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Review Article

Comparing Effects of Enteral and Parenteral Nutrition in Patients Admitted to Intensive Care Units: A Systematic Review

Abbas Heydari[1], Aliakbar Keykha[2]*

[1]*Nursing and Midwifery Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[2]*Mashhad University of Medical Sciences, Mashhad, Iran.*

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ABSTRACT

Background: With regard to critical illness and stress, medication side effects, decreased appetite, and increased nausea and vomiting; patients admitted to intensive care units (ICUs) are at particular risk of malnutrition. Feeding behavior i.e. time and method in these patients has still remained as an unresolved issue. Thus; enteral and parenteral nutrition, with their own benefits and complications, are two commonly used methods for such individuals. The present systematic review was to compare the effects of enteral and parenteral nutrition in patients admitted to ICUs.

Methods: This systematic review investigated a total number of 1642 articles on nutrition methods in ICU patients during 2010-2019 using keywords of "enteral nutrition, parenteral nutrition solutions, parenteral nutrition, critical care outcomes, critical illness, intensive care unit, and ICU" in the databases of SID, Iranmedex, MEDLIB-ED, PubMed, Scopus, Medline, Embase, Cochrane, Web of Science, and Google Scholar; and finally, 15 articles were analyzed in relation to the research objectives.

Results: Studies indicated that patient mortality was not different in enteral and parenteral nutrition groups. The incidence rate of infectious complications was also reported higher in parenteral nutrition group. However, there was no significant difference in the incidence rate of infections in studies meeting total standards for parenteral nutrition. Besides, there was no significant difference between the duration of undergoing mechanical ventilation and hospitalization time in both groups. Furthermore, the incidence rate of hypoglycemia was higher in enteral nutrition group; but serum protein levels had much better status compared with those in parenteral nutrition group.

Conclusion: If standards for infusion are observed and provided that rates of infectious complications are reduced, patients can benefit from starting parenteral nutrition immediately after admission to ICUs in the absence of enteral method.

Critical illness, stress, trauma, surgery, and burn cause systemic inflammatory syndromes and consequently increase nutrient needs of the body [1]. The onset of parenteral and enteral nutrition to prevent malnutrition and its complications is thus one of the essential care needs in patients admitted to intensive care units (ICUs) [2-3]. Studies have also indicated protein and calorie deficiency due to increased catabolism and reduced nutrient intake in these patients [4-5]. Accordingly; decreased appetite induced by illness, increased need for nutrients, and malabsorption are among major factors affecting occurrence and exacerbation of malnutrition [6]. The prevalence rates of malnourishment in ICU patients has been reported to be 44-88% [7]. Thus, the feeding method for these patients is assumed as a decisive factor shaping type and extent of

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*Corresponding author.
E-mail address: aliakbar.keykha@gmail.com

their effects on the body. Enteral nutrition is similar to normal physiology of patients and in addition to beneficial nutritional effects, it maintains integrity and functioning of the digestive system and prevents the spread of bacteria from the gastrointestinal tract to other organs of the body [8-10]. Enteral nutrition leads to the release of bile salts, gastrin, and motilin [11]. It also causes secretion of immunoglobulin A (IgA) that prevents bacterial adhesion to the intestinal epithelium [11-12]. In the absence of enteral nutrition, peristalsis of the intestines will be reduced, leading to an overgrowth of harmful bacteria such as Pseudomonas aeruginosa as well as bacteria adhesion to the intestinal walls, production of cytokines, and ultimately cell death [13]. However, if there is a digestive dysfunction or a malabsorption of nutrients in an acute illness, it is impossible to utilize this nutrition method for patients [10]. So, the use of parenteral nutrition is safer for these patients despite its complications [14].

A significant comparison of these two feeding methods is difficult due to their physiological differences. Appropriate nutritional clinical outcomes include mortality, morbidity, quality of life, and care costs, which need large-scale studies. Moreover, the use of some simple criteria such as measurement of serum protein levels or anthropometric indices fail to assess nutrition adequacy in patients and they can be only used as predictive factors of the outcomes [15]. The uses of enteral and parenteral methods in ICU patients have been reported between 33-92% and 12-71%; respectively. Several factors also influence the selection of enteral and parenteral nutrition including estimation of their advantages and disadvantages [16]. However, none of nutritional support methods are uncomplicated. In this regard, immediate onset of enteral nutrition increases gastric residual volume [17], bacterial colonization in the stomach, as well as increased risk of pneumonia caused by mechanical ventilators [18]. On the other hand, the use of parenteral nutrition results in gastrointestinal smooth muscle atrophy, overfeeding, hyperglycemia, and higher risks of infectious diseases and mortality rates [19]. Thus, proper care reduces the rate of central venous catheter contamination, despite the fact that its acceptable amount is zero in ICU patients [20]. However, it leads to safer utilization of parenteral nutrition since it reduces infections as the most common difference between these two feeding methods [21]. In a large-scale clinical trial by Harvey et al. on 2388 patients, it was reported that the incidence rate of infection and mortality in patients, who had received enteral and parenteral nutrition, was not different [22]. Accordingly; one nutrition method cannot be completely preferred over the other, and the use of any nutrition method should be consistent with patient conditions. Thus, the present systematic review was conducted to compare the effects of enteral and parenteral nutrition in patients admitted to ICUs.

Methods

The present systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model to investigate the effects of both enteral and parenteral nutrition methods in patients admitted to ICUs using a search for keywords of "enteral nutrition, parenteral nutrition, parenteral nutrition solutions, critical care outcomes, critical illness, intensive care unit, and ICU" with limitations including adult patients aged over 18 years and the time period of 2010-2019 in articles indexed in the databases of SID, Iranmedex, MEDLIB-ED, PubMed, Scopus, Medline, Embase, Cochrane, Web of Science, and Google Scholar.

Inclusion criteria

The inclusion criteria were: a comparative study on enteral and parenteral nutrition in patients admitted to ICUs and starting both feeding methods simultaneously in both groups, with regard to the time limit (2010-2019) and the age range of over 18 years. The evaluation of the studies also included mortality rate, comparison of infectious and gastrointestinal complications, length of stay in ICU, number of days undergoing mechanical ventilation, and effect of each method on blood factors relating to patient nutrition.

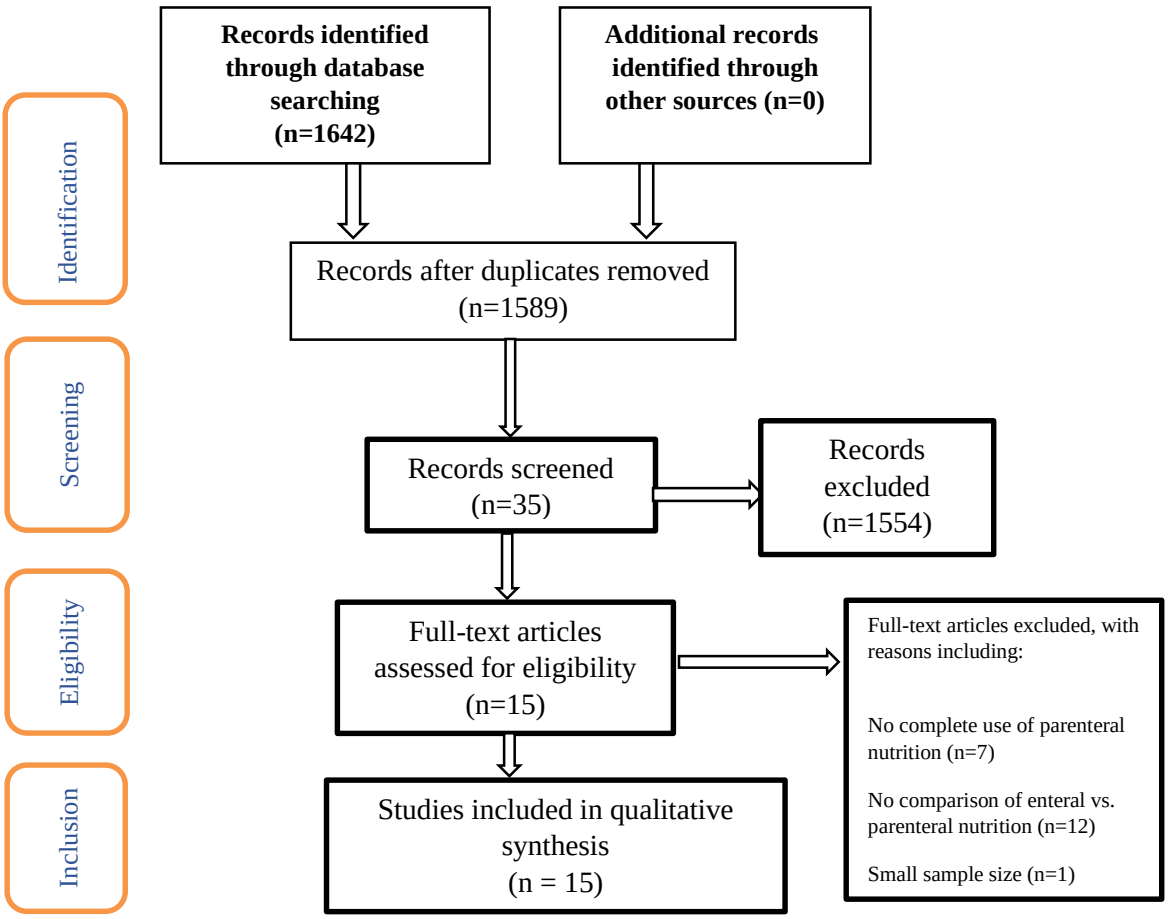
Exclusion Criteria

The exclusion criteria were: non-English and Persian studies, articles on patients aged below 18 years, no access to the full-texts of articles; abstracts of studies presented in congresses, seminars, and conferences; a letter to the editor-in-chief, as well as short reports, and case reports. It should be noted that some retrieved articles were reviewed and removed in several steps.

Intervention and Outcomes

The simultaneous onset of enteral and parenteral nutrition and comparing their effects on mortality, infectious and gastrointestinal complications, duration of undergoing mechanical ventilation and hospitalization time, as well as nutrition-related blood indices were systematically investigated using 4 steps in PRISMA model to search the articles. Utilizing the above-mentioned keywords, a total number of 1642 articles were retrieved, and then 1589 studies were obtained after removing the duplicate ones. Titles and abstracts of the given articles were then reviewed; and those related to feeding patients admitted to ICUs were selected, and finally 15 articles remained for analysis following a focus on comparison of enteral and parenteral nutrition with respect to the research objectives as well as consideration of inclusion and exclusion criteria.

Figure 1- Process of searching and selecting articles for analysis



Results

A total number of 1642 articles were initially retrieved through searching according to the above-mentioned keywords, and then 1589 articles remained after the removal of duplicate ones. Titles and abstracts of the articles were also reviewed and those relating to feeding patients admitted to ICUs were selected, and finally 15 articles remained by focusing on comparison of enteral and parenteral nutrition according to the research objectives and considering the inclusion and exclusion criteria for further analysis. The selected articles had investigated various aspects of effects of both nutrition methods, but since the main purpose of this study was to investigate the relationship between type of nutrition and mortality rate in patients, the results concerning this issue were initially reviewed. A total number of 9 articles had evaluated the effect of nutrition method on mortality rate in patients; however, the difference was not significant in 8 studies. (Table 1) presents results in separate articles.

Table 1- Comparison of mortality rate in patients using enteral and parenteral nutrition methods

Related studies	Type of study	Study group	Number of patients in enteral group/ died	Number of patients in parenteral group/ died	Effects of both enteral and parenteral nutrition methods on mortality rate
Altintas et al. [23]	Multicenter clinical trial	ICU patients affected with various disorders and undergoing mechanical ventilation	30 (8)	41 (18)	There was no significant difference in mortality rates of both groups.

Tao et al. [24]	Retrospective study	Patients with acute pancreatitis	89 (3)	96 (11)	Mortality rates were higher in patients receiving parenteral nutrition.
Doig et al. [25]	Multicenter clinical trial	Patients with different problems, admitted to ICU, and undergoing mechanical ventilation	680 (155)	678 (146)	There was no significant difference in 60-day mortality rates between both groups.
Fan et al. [26]	Single-center clinical trial	Patients with brain trauma	40 (12)	40 (17)	The mortality rate was lower in enteral group and the difference was significant.
Allingstrup et al. [27]	Single-center clinical trial	Patients with different problems, admitted to ICU, and undergoing mechanical ventilation	99 (21) 99 (32) 33 (34)	100 (20) 100 (30) 100 (37)	There was no significant difference between both groups in 28-day, 90-day, and 6-month mortality rates.
Reignier et al. [28]	Multicenter clinical trial	Patients with different problems, admitted to ICU, and undergoing mechanical ventilation	1202 (443)	1208 (442)	There was no significant difference between both groups in 28-day mortality rates.
Harvey et al. [22]	Multicenter clinical trial	ICU Patients with different problems	1195 (409)	1188 (393)	There was no difference in 30-day mortality rates between patients.

In another study in which patients had been divided into three groups; enteral and parenteral nutrition, and a combination of parenteral and enteral nutrition, the mortality rates were 46 (24) patients in the enteral group, 43 (17) individuals in the parenteral group, and 160 (69) cases in the combined one, so there was no difference between groups at p=0.440 [29].

Comparison of Enteral and Parenteral Nutrition in terms of Infection Incidence

A total number of 9 studies had compared the incidence of infections in both nutrition methods and had provided quite contradictory results. In patients, fed with parenteral method, the risk of sepsis was 11.9 times higher than that in individuals receiving enteral nutrition. Three factors could also increase the risk of sepsis including use of parenteral nutrition during stay in ICU regardless of duration of nutrition, late onset of nutrition, and delayed completion of nutrition, which could increase the risk of pneumonia in these patients by 17.9% compared with the other [30]. The early onset of parenteral nutrition had also led to more respiratory, urinary, blood, and ulcerative infections [21]. Comparison of enteral and parenteral nutrition in patients with pancreatitis also suggested a significant difference between both groups in terms of incidence rate of pancreatic abscess and infection (12.89 vs. 25.96 with p=0.0333). Furthermore, extra pancreatic infections had been reported lower in enteral nutrition group than parenteral one (14.99 vs. 27.96 with p= 0.0431), so there was a significant difference between both groups. Moreover, 8 cases of central venous catheter infection were observed in parenteral nutrition group. However, the number of individuals with urinary tract infections and ventilator-induced pneumonia was very close between both groups and thus no statistically significant difference was observed [24]. The incidence rate of aspiration-induced pneumonia was 40 (8) in the parenteral nutrition group, but it was 40 (20) in the enteral one with pneumonia by 50%; so there was a statistically significant difference (p=0.01). Given that patients had underwent head surgery, the rate of intra-cerebral infections in parenteral and enteral nutrition groups was 13 to 7 and it was statistically significant [26]. In a large-scale trial, 113 out of 1202 patients in enteral nutrition group had ventilator-induced pneumonia, 38 individuals had been affected with bacteremia, 29 cases were suffering from catheter-related infections, and 18 patients had urinary tract infections. On the contrary, 118 out of 1208 patients in parenteral nutrition group had catheter-

induced pneumonia, 55 of them had been affected with bacteremia, 27 individuals were suffering from catheter-related infections, and 16 ones had urinary tract infections. None of these differences were significant considering their p-values (0.75, 0.88, 0.79, and 0.73; respectively) [28]. The incidence rate of ventilator-induced pneumonia was not significantly different between both groups [23]. Other researchers also reported that the incidence rate of infectious complications between both nutrition groups was not significantly different [22]. Catheter-related infections and blood ones were directly related to parenteral nutrition, so that 20% of patients undergoing this method had catheter infections, while only 7.7% of patients had been affected in enteral group (p=0.004). Furthermore, 8.6% of patients with parenteral nutrition had blood infection, while it was by 8% in enteral nutrition group (p=0.004) [31]. The incidence rate of blood infections was not significantly different in enteral and parenteral groups [29].

Moreover; 5 out of 9 studies, examining infectious complications, had reported significantly higher infectious complications in parenteral group than those in enteral group; and 4 studies had reported the non-significant incidence of infectious complications.

Comparison of Enteral and Parenteral Nutrition in terms of Gastrointestinal Complications

The comparison of gastrointestinal complications indicated that the amount of treatment-required nausea in enteral nutrition group (1191 samples) was more than that in parenteral one (1197 samples) (53 vs. 44) (p=0.41), and vomiting was higher in enteral nutrition group compared with that in parenteral group (194 vs. 100) (p=0.001). The abdominal distension was also higher in enteral nutrition group (99 vs. 78) (p= 0.12), while the level of liver enzyme disorder was greater in parenteral one (212 vs. 179 people), but the difference was not statistically significant (p=0.047) [22]. Another clinical trial reported that, 406 out of 1202 patients in enteral nutrition group had vomiting, 432 of them were suffering from diarrhea, 19 had been affected with intestinal ischemia, and 11 had acute colonic pseudo-obstruction. In parenteral nutrition group; 246 had vomiting, 393 were suffering from diarrhea, and 3 had been affected with acute colonic pseudo-obstruction; and all of these complications were significantly different between both groups [28]. Tao et al. also reported that 9 out of 89 patients in enteral nutrition group and 3 out of 96 individuals in parenteral one had diarrhea; however, there was no statistically significant difference (p=0.0545) [24]. Another study, comparing the effects of gastrointestinal complications in patients receiving both enteral and parenteral nutrition methods indicated that the incidence rate of diarrhea was much higher in enteral nutrition group than that in parenteral one (24 vs. 6), while gastric and stress ulcers were higher in parenteral one (19 vs. 7), and both groups had a significant statistical difference [26].

All these three studies agreed that gastrointestinal complications were greater in enteral nutrition group than those in parenteral one, and only one article had examined the extent of gastric ulcers which was higher **in** parenteral nutrition group.

Comparison of Enteral and Parenteral Nutrition in terms of Nutrition-Related Blood Markers

The incidence rate of hypoglycemic attacks was 44 out of 1191 patients in parenteral nutrition group, while it was 74 out of 1119 individuals in enteral one (p= 0.006) [22]. Gavri et al. also reported that the average blood glucose level was 149 mg/dl (114-182) in patients in enteral nutrition group, 146 (110-196) in parenteral nutrition group, and 140 (111-180) in the group receiving a combination of enteral and parenteral nutrition; however, the difference of these three groups was not statistically significant (p=0.783). Serum albumin levels in patients were significantly different in three groups, and they were higher in enteral nutrition group with a mean of 3.1 (2.7- 3.7) than those in other groups [29] Tao et al. also reported that the incidence rate of hypoglycemic attacks was higher in enteral nutrition group than those in parenteral one (32 to 18) with p=0.0454 and the difference was significant [24]. In another study, measuring levels of albumin and pre-albumin, hemoglobin, and total protein on days 1 and 20 after the onset of study in patients with enteral and parenteral nutrition, it was reported that their values had more significant descending trends in parenteral nutrition group over twenty days, and it was statistically significant [26]. The intake of calorie and protein by parenteral nutrition group was better than that in enteral one and the comparisons of both groups were significant [32].

Among 4 studies investigating blood markers, the incidence rate of hypoglycemia was higher in enteral nutrition group, but the amount of protein markers was significantly lower in the group receiving parenteral nutrition.

Comparison of Parenteral and Enteral Nutrition in terms of Duration of Mechanical Ventilation and Hospitalization Time

The mean duration of undergoing mechanical ventilation was 9 (5-16) days in enteral nutrition group, 7 (3-11) days in parenteral nutrition group, and 15 (9-2) days in the group receiving a combination of enteral and parenteral nutrition. These differences were significant with regard to inter-group comparisons. The length of stay in ICU was significant and that was 12 (7-17) days in enteral nutrition group, 8 (5-21) days in parenteral nutrition group, and 18 (11-30) days in the combined nutrition group. There were also significant differences between groups [29]. The hospitalization time was 9 (5-16) days

in enteral nutrition group, and 10 (5-17) days in parenteral one, so there was no statistically significant difference. The hospitalization time was 17 (8- 32) days in enteral group and 18 (9-33) days in the parenteral one, and there were no statistically significant differences [28]. In another study, the duration of undergoing mechanical ventilation was 7 days with the interquartile range (IQR) of 4.75- 9.25 in enteral nutrition group and 9 (5-13.5) days in parenteral one, and they had a statistically significant difference (p=0.023). The length of stay in ICU was also by 15 (9-22) days in enteral nutrition group and 14 (10-27) days in parenteral one, so they had no significant difference (p=0.592). Furthermore, in one other study, hospitalization time was 32 (14-52.75) days in enteral nutrition group and 28 (18-47) days in parenteral one, and there was no significant difference between both groups (p=0.986) [23]. In another study, the mean and standard deviation of length of stay in ICU was 7.6±1.9 days in enteral nutrition group and 8.3±2.3 days in parenteral group; and hospitalization time was 21.1±7.3 days in enteral nutrition group and 22.4±4.3 days in parenteral one [24].

Besides, 2 studies had compared the duration of undergoing mechanical ventilation in patients. In the first study, the duration was very close in enteral and parenteral nutrition groups, but it was significantly different in the group receiving a combination of both nutrition methods. In the latter study, the mean days of undergoing mechanical ventilation and the IQR were close, but a statistically significant difference was reported.

Moreover, 4 studies had investigated and compared the length of stay in ICU and hospitalization time. In this respect, 3 studies had reported close and insignificant duration in both groups; and in only one study, recruiting three groups of comparison, the mean time was higher in the group receiving a combination of enteral and parenteral nutrition with significant differences, while there was no significant difference between enteral and parenteral nutrition groups

Discussion

The results of the present systematic review indicated no significant difference in mortality rates between parenteral and enteral nutrition groups. The use of this nutrition method also had no effect on duration of undergoing mechanical ventilation, length of stay in ICUs, and hospitalization time. Considering blood markers and despite higher incidence rate of hypoglycemia in enteral nutrition group, the mean blood glucose level of both groups was in an acceptable range. However, levels of albumin and other blood-related markers decreased in parenteral nutrition group and it could cause a big problem in diagnostic and therapeutic processes, and consequently increase requests for laboratory tests as well as treatment costs. Gastrointestinal complications were higher in patients with enteral nutrition than those in parenteral group, but the weaknesses of studies was that the effects of gastrointestinal problems such as nausea, vomiting, and diarrhea had been investigated in both nutrition groups, and the incidence rate of complications was higher in enteral nutrition group than those in parenteral one. Only one study had evaluated the incidence rate of gastric ulcers, and it had been reported higher in enteral nutrition group. None of the studies had evaluated and reported the preservation of integrity of patients' intestinal structure although it could affect recovery processes and prevent bacterial invasion from the gastrointestinal tract to the bloodstream. Thus, the use of total parenteral nutrition disturbs transitional operation of superficial mucosa resulting in mucosal atrophy, impairment of the immune system, and increased risk of infection [33-34]. Studies had also revealed higher infectious complications in parenteral nutrition group. The increased risk of developing multiple infections, especially development of catheter-related infections and sepsis in patients, could prove the superiority of enteral nutrition for patients. Hyperglycemia caused by total parenteral nutrition was the main cause of infection and other complications [1, 35-36]. However, when there was the contraindication of enteral nutrition, lack of feeding could result in a weakened immune system and increased risk of infections. Some researchers believed that regardless of nutrition method in critically ill patients, their energy supply should be provided in any possible way [1, 37-39]. However, if standards of care for total parenteral nutrition are observed, risk of infection will be reduced. These standard include use of ready-to-administer injection bags from each of the required materials and non-combination of materials and maintaining injection line sterilization [40-41]. In studies, using the above-mentioned methods for parenteral nutrition, levels of blood infections were not significantly different due to observance of standards [29]. However, other studies had not mentioned the use of standards, and infection rates, as the only side effect overshadowing parenteral nutrition, could be controlled if these methods had met the standards, and its benefits could be used to improve nutrition and to increase the immune system immediately after admission to ICU as long as it would be possible to carry on enteral nutrition. These effects remind that the selection and indication of using each nutrition method for ICU patients should be carefully performed and the use of nutrition-related guidelines should be taught to nurses and physicians as priorities in each medical and educational center. According to the results of some studies in Iran, ICU patients are suffering from severe malnutrition and handmade solutions fail to supply adequate nutrition for them, in a way that their

anthropometric indices and creatinine levels significantly decline during hospitalization [42]. Another study had also stated that gavage solution could not provide patients with energy, while its protein content was very high. It could also impair metabolic status of patients and was harmful to those with renal failure. Although standard solutions are being used to feed patients in most medical centers across the world, these materials are unknown for healthcare staff in Iran [43].

Comparison with other Systematic Reviews

Consistent with the results of the present study, another systematic review indicated that infection rate in parenteral nutrition group was higher than that in enteral one. In patients with malnutrition, the incidence rates of infection and mortality were higher in enteral nutrition group, but there was no significant difference in mortality rates of enteral and parenteral nutrition groups [44]. In line with both systematic reviews, a meta-analysis in 2004 found that mortality, admission, and duration of undergoing mechanical ventilation were not significantly different in enteral and parenteral nutrition groups, and the incidence rate of infection was the main difference between both methods (relative risk 0.64, 95% confidence interval (CI): 0.47 to 0.87, p=0.004). The enteral nutrition method should be put in the priority to reduce the incidence rate of infections and costs [16]. Unlike other studies, the mortality rate of parenteral nutrition group was lower in a systematic review by Simpson; confirming the benefits of early parenteral nutrition at the first 24 hours of admission if enteral nutrition was impossible (Odds ratio (OR): 0.51, 95% CI: 0.27-0.97, p=0.04; heterogeneity I2=0%, statistical heterogeneity, (p= 0.50). However, in this study, the rate of infectious complications was greater in parenteral nutrition group than that in enteral one [45]. In another meta-analysis, the mortality rates in ICU patients was not significantly different between both nutrition methods, but the incidence rate of gastrointestinal complications such as diarrhea was much higher in enteral nutrition group compared with parenteral one; whereas infectious complications, catheter-related infections, and length of stay in ICU were greater in parenteral nutrition group [1]. The obtained findings for gastrointestinal and infectious complications were similar to the results of the present systematic review, but they were different in terms of length of stay in ICU. Consistent with the results of this systematic review, a new meta-analysis concluded that the use of enteral nutrition against parenteral one had no effect on mortality rate, but it could reduce the risk of infection and length of stay in ICUs. It seems that decreased intake of nutrients following the use of enteral nutrition method could justify this issue. However, in patients tolerating enteral nutrition, this method will reduce treatment costs of and length of stay [46]. In another meta-analysis, examining clinical trials in which combined parenteral and enteral nutrition had been compared with the use of enteral nutrition method alone, it was reported that a combination of enteral and parenteral nutrition would reduce respiratory infections and length of stay in ICUs; and there was no significant difference between mortality rate and duration of undergoing mechanical ventilation and length of stay in ICUs, as well as albumin and pre-albumin levels in both groups [47]. However, the present study indicated that levels of albumin and pre-albumin and other nutrition-related markers were lower in parenteral nutrition group and that had a significant descending trend during hospitalization.

Conclusion

Given no difference in the results of studies on the main goals of the treatment process such as mortality rate, length of stay in ICU, and duration of undergoing mechanical ventilation; the beneficial effects of total parenteral nutrition can be utilized for patients having enteral nutrition contraindication, in case of controlling infectious complications of this feeding method.

Limitations

Due to the considerable heterogeneity between studies, we could not perform meta-analysis.

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Authors' contributions

Aliakbar Keykha: Determining the databases patterns to search, study design, reviewed titles, abstracts, Full Text and quality assessment of articles, analysis and interpretation of data for the work and writing this article.

Abbas Heydari: Determining the databases patterns to search, study design, consulting and supervision reviewed titles, abstracts and quality assessment of articles analysis and interpretation of data for the work.

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