicine. Eligible patients or their legal representatives signed an informed consent form after a full review of the inclusion and exclusion criteria and having the risks and benefits of the study explained to them. The study was approved by the related ethics committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Consecutive adult patients (>18 y old) meeting the following inclusion criteria were enrolled: start of study intervention within 48 h after ICU admission; receiving enteral nutrition for at least 72 h, aiming for full enteral nutrition, and receiving at least 80% of the enteral formula during the first 48 h; and submitting written informed consent by themselves or their legal representative. Patients were also excluded for one or more of the following criteria: >24 h from admission to the ICU; requiring other specific enteral nutrition (EN) for medical reason such as renal or liver failure; death or discharge before day 5; having any absolute contraindication to receive EN; pregnant or lactating with the intent to breastfeed; body mass index less than 18 kg/m^2 or greater than 40 kg/m^2; not being in ICU for more than 48 h because of imminent death; history of allergy or intolerance to the study product components; and enrollment or planned enrollment in a related ICU interventional study. Participation in the study was prematurely discontinued in the following situations: when further participation was a health risk for the patient; when a participant or legal representative who gave informed consent decided to resign from further participation in the study; or when a patient might require a hospital transfer.

Study design and interventions

The present study was a randomized, double-blind, placebo-controlled trial. At the first visit, patients who fulfilled the described criteria were randomly assigned to receive enteral formula plus 20 g/d bovine colostrum powder or isocaloric enteral formula plus maltodextrin for 10 d using a computer-generated randomization. Randomization was stratified by age (18–65 and ≥ 65 y) and admission category (medical, surgical, and trauma). Commercial enteral formula (ENTERA Meal; 54.6% carbohydrate, 14% protein, and 31.6% fat) and maltodextrin were provided by Karen Pharma & Food Supplement Co. (Tehran, Iran). The bovine colostrum was supplied by Neovite (London, UK). The energy content was approximately 311.5 kJ (74.4 kcal) per 20 g (i.e., 80% protein, 9% carbohydrate [lactose], and 1.8% fat). Participants, investigators, staffs, and outcome assessors were masked to the treatment assignment until the end of the study. There were no identifiable cointerventions associated with our intervention. Details about the recruitment, randomization, and follow-up of the present study are presented in the study flow diagram (Fig. 1).

Administration of intervention

The administration of all study products was initiated within 48 h after admission at the ICU and ended at discharge from the ICU or at end of the study (day 10). The study intervention consists of enteral colostrum 20 g/d versus isocaloric maltodextrin control delivered enterally. The supplements were administrated three times per day. Planned enteral tube feeding was initiated after stabilizing the hemodynamic condition of each patient. The enteral route (nasogastric or gastrostomy) chosen for a patient was at the discretion of the treating physician according to the patient's clinical condition. The volume (mL) of intermittent tube feeding was determined based on the calorie needs and tolerance of patients by starting from 50 mL. Through the first 24 h, if the patient could tolerate the feeding, it was increased by 50 to 100 mL until the goal volume was reached. The supplements were administrated three times a day. All patients were fed according to the last revision of American Society for Parenteral and Enteral Nutrition guideline [7]. General recommended energy and protein intakes for critically ill patients—based on weight and metabolic condition—were 25 to 30 kcal/kg and 1.2 to 2 g/kg, respectively. According to our calculation, if a patient had required an extra amount of protein, modular protein supplements would have been added to the enteral formula to increase the protein intakes. The volume and calorie intake were recorded on a daily basis. The volume ratio (VR) was calculated to determine the efficacy of daily nutritional administration as follows: VR (%) = (volume administered/volume prescribed) × 100.

Procedures

Each patient's age, sex, smoking behavior, heigth, medical history, preexisting conditions, medication, and nutritional supplements use, enteral route, feeding regimen, date of hospital and ICU admission, and diagnosis for ICU admission were recorded at the screening visit. The Acute Physiology and Chronic Health Evaluation [8], Sequential Organ Failure Assessment score [9], and Nutrition Risk Score in the Critically Ill [10] were determined over the first 24 h after admission at the ICU. From the start of feeding the study product until day 10, adverse events, GI intolerance, the net amount of tube feeding intake, and occurrence of sepsis were assessed on a daily basis. Venous blood samples were drawn at baseline within 2 h before the start of intervention and between 0700 h and 0900 h on day 5 and day 10 for laboratory data. Blood samples were collected in EDTA-containing tubes and plasma was obtained by centrifugation at 3000 rpm for 10 min at 4°C. Plasma samples were snap frozen and stored in small aliquots at -80°C until the laboratory analysis.

Primary and secondary outcomes

Plasma endotoxin concentration and plasma zonulin concentration were the primary outcome measures. Plasma concentrations of endotoxin were measured by a commercially available quantitative chromogenic endpoint Limulus Amebocyte Lysate QCL-1000 kit (Lonza, Walkersville, MD, USA). Zonulin levels were measured in plasma by enzyme-linked immunosorbent assay (Immundiagnostik, Bensheim, Germany). All assays were performed according to the respective manufacturer's recommendation and the tests were carried out in duplicate. Secondary outcomes included mortality at ICU; length of stay (LOS) in ICU; incidence of sepsis according to the American College of Chest Physicians and the Society of Critical Care Medicine [11]; and incidence of GI complications, including abdominal distention, vomiting, diarrhea, and constipation.

Statistical analysis

The analyses in this work were performed using the SPSS Software (Version 20; IBM Corp., Armonk, NY, USA). Data were presented as frequencies and percentages, means and 95% confidence intervals (CIs) or standard deviations, or medians and interquartile ranges (IQR), when appropriate. Fisher exact or χ^2 tests were used to examine the significance of the differences in the distribution of categorical variables. Because most of the variables were highly skewed and not normally distributed, continuous variables were analyzed using the Mann-Whitney test for the between-group comparisons and the Wilcoxon signed rank test for the within-group comparisons. According to the CONSORT guidelines, both intention to treat (ITT) and per-protocol analyses were done for all planned outcomes to interpret the effect of our intervention. The data are reported according to the ITT principle. Missing measurements of the primary and secondary outcome measures were imputed using the regression method. Means and 95% CIs for changes from baseline in plasma endotoxin concentration and plasma zonulin concentration were compared on days 5 and 10 using analysis of covariance. All hypothesis tests were two-tailed with a $P < 0.05$ statistical significance.

Results

Recruitment and follow-up

In this work, 70 patients were randomly assigned to two groups: colostrum ($n = 35$) and control ($n = 35$). The flowchart depicting the patient screening, enrollment, and retention by treatment group is shown in Figure 1. In the colostrum group, one patient died between the days 5 and 10 and one patient was withdrawn by physician between days 5 and 10. In the control group, four patients died between days 5 and 10 and one patient transferred to another hospital between days 5 and 10. Thus we had the baseline and 5th day data for two patients in the colostrum group and for five patients in the control group and missing measurements were imputed for these patients. A total of 32 patients in the colostrum group and

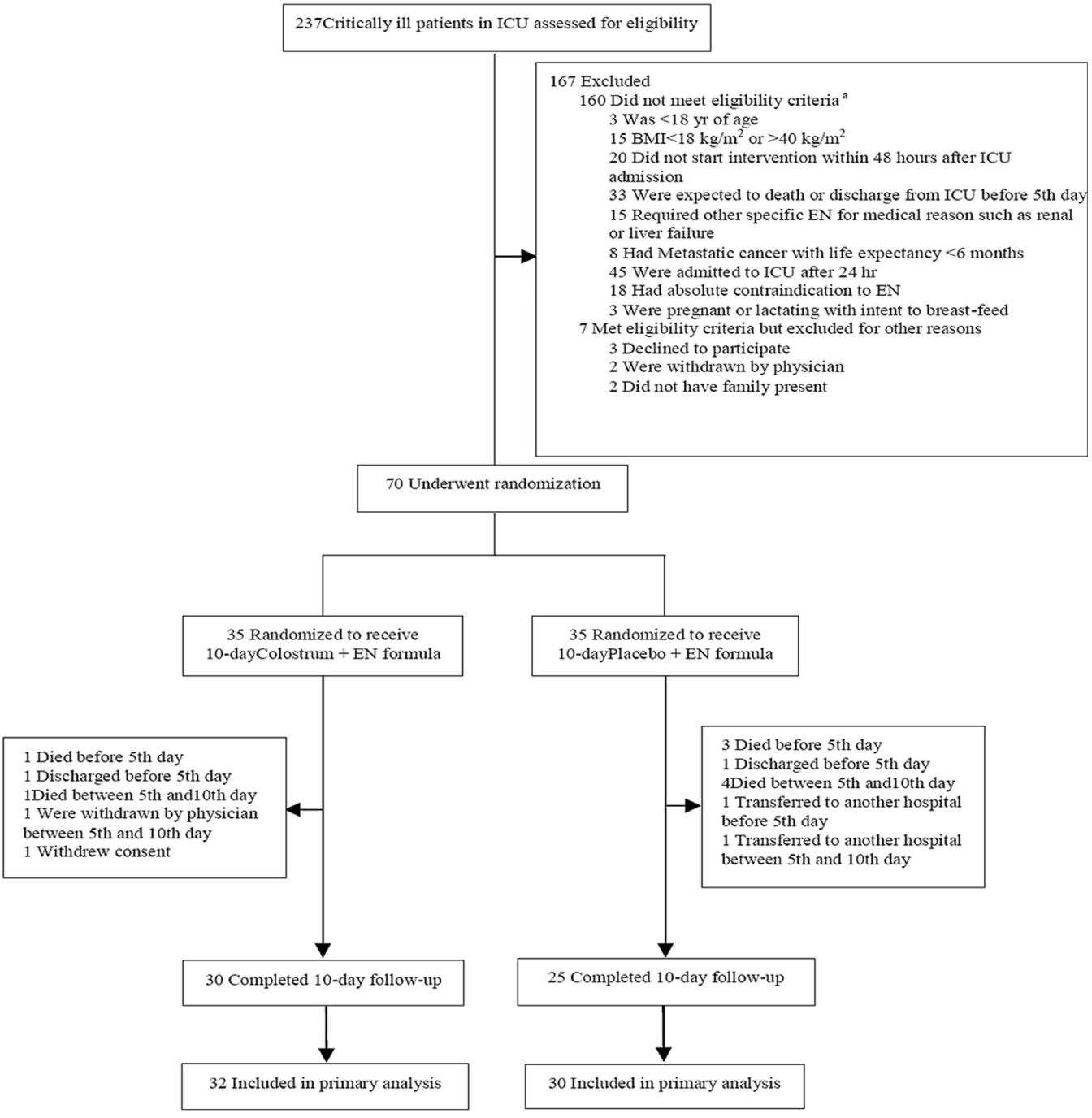

Fig. 1. Flow chart depicting the study design. BMI, body mass index; EN, enteral nutrition; ICU, intensive care unit.

30 patients in the control group were included in the final ITT analysis. Baseline characteristics of participants completing the study were not significantly different from those who did not complete the protocol of the study ($P > 0.05$ for all variables).

Baseline characteristics of the patients

The baseline clinical and demographic characteristics of both groups are presented in Table 1. It is of note that the randomly allocated groups shared similar baseline characteristics. The study participants had a mean age of 62 y, and 56% ($n = 35$) of them were male. The results obtained from the analysis of feeding details are presented in Table 2. There was no significant difference in terms of duration of study product administration, time of starting nutritional support, energy intake, protein intake, or total volume of study product administered.

Primary outcome

The baseline median (IQR) plasma zonulin of participants was 5.5 (3.3–8.1) and 4.9 (3.4–7.5) ng/mL in colostrum and control groups, respectively, indicating no statistically significant difference ($P = 0.855$).

Table 1
Baseline characteristics of the study participants

Characteristic	Colostrum group $n = 32$	Control group $n = 30$	P
Age, y, median (IQR)	64 (52–70)	66 (58–71)	0.401*
Sex, No. (%)			0.290†
Male	16 (50)	19 (63)	
Female	16 (50)	11 (37)	
Admission category, No. (%)			0.508†
Medical	15 (47)	14 (47)	
Surgical	8 (25)	11 (36)	
Trauma	9 (28)	5 (17)	
Admision scores, median (IQR)			
APACHE-II	23 (19–39)	24 (18–38)	0.983*
NUTRIC	5 (4–6)	5 (4–6)	0.913*
SOFA	6 (5–7)	6 (5–7)	0.742*
Baseline blood levels, median (IQR)			
Albumin, g/dL	2.8 (1.9–3.3)	2.5 (1.7–4.3)	0.789*

APACHE-II, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; NUTRIC, Nutrition Risk in the Critically Ill; SOFA, Sequential Organ Failure Assessment
*Mann-Whitney test.
†χ^2 Test or Fisher exact test.

Table 2
Feeding details of the study participants

Enteral feeding administration	Colostrum group $n = 32$	Control group $n = 30$	P
Time from ICU admission to study EN start, median (IQR), h	29 (25–35)	29 (24–35)	0.762*
Duration of administration, median (IQR), d	10 (8–10)	10 (9–10)	0. 879*
Mean planned energy intake, median (IQR), kcal/d	1479 (1400–1547)	1488 (1386–1575)	0.773*
Mean planned protein intake, median (IQR), g/d	65 (62–69)	64 (61–68)	0.632*
VR at day 1,median (IQR), %	87 (85–92)	85 (83–93)	0.170*
VR at day 5, median (IQR), %	91 (87–96)	89 (85–92)	0.063*
VR at day 10, median (IQR), %	93 (85–98)	90 (83–94)	0.200*
Mean energy intake, median (IQR), kcal/d	1350 (1254–1400)	1317 (1250–1358)	0.268*
Mean protein intake, median (IQR), g/d	60 (56–61)	57 (55–60)	0.124*
Patients with supplemental parenteral nutrition, No. (%)	4 (12.5)	4 (13.3)	0.922†

EN, enteral nutrition; ICU, intensive care unit; IQR, interquartile range; VR, volume ratio
*Mann-Whitney test.
†χ^2 Test.

The plasma zonulin and endotoxin concentrations on days 1, 5, and 10 are shown in Table 3. Early enteral bovine colostrum supplementation produced a significant difference in the plasma levels of zonulin results obtained before and after the supplementation period. At the end of day 10 of the treatment period, the plasma zonulin concentration decreased in the colostrum group and increased in the control group and led to a statistically significant difference ($P < 0.001$) when comparing the postintervention to baseline changes between the two groups. The change in the zonulin concentration on days 5 and 10 (Table 3) had a statistically significant difference between those treated with colostrum or placebo after the adjustment for albumin and energy intake ($P < 0.001$). The baseline plasma levels of endotoxin of the two groups were similar ($P = 0.297$). Colostrum supplementation produced a significant decrease in the plasma endotoxin concentration on days 5 and 10. Comparing the baseline and end of the study results revealed a significant decrease in the plasma levels of endotoxin within the

Table 3
Intestinal permeability outcomes at baseline, day 5, and day 10 by treatment group

	Colostrum group $n = 32$	Control group $n = 30$	P
Plasma endotoxin concentration (EU/mL)			
Baseline, median (IQR)	0.59 (0.45–0.78)	0.56 (0.45–0.69)	0.607*
Day 5, median (IQR)	0.35 (0.13–0.50)	0.46 (0.29–0.55)	0.066*
Day 10, median (IQR)	0.15 (0.10–0.39)	0.57 (0.40–0.66)	<0.001*
Mean changes in day 5 from baseline (95% CIs)	−0.27 (−0.34 to −0.20)	−0.15 (−0.22 to −0.08)	0.018†
Mean changes in day 10 from baseline (95% CIs)	−0.40 (−0.48 to −0.27)	−0.04 (−0.10–0.03)	<0.001†
Plasma zonulin concentration (ng/mL)			
Baseline, median (IQR)	5.5 (3.3–8.1)	5.0 (3.4–7.5)	0.855*
Day 5, median (IQR)	4.1 (3.1–7.0)	6.1 (4.5–7.7)	0.018*
Day 10, median (IQR)	3.5 (2.9–5.9)	7.2 (5.7–8.4)	<0.001*
Mean changes in day 5 from baseline (95% CIs)	−0.97 (−1.47 to −0.47)	0.69 (0.24–1.14)	<0.001†
Mean changes in day 10 from baseline (95% CIs)	−1.79 (−2.55 to −1.03)	1.72 (1.05–2.39)	< 0.001†

ANOVA, analysis of covariance; CI, confidence interval; IQR, interquartile range
*Mann-Whitney test.
†Based on an ANCOVA model that regressed changes from baseline on treatment group, baseline value of the outcome, albumin, and energy intake.

colostrum group ($P = 0.007$). The change in the plasma endotoxin concentration (Table 3) had a statistically significant difference ($P = 0.01$) between those treated with colostrum or placebo on days 5 and 10 after the adjustment for albumin and energy intake.

Secondary outcomes

Table 4 shows the analysis of the incidence of gastrointestinal complication. Neither placebo nor colostrum supplementation produced a significant difference in the incidence of abdominal distention, vomiting, and constipation. The incidence of diarrhea was significantly lower in colostrum group (9%) than the control group (33%).

There were not any statistically significant differences in mortality at ICU between the colostrum group (12%, 95% CI 3%–24%) and the control group (17%, 95% CI 6%–30%; $P = 0.642$). There were no statistically significant differences for the incidence of new severe sepsis between groups. Overall, 6% of those in the colostrum group (95% CI 0%–16%) versus 10% in the control group (95% CI 0%–21%; $P = 0.588$) had new severe sepsis. The median (IQR) LOS in ICU was 10 (8–15) and 17 (8–30) days for the colostrum group and the control group, respectively, indicating a statistically significant difference ($P = 0.045$).

Adverse events

Most patients tolerated enteral nutrition and achieved the planned caloric goal within the first 2 d of intervention. Enteral bovine colostrum was generally well tolerated, and none of the patients completing the study had any serious clinical adverse reactions.

Table 4
Comparision of gastrointestinal complication diagnosed after initiation of intervention between groups

Gastrointestinal complication, No. (%)	Colostrum group $n = 32$	Control group $n = 30$	P*
Abdominal distention	7 (22)	8 (27)	0.660
Vomiting	2 (6)	2 (7)	0.947
Diarrhea	3 (9)	10 (33)	0.021
Constipation	6 (19)	10 (33)	0.190

*χ^2 Test, Fisher exact test.

Discussion

To our knowledge this study is the first randomized double-blind clinical trial to evaluate the effects of early enteral bovine colostrum supplementation on intestinal permeability in ICU-hospitalized patients. Our results indicated that intestinal permeability as assessed by the plasma endotoxin and zonulin concentrations was improved after a short period of colostrum-supplemented enteral feedings. Moreover, administration of the bovine colostrum had beneficial effects on diarrhea and LOS in ICU; however, it did not affect any other gastrointestinal complications, mortality, or severe sepsis.

Intestinal permeability is a key feature of gut barrier function and can be assessed through enteral administration of non-digestible markers, including sugars, radioisotopes, and polyethylene glycols [12]. In most previous clinical trials in critical care, the dual sugar absorption tests were used as gut permeability assessment [13]; however, there are no standardized protocols for this purpose [3]. Furthermore, conducting these tests for ICU-hospitalized patients is challenging considering the time of urine collection and fasting time [3]. Thus we used the plasma concentration of endotoxin, lipopolysaccharide constituents of the outer membrane of gram-negative bacteria [14], and plasma concentration of zonulin as a master regulator of intercellular tight gap junctions [15]. In our study, colostrum bovinum supplementation was well tolerated and effective in decreasing the plasma endotoxin compared with the control group. In agreement with our study, Bölke et al. [16] found that the oral application of immunoglobulin-enriched colostrum milk (lactobin 56 g/d) for 3 d before abdominal surgery reduced perioperative endotoxemia. In contrast to our study, Bölke et al. [17] found the enteral application of 42 g of bovine colostrum milk per day for 2 d preoperatively failed to curtail perioperative endotoxemia in patients undergoing coronary bypass surgery. The exact mechanisms by which colostrum might influence endotoxemia are unknown, but studies suggest that their influence is mediated by lactoferrin, which is able to bind the lipid A part of the lipopolysaccharide molecules to prevent their uptake into the systemic circulation [18]. Our results indicated that bovine colostrum supplementation was able to reduce the plasma zonulin level. To our knowledge, zonulin was not considered as an outcome in previous clinical trials in ICU-hospitalized patients. Greis et al. [19] found that patients at ICU admission had higher serum concentrations of zonulin 1. A recent study reported that 20 d of bovine colostrum supplementation can reduce stool concentrations of zonulin in athletes [20]. Bovine colostrum may also have a beneficial role in athletes [20–22] and in some patients [23] in whom intestinal permeability rises as a result of various pathologic conditions, and it can help restore gut health after use of antibiotics or non-steroidal antiinflammatory drugs, both of which can increase intestinal permeability [24].

The majority of ICU patients have at least one gastrointestinal symptom during their ICU stay [25]. In our study there was no discernible difference in the secondary outcomes relating to the incidence of GI complications except diarrhea. Our results indicated that enteral bovine colostrum supplements lower the incidence of diarrhea. This result is consistent with a few studies that have investigated the effects of immunoglobulin-enriched colostrum milk on diarrhea caused by protozoal pathogens in HIV-infected patients [18]. Tacket et al. [26] found that hyperimmune bovine colostrum significantly reduced the incidence of diarrhea resulting from challenge with *Shigella flexneri* in healthy adult volunteers. Otto et al. [27] along with the mentioned researchers found that a tablet formulation of hyperimmune bovine colostrum was significantly more effective in protecting healthy adult volunteers against the development of diarrhea caused by *Escherichia coli*. Bovine colostrum has been reported to positively influence infective diarrhea in both human and animal studies [5]. Previous clinical trials on the use of bovine colostrum in children have also reported a significant reduction in the number of diarrhea episodes [18,23]. Possible mechanisms by which colostrum might improve diarrhea include the effect of increased mucosal resistance caused by epidermal growth factor and lactoferrin [27–29].

The principal goal of implementing the interventions in ICU was to decrease mortality in critically ill patients [30]. In addition to mortality, assessing another clinical outcome could help define the usefulness of an intervention. After 10 d of our intervention, LOS in ICU group was significantly reduced in the colostrum group compared with the control group. However, no effect on ICU-acquired sepsis and mortality was noted in our study.

The most important strength of this study was the stratified randomization of patients. Our study has certain limitations. It was a single-center trial with a small sample size. Body weight was recorded according to the patients' or relative's statement at enrollment or based on recent patient file information. The diversity of critically ill patients makes it difficult to select a homogenous population with minimal variation in outcome parameters. The ICU length of stay of patients also differs greatly depending on whether patients are being tube fed for only a few days or for more than a month. Another limitation is that the participants were not followed up further to assess the sustainability of the findings obtained after the termination of intervention. These findings should be confirmed in future studies.

Conclusions

This clinical trial was among the first to find preliminary evidence of the beneficial effects of bovine colostrum supplementation on intestinal permeability, LOS in ICU, and diarrhea in ICU-hospitalized patients. We suggest that it may be feasible and justifiable to use bovine colostrum as a supplement with various doses in further studies to confirm our finding. To date, there is little consensus on the effect of colostrum on clinical outcomes in critically ill patients. Therefore future randomized placebo-controlled trials are needed to investigate the mechanism of action of these effects.

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