

Original Article

Efficacy of volume-based feeding (VBF) protocol on critically ill patients: A meta-analysis and systematic review

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Background and Objectives: We aim to evaluate the efficacy and safety of VBF on critically ill patients. **Methods and Study Design:** We systematically retrieved the related literature from January 1, 2000, to March 30, 2021, sources include MEDLINE, Web of Science, Cochrane Library and China National Knowledge Infrastructure. Randomized controlled trials or cohort studies of enteral nutrition based on VBF versus rate-based feeding (RBF) in critically illness of adult participants were selected. **Results:** After screening, seven studies involving 691 patients were finally included. Six of them were high quality. The percentage of goal energy received in the VBF group was significantly higher than that in the RBF group [MD=9.11, 95% CI (5.82, 12.41), $p<0.001$]. ICU length of stay in the VBF group [MD=-0.8, 95% CI (-1.59, -0.01), $p=0.05$], mechanical ventilation length [MD=-1.27, 95% CI (-2.04, -0.51), $p=0.001$] were significantly shorter in the VBF group, but hospital length of stay [MD=0.62, 95% CI (-4.46, 5.69), $p=0.81$] was not significantly different. Our study shows that VBF has some non-significant advantages in reducing mortality [RR=0.70, 95% CI (0.44, 1.11), $p=0.13$]. The rates of adverse reactions, such as diarrhea RR=1.17, 95% CI (0.91, 1.50), $p=0.23$, emesis (RR=0.80, 95% CI (0.42, 1.55), $p=0.51$), feeding intolerance [RR=0.97, 95% CI (0.64, 1.48), $p=0.90$] were not significantly different between the two groups. **Conclusions:** The VBF protocol significantly improves the successive rate of enteral nutrition in critically ill patients.

Key Words: volume-based feeding (VBF), enteral nutrition, intensive care unit (ICU), nutritional Support, critical care

INTRODUCTION

Intensive care unit (ICU) patients face high nutritional risks. Enteral nutrition is one of the most important treatments for these patients.¹ Unfortunately, many studies have found most of these patients are not administered sufficient enteral nutritional products.^{2,3} During the past decade, researchers have been well aware that consistent energy and protein deficits caused energy and protein debts that lead to poor prognosis, such as longer length of ICU stay, higher infection rate and higher mortality.⁴⁻⁶ To improve nutritional product delivery, Heyland et al proposed a new strategy of enteral feeding, which is called VBF protocol. It is also named as Enhanced Protein-Energy Provision via the Enteral Route Feeding (PEP-uP) in 2013.⁷ Compared with ordinary EN delivery protocol RBF, VBF focuses on accomplishing the feeding goal set by physician/dietitian. In VBF protocol, the interruption

of feeding is considered such that un-feed volume during the interruption shall be added to the rest of the day. Hence, VBF is expected to significantly increase the actual administration both in energy and protein for individuals admitted to the ICU. However, clinical studies have not reached consensus on the efficacy and safety of

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VBF, and most are small sample studies. In this work, we conducted a systematic review and meta-analysis to assess the efficacy and safety of VBF, to provide comprehensive evidence for clinical practitioners and researchers.

METHODS

Inclusion and exclusion criteria

The study inclusion and exclusion criteria were determined using the PICOS methods. Listed below are the PICOS (P: participants; I: intervention; C: comparison; O: outcomes; S: study design):

Inclusion criteria

1. Participants: Adult patients in ICU (≥ 18 years) regardless of race, nationality, and region.
 2. Interventions: The experimental group received enteral nutrition support with VBF proto-coll.
- Comparisons: The control group received enteral nutrition support with RBF protocol.

Outcomes

Major outcome: Percentage of goal energy received.

Secondary outcome: mortality: length of ICU stays, length of hospital stays, mechanical ventilation duration, incidences of adverse reactions such as emesis, diarrhea and feeding intolerance.

Study design

RCTs and cohort studies.

Exclusion criteria

1. Duplicated literature.
2. Animal experiment.
3. Patient's age < 18 years.
4. Studies not reporting the outcomes mentioned above.

Literature retrieval strategy

We systematically searched the literature related to VBF from January 1, 2000, to March 30, 2021, sources include MEDLINE (through PubMed), Web of Science, Cochrane Library and China National Knowledge Infrastructure (CNKI). Detailed search strategy for each database is listed in Table 1. In addition, we searched the Chinese Clinical Trial Registry (www.chictr.org.cn). Whenever necessary, we consulted relevant principal investigators and experts in this field.

Literature screening and data extraction

Literature screening and data extraction are conducted by two authors (Lu Wang and Yu Wang) independently following the inclusion and exclusion criteria, then cross-checked. If there were any disagreements between these two authors, a senior author (Hua Jiang) is asked to de-

Table 1. Literature research strategy, databases and key words

| Databases | Strategy |
|------------------|---|
| PubMed | ((volume-based [Title/Abstract]) OR (Enhanced Protein-Energy Provision via the Enteral Route Feeding [Title/Abstract] OR (PEP uP [Title/Abstract])) AND (rate-based [Title/Abstract])) AND ((enteral nutrition [Title/Abstract] OR (nutrition [Title/Abstract])) AND ((critical [Title/Abstract] OR (intensive care [Title/Abstract]))) |
| Web of Science | #1:TS=(volume-based) =(Enhanced Protein-Energy Provision via the Enteral Route Feeding) #3:TS= (PEP uP) #4:TS= Rate-based #5:TS= (enteral nutrition) #6:TS= (enteral nutrition) #7:TS= (critical) #8:TS= (intensive care) #9: #1 OR #2 OR #3 #10: #5 OR #6 #11: #7 IR #8 #12: #9 AND #10 and #11 time span:2000.01.01-2021.01.31. Index: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC. |
| Cochrane Library | #1:TS= volume-based = Enhanced Protein-Energy Provision via the Enteral Route Feeding #3:TS= PEP uP #4:TS= Rate-based #5:TS= enteral nutrition #6:TS= enteral nutrition #7:TS= critical #8:TS= intensive care #9: #1 OR #2 OR #3 #10: #5 OR #6 #11: #7 IR #8 #12: #9 AND #10 and #11 |
| SINOMED | ("Ji Yu Rong Liang"[Abstract: Intelligent] OR "Tong Guo Chang Dao Tu Jing Zeng Qiang Dan Bai Zhi-Neng Liang Gong Ying" [Abstract: Intelligent] AND "Ji Yu Su Lv"[Abstract: Intelligent] AND "Chang Nei Ying Yang"[Abstract: Intelligent] AND "Zhong Zheng"[Abstract: Intelligent]) |
| CNKI | Search Condition: (((Abstract = Ji Yu Rong Liang) OR (Abstract = Tong Guo Chang Dao Tu Jing Zeng Qiang Dan Bai Zhi-Neng Liang Gong Ying)) AND (Abstract = Ji Yu Su Lv) AND (Abstract = Chang Nei Ying Yang) AND (Abstract = Zhong Zheng)) and dateline between (2000-01-01,2021-01-31) |

tics of included trials are listed in Table 3. We found the per-centage of goal energy received of VBF group in every enrolled study is higher than RBF group. In addition, four trials report at least one type of adverse reaction on EN administration.

Results of meta-analysis

Percentage of goal energy received

Five studies involving 515 patients reported the percentage of goal energy received, of whom 233 received VBF.^{11,14-17} There was high heterogeneity between the studies ($p < 0.001$, $I^2 = 84\%$), and random effects model was employed to pool data. The result showed that the percentage of goal energy received in the VBF group was significantly higher than that in the RBF group [MD=13.59, 95% CI (5.33, 21.85), $p = 0.001$] (Figure 2). To explore the source of heterogeneity, we conducted sensitivity analysis. Firstly, we excluded the low-quality study, there was no significant change in the heterogeneity of relevant data analysis results ($p < 0.001$, $I^2 = 85\%$). Then we pooled these high-quality studies by using random effect model. Percentage of goal energy received in the VBF group was still significantly higher than that in the RBF group [MD=13.94, 95% CI (5.20, 22.68), $p = 0.002$], which shows the study with low quality did not significantly influence the effect size. Then we analyzed the included data and found that patient type of the study by Qi G was different from the rest of the studies. This study enrolled mechanic ventilation patients, who are more severe than patients from the other studies. And as is well known, mechanically ventilated patients suffering from significantly higher chest and abdomen pressure may impede EN delivery. We therefore excluded this study and found no heterogeneity among the remaining studies ($p = 0.88$, $I^2 = 0\%$). We pooled these studies by using fixed model, the result showed that the percentage of goal energy received of VBF group was significantly higher than that of RBF group [MD=9.11, 95% CI (5.82,

12.41), $p < 0.001$].

Numbers of patients who received 80% or more of goal energy requirement

Only one study mentioned the numbers of patients who received 80% or more of goal energy requirement (32% vs 17%).¹⁵ According to the result, the VBF protocol may improve energy intake of patients.

Percentage of goal protein received

Two studies mentioned percentage of goal protein received, that of Krebs E (86.2% vs 77.4%, $p = 0.005$) and McClave S (90% vs 57%, 95% CI 24-43, $p = 0.02$).^{11,13} According to the results reported, the VBF protocol may improve percentage of goal protein received.

Numbers of patients who received 50% or more of goal protein requirement

Only one study (Krebs E) mentioned the numbers of patients who received 50% or more of goal protein requirement (1% vs 1%, $p = 0.07$).¹³ According to the result, the VBF protocol did not show superiority in improving adequate protein intake of patients.

Mortality

Five studies involving 578 patients reported mortality,^{11,13-15,17} 257 of the patients received VBF. There is no heterogeneity between the studies ($p = 0.98$, $I^2 = 0$), and we analyzed the merged data with the fixed effects model (Figure 3). The meta-analysis result indicated a reduction trend of mortality in VBF group. [RR=0.70, 95% CI (0.44, 1.11), $p = 0.13$].

ICU length of stay

Three studies involving 402 patients reported ICU length of stay,^{14,15,17} 169 patients received VBF. There was no heterogeneity between the studies ($p = 0.43$, $I^2 = 0$), and we analyzed the merged data with the fixed effects model.

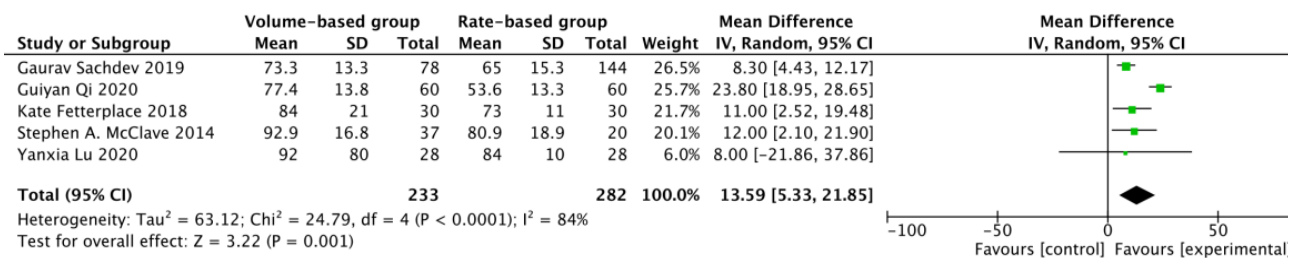


Figure 2. Forest plot of meta-analysis of percentage of goal energy received in the two groups.

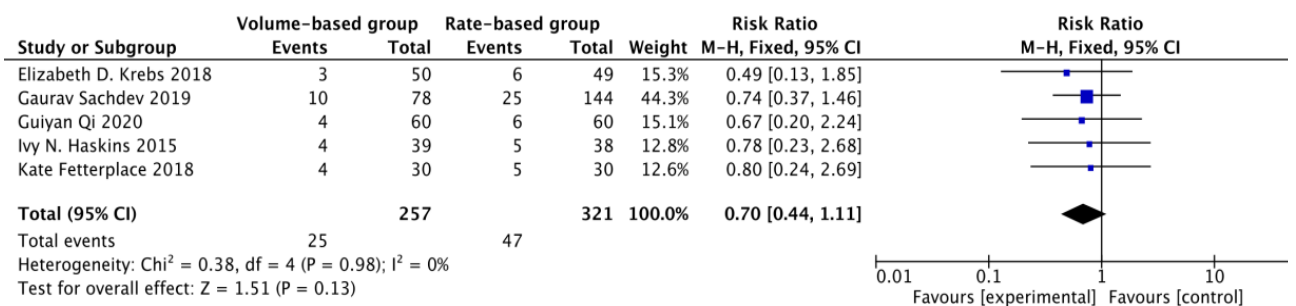


Figure 3. Forest plot of meta-analysis of mortality in the two groups.

Table 3. Basic information of included studies

| Author, year | Type | P.T. | N.O.P (ITT) | Percentage of goal energy received (%) | | Feeding intolerance (n/N) | | Emesis (n/N) | | Diarrhea (n/N) | | Hospital length of stay (d) | |
|-------------------------------------|---------------|---|------------------|---|---------------------|------------------------------|-------|-----------------|-------|-------------------|-------|--------------------------------|-------------------|
| | | | | VBF | RBF | VBF | RBF | VBF | RBF | VBF | RBF | VBF | RBF |
| McClave S 2014 ¹¹ | RCT | Critical patients | 57 (37vs20) | 92.9 (±16.8) | 80.9 (±18.9) | NR | NR | NR | NR | NR | NR | NR | NR |
| Haskins LN 2015 ¹² | Cohort trials | Critical patients | 77 (39vs38) | 74.01 | 57.02 | NR | NR | NR | NR | NR | NR | 25 (16-29) | 19 (9-29) |
| Krebs E 2018 ¹³ | Cohort trials | Trauma, burn and surgical critical patients | 99 (50vs49) | 84.5 (67.5-91.9) | 73.4 (58.6-83.6) | 9/50 | 15/49 | 6/50 | 7/49 | 32/50 | 26/49 | 27.5 (19.0-46.0) | 23 (17.0-33.0) |
| Fetterplace K 2018 ¹⁴ | RCT | Critical patients | 60 (30vs30) | 84 (±21) | 73 (±11) | 9/30 | 8/30 | NR | NR | 16/30 | 16/30 | 27.4 (±19.0) | 18.8 (±10.9) |
| Sachdev G 2019 ¹⁵ | Cohort trials | Trauma critical patients | 222 (78vs144) | 73.3 (±13.3) | 65 (±15.3) | NR | NR | 1/78 | 2/144 | 4/78 | 6/144 | 23 (±14.8) | 25 (±19.4) |
| Lu Y 2020 ¹⁶ | RCT | Critical patients | 56 (28vs28) | 92 (±80) | 84 (±10) | NR | NR | 6/28 | 8/28 | 13/28 | 10/28 | NR | NR |
| Qi G 2020 ¹⁷ | RCT | Critical patients with ventilation | 120 (60vs60) | 77.4 (±13.8) | 53.6 (±13.3) | 27/60 | 23/60 | NR | NR | NR | NR | 18.2 (±10.9) | 19.8 (±10.1) |

| Author, year | ICU length of stay(d) | | Mechanical ventilation duration (d) | | Mortality (n/N) | |
|-------------------------------------|-----------------------|-------------------|--|---------------|-----------------|--------|
| | VBF | RBF | VBF | RBF | VBF | RBF |
| McClave S 2014 ¹¹ | NR | NR | NR | NR | NR | NR |
| Haskins LN 2015 ¹² | 14 (10-21) | 9 (5-19) | 9 (7-16) | 5 (3-12) | 4/39 | 5/38 |
| Krebs E 2018 ¹³ | 14 (10.0-23.0) | 15 (11.0-22.0) | NR | NR | 3/50 | 6/49 |
| Fetterplace K 2018 ¹⁴ | 10.6 (±8.3) | 9.1 (±5.5) | 8.7 (±7.5) | 7.0 (±5.0) | 4/30 | 5/30 |
| Sachdev G 2019 ¹⁵ | 13 (±6.2) | 14 (±7.6) | 13 (±7.7) | 14 (±11.3) | 10/78 | 25/144 |
| Lu Y 2020 ¹⁶ | NR | NR | NR | NR | NR | NR |
| Qi G 2020 ¹⁷ | 8.1 (±2.2) | 9.0 (±2.8) | 6.6 (±2.2) | 7.9 (±2.3) | 4/60 | 6/60 |

Meta-analysis result showed that ICU length of stay in VBF group was significantly reduced than that in RBF group [MD=-0.8, 95% CI (-1.59, -0.01), $p=0.05$] (Figure 4).

Hospital length of stay

Three studies involving 402 patients reported hospital length of stay,^{14,15,17} 169 patients received VBF. There was moderate heterogeneity between the studies ($p=0.05$, $I^2=66%$), and we analyzed the merging data with the random effects model. Meta-analysis result showed that there was no significant difference in length of hospital stay between the two groups [MD=0.62, 95% CI (-4.46, 5.69), $p=0.81$] (Figure 5). To explore the source of heterogeneity, we analyzed the included data and found that the patients in different studies are of different ages. The age of patients in Qi G are 61.1±12.2 in for the VBF group and 60.2±12.0 for the RBF group, 55±13 vs 57±16 in Fetterplace K and 44.3±18.6 vs 44.9±17.9 in Sachdev G.

Mechanical ventilation duration

Three studies involving 402 patients reported mechanical ventilation duration,^{14,15,17} 169 patients received VBF. There was low heterogeneity between studies ($p=0.21$, $I^2=36%$), and the random effects model was used to pool data. The meta-analysis result showed that the mechanical ventilation in the VBF group was significant when compared to that of the RBF group [MD=-1.11, 95% CI (-1.86, -0.37), $p=0.003$] (Figure 6). To explore the source of heterogeneity, we analyzed the including data and found that the patients in Fetterplace K had lower

APACHE II scores and higher BMI than the other studies. After exclusion, there was no heterogeneity among the studies ($p=0.82$, $I^2=0%$), and the results showed that the mechanical ventilation duration of the VBF group was significantly reduced compared to that of the RBF group [MD=-1.27, 95% CI (-2.04, -0.51), $p=0.001$].

Diarrhea

Four studies involving 437 patients reported the incidence of diarrhea,¹³⁻¹⁶ 186 patients received VBF. There was no heterogeneity between the studies ($p=0.90$, $I^2=0$), and we analyzed the merged data with the fixed effects model (Figure 7). The meta-analysis result showed that there was not significant difference in the incidence of diarrhea between the two groups [RR=1.17, 95% CI (0.91, 1.50), $p=0.23$].

Emesis

Three studies involving 377 patients reported the incidence of emesis,^{13,15,16} 156 patients received VBF. There was no heterogeneity between the studies ($p=0.98$, $I^2=0$), and we analyzed the merged data with the fixed effects model (Figure 8). The meta-analysis result showed that there was no significant difference in the incidence of emesis between two groups [RR=0.80, 95% CI (0.42, 1.55), $p=0.51$].

Feeding intolerance

Three studies involving 279 patients reported the incidence of feeding intolerance,^{13,14,17} 140 patients received VBF. There was low heterogeneity between the studies ($p=0.26$, $I^2=26%$), and we analyzed the merged data with

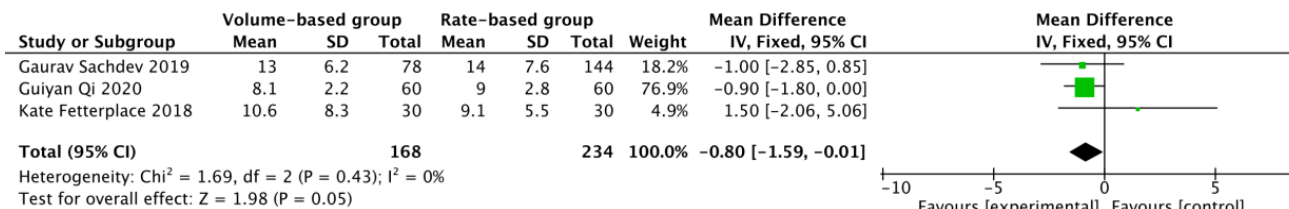


Figure 4. Forest plot of meta-analysis of ICU length of stay in the two groups.

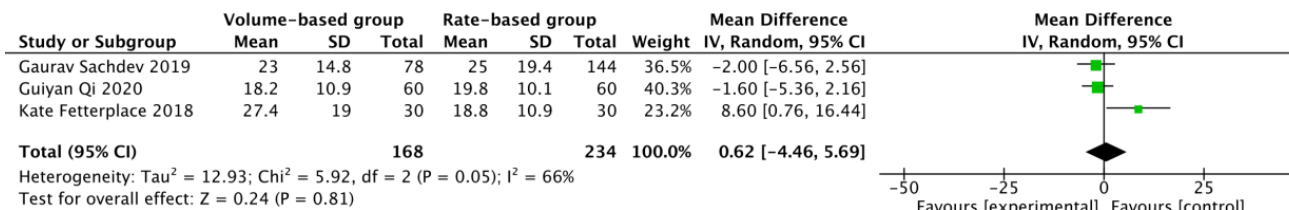


Figure 5. Forest plot of meta-analysis of length of hospital stay in the two groups.

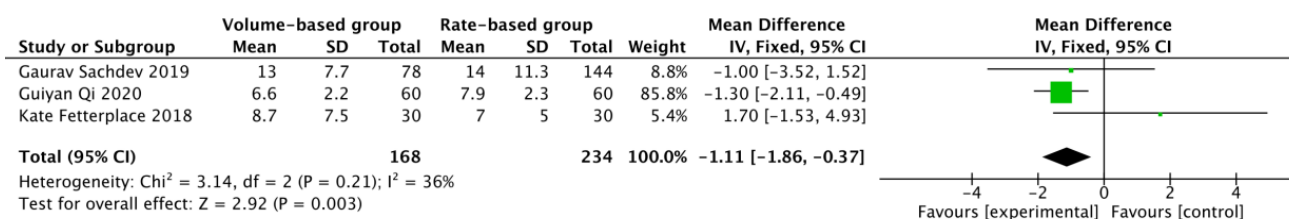


Figure 6. Forest plot of meta-analysis of mechanical ventilation duration in the two groups.

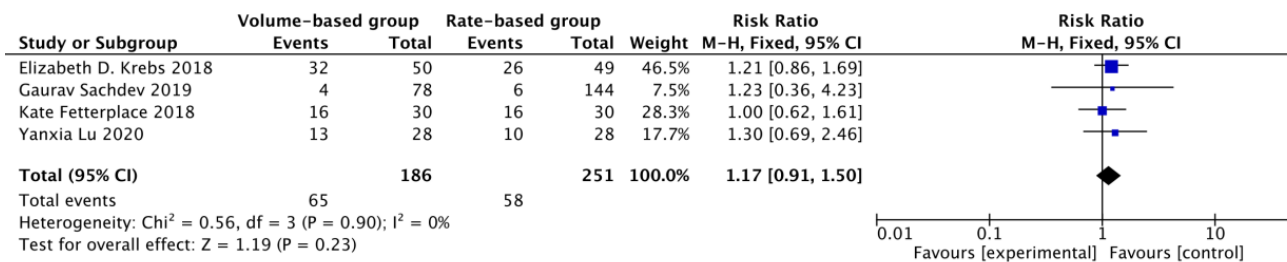


Figure 7. Forest plot of meta-analysis of diarrhea in the two groups.

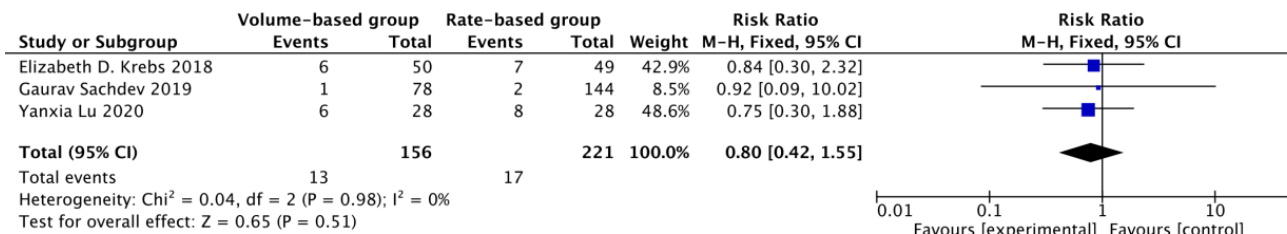


Figure 8. Forest plot of meta-analysis of emesis in the two groups.

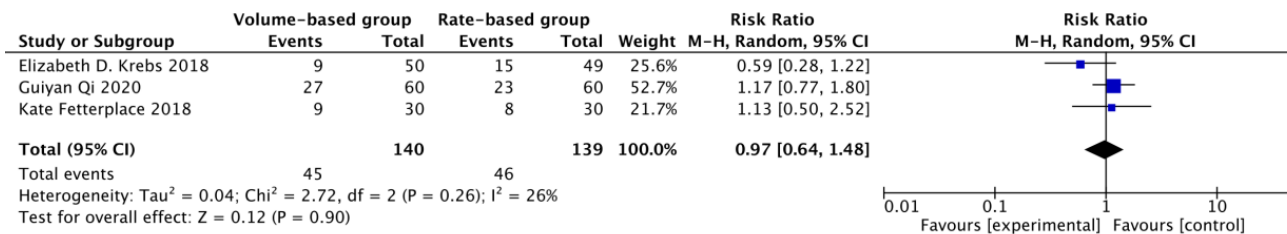


Figure 9. Forest plot of meta-analysis of patients with feeding intolerance in the two groups.

the random effects model (Figure 9). The meta-analysis result showed that there was no significant difference in the incidence of feeding intolerance between the two groups [RR=0.97, 95% CI (0.64, 1.48), $p=0.90$]. To explore the source of heterogeneity, we analyze the included data and found that the APACHE II scores of patients in Krebs E are much lower than that of the other studies, and the BMI of patients in Qi G are lower than the other studies. The heterogeneity may be caused by varying severity of patients in different studies.

DISCUSSION

Our work demonstrated that VBF can improve the success of enteral nutrition for critically ill patients in the ICU. We systematically retrieved the literature related to VBF from January 1, 2000 to March 30, 2021, sources include MEDLINE (through PubMed), Web of Science, Cochrane Library and China National Knowledge Infrastructure (CNKI). Randomized controlled trials or cohort studies of enteral nutrition based on VBF versus RBF in critically illness of adult participants were selected. After screening, seven studies involving 691 patients were finally included, 322 patients received enteral nutrition based on VBF. Six studies were high-quality from quality assessment. The results of our study indicated that the percentage of goal energy received in the VBF groups was significantly higher than that in the RBF group [MD=9.11, 95% CI (5.82, 12.41), $p<0.001$]. The length of ICU stays [MD= -0.8, 95% CI (-1.59, -0.01), $p=0.05$] and mechanical ventilation duration (MD=-1.27, 95% CI (-

2.04, -0.51), $p=0.001$) in the VBF group were also significantly reduced. Meanwhile, we found that the side effects are similar with the two feeding protocols, e.g., diarrhea (RR=1.17, 95% CI (0.91, 1.50), $p=0.23$), emesis (RR=0.80, 95% CI (0.42, 1.55), $p=0.51$). Feeding intolerance (RR = 0.97, 95% CI (0.64, 1.48), $p=0.90$) was not significantly different either. And our study indicated that VBF may be associated with decreased death risk, although it is not a significantly (RR=0.70, 95% CI (0.44, 1.11), $p=0.13$). It is likely because of the small sample size of the current trials.

According to the survey, more than 80% of the critically ill patients face an elevated risk of malnutrition due to the stress catabolism state predisposition.¹⁸ Therefore, it is particularly important to provide adequate nutrition to ICU patients. Unfortunately, underfeeding is still common.^{19,20} Up to 2009, only 47.7% of the critically ill patients achieved 80% of prescribed energy and protein goals.²¹ In addition, researchers found that the increase of cumulative energy loss and energy debt is associated with poor clinical outcomes. In addition, inadequate nutrition provision is associated with the increasing incidence of ARDS, sepsis, renal failure, and even significantly increased the operative rate.^{22,23} Therefore, inadequate energy-protein supplementation becomes a vitally challenge for ICU patients and it is critical for clinical practitioners to take notice. In 2013 Daren K Heyland et al introduced a new enteral nutrition protocol - PEPuP protocol. Its purpose was to overcome the main obstacles to provide

ad-equate energy by refocus the consideration from rate-based to volume-based feeding.²⁴

Based on existing evidence, we conducted this meta-analysis and systematic review to verify the efficacy and safety of the VBF protocol. We found that VBF have significant advantages in improving energy and protein intake for critically ill patients than the RBF protocol. VBF protocol focused on minimizing the impact of feeding interruptions on energy delivery. In EN practicing, feeding interruptions is one of the main factors of underfeeding, especially with "early enteral nutrition." There are a variety of reasons for prolonged interruptions such as increased gastric residual volumes, weaning because of additional examinations, and so on, and it is difficult to address these one by one.²⁵ The VBF protocol provides a new strategy for solving the problem of insufficient feeding. In 2009, Sue Brierley-Hobson conducted a before-and-after study that showed volume ($p \leq 0.001$), energy ($p \leq 0.001$) and protein ($p = 0.02$), and patients meeting >90% of energy and protein requirements in the VBF group nearly doubled ($p \leq 0.02$) from the RBF group.²⁶ Holyk A et al conducted a research called FEED MORE which showed that VBF demonstrated a significant increase in energy (75% RBF, 102% VBF; $p < 0.001$) and protein (68% RBF, 87% VBF; $p < 0.001$).²⁷ It was worth mentioning that the GRV (gastric residual volume) is a strong factor in reducing actual energy intake. The study conducted by Heyland et al posited that the VBF protocol can raise the threshold of GRV. VBF can also potentially prevent the excessive accumulation of GRV by including prokinetic agents as part of the bundle treatment. Metoclopramide was used as a second line prokinetic agent due to its strong extra-vertebral system effect. Daren K Heyland et al conducted an RCT that compared ulimorelin and metoclopramide in the treatment of critically ill patients with enteral feeding intolerance showing similar rates of feeding success and no safety differences (median [Q1, Q3]: 82.9% [38.4%, 100.2%] and 82.3% [65.6%, 100.2%], respectively, $p = 0.49$).²⁸

For clinical outcomes, we found the VBF protocol is associated with shorter length of ICU stay and mechanical ventilation. Although there is no significant difference in mortality, there was still a slight reduction in the VBF group. Researchers have found that the calorie debt may reach 5000-9000 kcal during the first week of ICU admission, and this debt is very difficult to replenish at the later stage of hospitalization.²⁹ Mortality rate could reach 85% while cumulative energy loss reached 10,000 kcal during the whole of ICU stay.³⁰ As we can see, a large amount of energy debt will lead to the high mortality directly. It is rational to conclude that the VBF protocol likely provides survival benefit to patients.

We observed that adverse events did not increase in patients receiving VBF. It is consistent with the evidence from surgical patients who received VBF intervention.³¹ And we noticed that ACG (American College of Gastroenterology) has published clinical guidelines for nutrition therapy in adults (2016) recommending the VBF protocol as a validated protocol should be used to provide adequate EN.³²

There are some limitations to our current study. First, we found the energy and protein targets are different be-

tween enrolled studies that produced a measurement bias. Second, the percentage of goal energy received is calculated manually and the accuracy is not guaranteed. We found only one study that reported the numbers of patients who received 80% or more of goal energy requirement, and only two studies reported the protein intake of patients. It is well known that protein intake is closely related to the immune system, and adequate protein intake will improve clinical outcomes. We suggest that for future studies, the researchers pay more attention to the intake of protein. In summary, although our study has observed the benefit of VBF on the clinical outcomes, further large sample and rigorous designed randomized control trials are still urgent needed.

Conclusion

The VBF protocol significantly improves the successive rate of enteral nutrition in critically ill patients while shortening the length of ICU stay and mechanical ventilation.

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AUTHOR DISCLOSURES

In the manuscript, all authors have completed the financial and personal relationships disclosure form and declare that: (i) we have financial support for study, that is Science and Technology Department of Sichuan Province (2019YFS0534, 2019YFS0303); and (ii) there was no conflict of interest in the study; and (iii) there are no other relationships or activities that could appear to have influenced the submitted work.

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