Comparisons between small intestinal and gastric feeding in severe traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials

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OBJECT Nutritional support is highly recommended for reducing the risk of nosocomial infections, such as pneumonia, in patients with severe traumatic brain injury (TBI). Currently, there is no consensus for the preferred route of feeding. The authors compared the risks of pneumonia and other important outcomes associated with small intestinal and gastric feeding in patients with severe TBI.

METHODS This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant randomized controlled trials (up to December 16, 2013) that compared small bowel to gastric feeding in patients with severe TBI were identified from searches in the PubMed and Embase databases. The primary outcome was risk of pneumonia. Secondary outcomes included ventilator-associated pneumonia, mortality, length of intensive care unit stay, length of hospital stay, duration of mechanical ventilation, total number of complications, aspiration, diarrhea, distention, Glasgow Coma Scale score, Injury Severity Score, and Acute Physiology and Chronic Health Evaluation II score.

RESULTS Five randomized controlled trials with 325 participants in total were included in the meta-analysis. Compared with gastric feeding, small bowel feeding was associated with a significant reduction in the incidence of pneumonia (risk ratio [RR] 0.67; 95% CI 0.52–0.87; p = 0.002; I² = 0.0%) and ventilator-associated pneumonia (RR 0.52; 95% CI 0.34–0.81; p = 0.003; I² = 0.0%). Small intestinal feeding was also associated with a decrease in the total number of complications (RR 0.43; 95% CI 0.20–0.93; p = 0.03; I² = 68%). However, small intestinal feeding did not seem to significantly convert any of the other end points in the meta-analysis.

CONCLUSIONS The limited evidence suggests that small bowel feeding in patients with severe TBI is associated with a risk of pneumonia that is lower than that with gastric feeding. From this result, the authors recommend the use of small intestinal feeding to reduce the incidence of pneumonia in patients with severe TBI.

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KEY WORDS enteral nutrition; traumatic brain injury; small bowel feeding; gastric feeding; meta-analysis

Severe traumatic brain injury (TBI) is a catastrophic event that often has destructive familial, economic, and societal consequences. It contributes to many deaths and cases of permanent disability, especially among patients 15–30 years old.8,10 The average mortality rate for patients with severe TBI is 39%, and 60% of these patients have an unfavorable outcome on the Glasgow Outcome Scale.24,26 Furthermore, those who survive tend to have significant disabilities, which also can cause a major socioeconomic burden.

Patients with severe TBI have reduced immune function and higher risks of nosocomial infections as a result of decreased energy and increased protein catabolism.4,7 By providing additional daily calories, nutrition support

ABBREVIATIONS APACHE II = Acute Physiology and Chronic Health Evaluation II; GCS = Glasgow Coma Scale; ICU = intensive care unit; ISS = Injury Severity Score; MV = mechanical ventilation; RCT = randomized controlled trial; RR = risk ratio; TBI = traumatic brain injury; VAP = ventilator-associated pneumonia; WMD = weighted mean difference.


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therapy has been shown to improve the treatment for this metabolic disorder in patients with severe TBI. Because of its secretagogue and immunological effects on intestinal function, the enteral route is preferred for providing nutrition support therapy. This route is also associated with a lower rate of nosocomial infections, particularly for episodes of pneumonia, and the frequency of its incorporation into the management of critically ill patients has been increasing. However, the enteral route is often underestimated and neglected for patients with severe TBI.

Although the recommendation by the Brain Trauma Foundation is to achieve full caloric replacement within 7 days after severe TBI, there is still no consensus regarding the optimal route of feeding (i.e., via small intestinal or gastric feeding). Patients with severe TBI have an increased incidence of gastrointestinal complications, particularly gastric residuals; not only is the brain trauma itself associated with this increase, but the therapeutics used to control intracranial hypertension and other measures of patient support may also contribute to this effect. One advantage of small intestinal feeding over gastric feeding may be a reduced risk of gastroesophageal reflux and subsequent aspiration pneumonia.

The ideal route for enteral feeding remains to be established. Adequately powered data derived from randomized controlled trials (RCTs) in which small intestinal feeding and gastric feeding in patients with severe TBI were compared are scarce. Therefore, we performed this meta-analysis and systematic review to compare small intestinal and gastric feeding in patients with severe TBI in regard to the risks of pneumonitis and other important outcomes.

Methods

Literature Search and Inclusion Criteria

This systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant articles, published up to December 16, 2013, were identified by 2 of the authors (D.W. and S.Q.Z.) through searches of the PubMed and Embase databases. Limiting the search to RCTs in which human subjects were used, the search strategy was (gastric OR nasogastric) AND (small bowel OR small intestinal OR duodenal OR jejuno OR nasojejunal OR nasoduodenal OR postpyloric OR transpyloric) AND (feeding OR enteral nutrition) AND (trauma OR burn). Only articles written in the English language were included. In addition, manual checks of the reference lists of identified studies were performed to include other potentially eligible trials. This entire process was repeated until we could not identify any additional articles. We used only the studies that included patients with severe TBI who required mechanical ventilation (MV), compared small intestinal and gastric feeding, and had data available on the incidence of pneumonitis. Disease severity was determined from the Glasgow Coma Scale (GCS) scores, Injury Severity Scores (ISSs), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores.

Data Extraction and Outcome Measures

Two authors (D.W. and S.Q.Z.) independently extracted the following data from each report: first author name, year of publication, country, number of patients, participant characteristics, severity of illness, tube type and placement technique for patients in the small intestinal feeding group and those in the gastric feeding group, and the study’s definition of pneumonitis. Two additional authors (S.W.J. and H.B.C.) checked the data after they were entered into a standardized Excel (Microsoft Corp.) file. After discussion, any disagreements were resolved and a consensus was formed. The incidence of pneumonitis was the primary outcome of the study. However, the definitions of pneumonitis varied among the studies. The secondary outcomes included ventilator-associated pneumonia (VAP), mortality, length of intensive care unit (ICU) stay, length of hospital stay, duration of MV, total number of complications, aspiration, diarrhea, distention, GCS score, ISS, and APACHE II score.

Quality Assessment

The Cochrane risk-of-bias tool was used to evaluate the methodologic quality of each trial. In each included trial, the risk of bias for each outcome was reported as low, unclear, or high in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. We used a funnel plot to uncover potential publication bias.

Statistical Analysis

Differences are expressed as risk ratios (RRs) with 95% CIs for dichotomous outcomes and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. Heterogeneity across the studies was tested using the I² statistic, which is a quantitative measure of inconsistency across studies. Studies with low heterogeneity have an I² value of 25%–50%, those with moderate heterogeneity have an I² value of 50%–75%, and those with high heterogeneity have an I² value of > 75%. Additional analyses were performed for pneumonitis only, because only a small number of studies examined other outcomes.

The Begg funnel plots (log odds ratios vs standard errors) were visually inspected to assess potential publication bias. The presence of publication bias was also evaluated by using the Begg and Egger tests. A p value of < 0.05 was judged to be statistically significant, except where otherwise specified. All statistical analyses were performed using Review Manager (RevMan) version 5.
Identification and Selection of Studies

In the initial database search, we identified 18 RCTs. Four RCTs were excluded because of duplicate studies, and 11 RCTs were excluded based on the titles and abstracts. The remaining 3 full-text articles were reviewed for more detailed evaluation, and one of them was excluded because pneumonia was not an outcome. Three additional RCTs were identified through manual searching. Finally, 5 RCTs that met our inclusion criteria were included in the meta-analysis. The search flow diagram is shown in Fig. 1.

Study Characteristics

The main characteristics of the patients and related definitions of pneumonia in the 5 included RCTs, which were published between 1989 and 2010, are presented in Tables 1 and 2. The sample sizes of these RCTs ranged from 27 to 104 (total sample size 325).

Risk of Bias

A funnel plot (Fig. 2) of the included studies did not suggest the presence of publication bias. This result was confirmed statistically by using the Egger test (bias 0.05; 95% CI –1.29 to 1.33; p = 0.965).

5.2.6 (Nordic Cochrane Centre) and Stata version 12.0 (Stata Corp).
In Figs. 3 and 4, we report the methodologic quality assessment, for which the Cochrane risk-of-bias tool was used for each trial. Overall, 1 study was judged to be at low risk of bias and 4 at high risk of bias, and 2 had an unclear risk of bias. A lack of blinding was considered to have a low effect on mortality outcome; therefore, this outcome was to have a low risk of bias. However, when assessing other less objective outcomes (e.g., pneumonia), a lack of blinding can introduce performance or ascertain-ment bias; therefore, these outcomes were considered to have a high risk of bias in this setting.3

Primary Outcome
A total of 325 patients—157 in the small intestinal feeding group and 168 in the gastric feeding group—were included in this analysis. Figure 5 shows the pooled results from the random-effects model combining the RRs for overall pneumonitis. Compared with gastric feeding,
small intestinal feeding was associated with a significant reduction in the overall incidence of pneumonitis (risk ratio [RR] 0.67; 95% CI 0.52–0.87; p = 0.002), with low heterogeneity among the studies (I² = 0.0%; p = 0.73). Further exclusion of any single study did not materially alter the overall combined RR for pneumonitis, which ranged from 0.63 (95% CI 0.48–0.83; p = 0.001) to 0.73 (95% CI 0.53–0.89; p = 0.04).

Secondary Outcomes
Tables 3 and 4 outline the secondary outcomes. Compared with gastric feeding, small intestinal feeding was associated with a significant reduction in VAP (RR 0.52; 95% CI 0.34–0.81; p = 0.003), with low heterogeneity among the studies (I² = 0.0%; p = 0.38), and was associated with a decrease in the total number of complications (RR 0.43; 95% CI 0.20–0.93; p = 0.03). However, small intestinal feeding was not associated with decreases in mortality (RR 0.81; 95% CI 0.44–1.47; p = 0.49), aspiration (RR 0.23; 95% CI 0.03–1.90; p = 0.17), diarrhea (RR 1.05; 95% CI 0.29–3.86; p = 0.94), or distention (RR 0.71; 95% CI 0.32–1.58; p = 0.41) in comparison with gastric feeding.

Small intestinal feeding also had no impact on length of ICU stay (WMD 2.25 days; 95% CI −6.74 to 11.24 days; p = 0.62), length of hospital stay (WMD 2.66 days; 95% CI −8.80 to 14.12 days; p = 0.65), or duration of MV (WMD 1.03 days; 95% CI −5.06 to 7.12 days; p = 0.74). Furthermore, the patients who received small intestinal feeding did not significantly differ from those who received gastric feeding in GCS score (WMD 0.00; 95% CI −0.82 to 0.82; p = 1.00), ISS (WMD 2.61; 95% CI −1.46 to 6.68; p = 0.21), or APACHE II score (WMD −1.38; 95% CI −3.19 to 0.43; p = 0.13).

Publication Bias
Visual inspection of the funnel plot (Fig. 2) did not indicate a publication bias. However, the low power of this analysis, resulting from the inclusion of only 5 studies, limited the interpretability of this finding.

Discussion
This systematic review and meta-analysis of RCTs comparing the route of feeding in patients with severe TBI demonstrates that delivery of nutrients directly into the small intestine may be associated with a reduction in the incidence of pneumonia (including VAP) and total complications when compared with gastric delivery. However, the route of feeding did not affect mortality, length of ICU stay, length of hospital stay, duration of MV, aspiration, diarrhea, or distention. Also, there was an indication that feeding into the small intestine increased nutrient intake, but a meta-analysis was not conducted because of the marked variation in the reporting of nutritional outcomes.

The mechanism by which small intestinal feeding may reduce pneumonia rates remains unclear. One hypothesis, which explains the unfavorable outcome of gastric feeding, is that the increased gastric residual volume leads to regurgitation and aspiration, which leads to a higher incidence of nosocomial pneumonia. However, the results of
multiple studies have indicated that there is no relationship between residual gastric volume and the risk of aspiration and that the absence of gastric-volume monitoring is not inferior to routine residual gastric-volume monitoring in the development of VAP.22,23 Our meta-analysis also did not find a significant difference in the risk of clinically detected aspiration of feeding.

Because of their intense catabolism and prolonged fasting, patients with TBI require specialized nutritional support. The gastrointestinal route is optimal for nutrient administration.2 Although the data on feeding complications are scarce, we are inclined to agree with Spanish Society of Intensive Care Medicine and Coronary Units–Spanish Society of Parenteral and Enteral Nutrition (SEMICYUC-SENPE) and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, which recommend enteral nutrition by the transpyloric route for patients with brain injury. In comparison with the gastric route, the transpyloric route is well tolerated, improves the efficacy in enteral supply, and reduces the incidence of late pneumonia.2,11,17

Using the Cochrane risk-of-bias tool, we evaluated the methodologic quality of each trial included in this study.

**FIG. 4.** Risk-of-bias graph. Using the Cochrane risk-of-bias tool, each risk-of-bias item is presented as a percentage across all included studies in this meta-analysis. Figure is available in color online only.

**FIG. 5.** Pneumonia. Five studies reported the incidence of overall pneumonia. Shown is a forest plot comparing small bowel feeding and gastric feeding with respect to pneumonia outcome. Results are shown by using a random-effects model with RR and 95% CIs. M-H = Mantel-Haenszel (method). Figure is available in color online only.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Small Intestinal</th>
<th>Gastric</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham 1998</td>
<td>2/17 3/15 2.5%</td>
<td>0.59 [0.11, 3.06] 1989</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kortbek 1999</td>
<td>10/37 18/43 16.6%</td>
<td>0.65 [0.34, 1.22] 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor 1999</td>
<td>18/41 26/41 38.7%</td>
<td>0.69 [0.46, 1.05] 1999</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minard 2000</td>
<td>6/12 7/15 11.0%</td>
<td>1.07 [0.49, 2.34] 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acosta-Escribano 2010</td>
<td>16/50 31/54 31.2%</td>
<td>0.56 [0.35, 0.89] 2010</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>157/168 100.0%</strong></td>
<td><strong>0.67 [0.52, 0.87]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3. Clinical outcomes: dichotomous data**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients</th>
<th>No. of Trials</th>
<th>Small Bowel Group (n/N)</th>
<th>Gastric Group (n/N)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>I² (%)</th>
<th>p Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP</td>
<td>189</td>
<td>2</td>
<td>21 of 87</td>
<td>45 of 97</td>
<td>0.52 (0.34–0.81)</td>
<td>0.0003</td>
<td>0</td>
<td>0.38</td>
</tr>
<tr>
<td>Mortality</td>
<td>293</td>
<td>4</td>
<td>13 of 140</td>
<td>22 of 153</td>
<td>0.81 (0.44–1.49)</td>
<td>0.49</td>
<td>0</td>
<td>0.64</td>
</tr>
<tr>
<td>Total complications</td>
<td>186</td>
<td>2</td>
<td>22 of 91</td>
<td>52 of 95</td>
<td>0.43 (0.20–0.93)</td>
<td>0.03</td>
<td>68</td>
<td>0.08</td>
</tr>
<tr>
<td>Aspiration</td>
<td>131</td>
<td>2</td>
<td>0 of 62</td>
<td>4 of 69</td>
<td>0.23 (0.03–1.90)</td>
<td>0.17</td>
<td>0</td>
<td>0.95</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>131</td>
<td>2</td>
<td>15 of 62</td>
<td>16 of 69</td>
<td>1.05 (0.29–3.86)</td>
<td>0.94</td>
<td>78</td>
<td>0.03</td>
</tr>
<tr>
<td>Distention</td>
<td>131</td>
<td>2</td>
<td>5 of 62</td>
<td>10 of 69</td>
<td>0.71 (0.32–1.58)</td>
<td>0.41</td>
<td>0</td>
<td>0.39</td>
</tr>
</tbody>
</table>
We presume that the patients were allocated randomly, because earlier reports from the same investigators described the use of random sequences. In an earlier study by Acosta-Escribano and coworkers, randomization was achieved by using sealed envelopes, and in earlier studies by Minard and coworkers, the patients were allocated randomly by using a randomization table generated by computer before institution of the study. Therefore, the risk of selection bias for random sequence generation was reported as low. Lack of blinding was considered to have a low effect on mortality outcomes; thus, this outcome was considered to have a low risk of bias.

Our meta-analysis had many limitations. Although 5 RCTs with a total of 325 participants (sample sizes ranged from 27 to 104) were included, the numbers of subjects in our study and all included studies were quite small. Because of the small sample sizes, 4 studies did not find a significant difference in the primary outcome, and only 1 study found a decreased risk of pneumonia associated with feeding via the small bowel route in patients with severe TBI. Therefore, it is possible that the positive findings were obtained from a single RCT.

Another limitation is that, of 80 ventilated trauma patients in the Kortbeek et al. study, 62 patients with severe TBI were included in our study. Nevertheless, the point estimate was unaffected when the Kortbeek et al. study was removed (RR 0.67; 95% CI 0.51–0.89; p = 0.006; I² = 0%).

Although the ideal route for enteral feeding continues to be debated, we believe that the optimal clinical decision for the delivery of enteral nutrition should be personalized according to the individual profile, which includes nutritional status, severity, complications, feeding tolerance, and day-to-day changes in clinical conditions. Additional studies by nutritionists and clinicians are needed for better management of the delivery of enteral nutrition for patients with severe TBI.

Conclusions

The limited available evidence suggests that, in comparison with gastric feeding, small bowel feeding decreases the risk of pneumonia in patients with severe TBI. Our study lends support for the use of small intestinal feeding to reduce the incidence of pneumonitis in patients with severe TBI. However, our results should be interpreted with caution, given the various limitations of the study. In addition, well-designed RCTs are necessary to clarify the optimal nutritional strategies for patients with severe TBI.

Acknowledgments

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References


TABLE 4. Clinical outcomes: continuous data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Patients</th>
<th>No. of Trials</th>
<th>WMD (95% CI)</th>
<th>p Value</th>
<th>I² (%)</th>
<th>p Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of ICU stay</td>
<td>211</td>
<td>3</td>
<td>2.25 (−6.74 to 11.24)</td>
<td>0.62</td>
<td>86</td>
<td>0.007</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>211</td>
<td>3</td>
<td>2.66 (−8.80 to 14.12)</td>
<td>0.65</td>
<td>59</td>
<td>0.12</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>211</td>
<td>3</td>
<td>1.03 (−5.06 to 7.12)</td>
<td>0.74</td>
<td>80</td>
<td>0.02</td>
</tr>
<tr>
<td>GCS score</td>
<td>293</td>
<td>4</td>
<td>0.00 (−0.82 to 0.82)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ISS</td>
<td>189</td>
<td>3</td>
<td>2.61 (−1.46 to 6.68)</td>
<td>0.21</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>266</td>
<td>3</td>
<td>−1.38 (−3.19, 0.43)</td>
<td>0.13</td>
<td>22</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Small intestinal and gastric feeding in severe TBI


Author Contributions


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