Safety and efficacy of continuous or intermittent enteral nutrition in ICU patients: Systematic review of clinical evidence

Francesco De Lazzaro[1] M.D., Francesco Alessandri[1] M.D., Maria Grazia Tarsitano[2] M.D., Federico Bilotta[1] M.D. and Francesco Pugliese[1] M.D.

[1]Department of Anesthesiology, Critical Care and Pain Medicine, "Sapienza" University of Rome, Policlicnico Umberto I, Rome, Italy

[2]Department of Experimental Medicine, Sapienza University of Rome, Italy

Words: 3189

Corresponding Author: Francesco De Lazzaro M.D.

Department of Anesthesiology, Critical Care and Pain Medicine,

"Sapienza" University of Rome, Policlinico Umberto I, Rome, Italy

Viale del Policlinico 155,

Rome, Italy 00161

Tel. +39-0649978024

E-mail: franzdelazzaro@gmail.com;

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Abstract

The best mode of delivering enteral nutrition (EN) in ICU is still debated: several consensus guidelines (ASPEN and ESPEN) suggest that EN in ICU should be preferably delivered continuously rather intermittently but some authors highlight that the first is unphysiological. The aim of this systematic review (SR) is to summarize available clinical evidence related to safety and efficacy of continuous enteral nutrition (C-EN) or intermittent enteral nutrition (I-EN) in ICU patients, in relation to appropriated supply on nutritional status, gastrointestinal symptoms or tolerance, risks on respiratory tract infections. A literature search of Pubmed, EMBASE and Google Scholar was performed comparing C-EN vs I-EN and 4196 published studies were screened. Nineteen studies were selected for this SR reporting types of ICU, nutritional protocols and study period. Effects of C-EN vs I-EN were presented according to the impact on: nutritional status, digestive tract and respiratory tract. The contrasting results confirmed that the optimal delivering mode of EN remains controversial. Future studies dedicated to identify the benefits and limitations of C-EN or I-EN should be realized.

Introduction

Enteral nutrition (EN) is a relevant therapeutic support for ICU patients. A delayed commencement is associated with a higher rate of infective complications and an increased mortality in some particular subsets of patients (i.e. traumatic brain injury) [1-3]. Appropriate nutrition should address 2 major endpoints: adequate energy supply and optimal composition of macronutrients [4-6]. EN can be delivered in a continuous (C-EN) or intermittent (I-EN) mode, and I-EN can be administered in cyclic, intermittent or bolus infusions [7]. Several consensus guidelines as those delivered by the Society of Critical Care Medicine (SCCM), the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parental and Enteral Nutrition (ESPEN) suggest that -when possible- EN should be initiated within the first 48 hours after ICU admission [1,5]. According to the ESPEN guidelines EN in ICU should be preferably delivered as C-EN rather than I-EN because of the lower incidence of associated diarrhea [5]. The same guidelines underline the lack of proven benefits in other outcome measures and highlight the uncertainty on the impact of either C-EN or I-EN on major outcomes as morbidity and mortality [5]. Despite this background, several authors have challenged the superiority of C-EN when compared with I-EN and highlighted that C-EN is unphysiological and I-EN is

associated with more pronounced stimulatory effect on protein synthesis in healthy volunteers and in animal models [8-12]. The optimal mode of EN delivery in ICU patients remains controversial being listed among the top 10 “open questions” [12-14].

The aim of this systematic review (SR) is to summarize available clinical evidence on the safety and efficacy of C-EN vs I-EN in ICU patients.

Methods

This SR was performed in accordance with the PRISMA (Preferred Reporting and Items for Systematic Reviews and Meta Analyses) recommendations and was recorded in the Prospero register (registration number: CRD42020148483). Two authors (FDL and FA) independently screened and assessed titles, abstracts and full text of retrieved articles of papers published between January 1980 to April 2020 [15-17]. To identify articles suitable for this SR, a literature search of PubMed, EMBASE and Google Scholar was completed and the reference section of related studies was searched. Studies conducted as prospective randomized controlled trials (RCT), prospective and retrospective observational studies, case series, and case reports, published as full paper in English were considered eligible. The following key words were searched: “enteral nutrition” “enteral feeding”, “nasogastric feeding” combined with “or”, “vs”, or “and” with “continuous”, “intermittent” and “bolus”. We selected studies on ICU patients receiving C-EN or I-EN, delivered through naso, oro-gastric, jejunal, or percutaneous enteral gastrostomy (PEG) tube feeding. We excluded studies involving pediatric and non-ICU patients as well as studies whose population received combined EN and PN supply. Disagreement over eligibility was resolved through open discussion. After screening and revision of

the full text, duplicates were eliminated. Details of the studies were recorded using a dedicated data-extraction form. GRADE Cochrane approach was used for quality of evidence of the studies and to eliminate risk of bias. Outcomes were categorized in 3 major outcomes: C-EN vs I-EN on nutritional status, gastrointestinal symptoms or tolerance and respiratory tract.

Results

Of the 4196 published studies screened 19 were selected as appropriate for this SR: 15 RCTs, 3 prospective and 1 retrospective observational studies (Figure 1) [18-36]. Out of the 18 selected studies, 12 were conducted in general mixed ICU, 4 in neurosurgical or neurological ICU, 2 in trauma ICU (1 medical ICU and 1 surgical ICU), and 1 in general mixed and in cardiac surgery ICU. Nutritional protocols tested in these studies were evaluated for safety and efficacy of C-EN vs. I-EN; study period ranged from 24 hours to 17 days (in 1 study the duration of the study was not specified); the follow up ranged between 24 hours to 66 days. Target energy supply differed between studies: 25 kcal/kg/day in 5, 25/30 kcal/kg/day in 2, 30 kcal/kg/day in 2, calculated using Harris-Benedict formula in 2, according Wilmore measurement in 1, estimated requirement by physician in 1 and it was not specified in 6 (Table 1).

Nutrition protocols, according the description reported by the authors, included various modes: in 15 studies C-EN was infused for 24 hours at 10 to 120 ml/h rate and compared with I-EN infused as “bolus with electronic infusion pump” in 4 studies (with 6-8 injection/day of 40 to 480 ml in 30-60 min); as “bolus with manual syringe” in 4 studies (6 injection/day of 40 to 320 ml from 5 min to 1 hour); as “bolus forced by gravity” in 2 studies (4-6 injections/day of 125 to 350 ml in 15-20 min); as “cyclic” in 5 studies at 28 to 112 ml/h rate, with continuous infusion for 16 hours

followed by 8 hours interruption during the night in 2 studies and continuous for 18 hours followed by 6 hours interruption in 3 studies (Supplementary 1). In two studies C-EN was not infused continually: in 1 it was infused for 18 hours with 6 hours interruption during the night and compared with I-EN administered as 6 boluses/day (every 3 hours for 18 hours and 6 hours interruption during the night); in 1 study C-EN was infused for 4 hours followed by 1 hour of interruption and compared with I-EN administered with 6-8 boluses/day followed by 6 hours of suspension during the night. In 2 studies the C-EN and I-EN protocols were not specified. Nutrition, either C-EN or I-EN, was delivered by enteral route using various approaches: through nasogastric tube in 11 studies, orogastric tube in 1, nasogastric or orogastric tube in 2, nasogastric or nasojejunal in 1, PEG in 1 and was not specified in 3 (Table 2). Effects of C-EN vs I-EN will be presented according to the impact on: nutritional status, gastrointestinal symptoms or tolerance and respiratory tract (Table 3-5). The risk of bias in RCT and in non-RCT is also reported (Tables 5 and 6). Within each presented end point, data supported by the larger number of patients will be displayed first.

C-EN vs I-EN and effects on nutritional status

Nutritional status, achieved with C-EN or I-EN, was recorded in 14 of the selected studies (11 RCT, 2 prospective and 1 retrospective observational studies) that enrolled a total of 921 patients [16, 22-27, 29, 30, 32-36]. Measured variables to describe the impact of C-EN or I-EN on the nutritional status, included: number of days in whom “caloric prescribed goal” was achieved, daily amount of delivered feeding volume, time to achieve “caloric prescribed goal”, number of patients

achieving target of caloric and protein goal, serum concentration of prealbumin or blood glucose, mean weight loss, mean daily calorie intake, glycemic variability and insulin utilization, incretion of grelin and leptin, respiratory quotient (RQ) and resting energy expenditure (REE), change in rectus femoris cross-sectional area and plasma concentrations of amino acids (Table 2).

The number of days in which the caloric target was reached, was recorded in 4 RCTs that enrolled a total of 247 patients and reported conflicting results: in 1 RCT patients assigned to C-EN achieved “caloric prescribed goal” less days than those that received I-EN; 1 RCT reported that patients assigned to C-EN achieved “caloric prescribed goal” more days than those that received I-EN and 2 RCTs showed no difference between C-EN or I-EN [22, 25, 27, 32]. Daily amount of delivered feeding volume was recorded in 4 RCTs that enrolled a total of 225 patients and reported conflicting results: in 1 RCT patients assigned to C-EN received smaller feeding volume than those that received I-EN; in 2 RCTs patients assigned to C-EN received larger feeding volume than those receiving I-EN on day 1st but feeding volumes were equivalent on day 3rd and 1 RCT showed no difference between the 2 groups [25, 26, 30, 34]. Time (in days) necessary to achieve “prescribed caloric goal” was recorded by 4 studies that enrolled a total of 396 patients and reported conflicting results: 1 RCT reported that patients assigned to C-EN achieved “prescribed caloric goal” later than those treated with I-EN; 1 retrospective observational study reported that patients assigned to C-EN achieved prescribed caloric goal earlier than those treated with I-EN and 2 studies showed no differences between C-EN and I-EN treated patients [19, 23, 27, 34]. Number of patients achieving 80 % of caloric and protein goal was recorded in 1 RCT that enrolled a total of 121 patients: there were more patients assigned to I-EN group who achieved 80% of caloric and protein goal than

those treated with C-EN [36]. Prealbumin serum concentration was recorded in 3 studies that enrolled a total of 104 patients and reported conflicting results: 2 RCTs showed no difference between C-EN or I-EN and 1 prospective observational study reported an increase in prealbumin serum concentration in patients treated with C-EN after 3 days while in those that received I-EN it remained constant [22, 33, 35]. Effects of C-EN or I-EN on blood glucose concentration was recorded in 2 studies that enrolled a total of 89 patients: these studies showed that both C-EN and I-EN ensure blood glucose concentration values consistently within the normal range [29, 33]. Daily mean caloric intake was evaluated in 1 RCT that enrolled a total of 43 patients divided in 3 sub-groups: I-EN, C-EN or jejunal C-EN. Patients assigned to jejunal C-EN received higher daily caloric intake, due to lower rate of interruptions in delivery, than those in the other 2 study groups [24].

C-EN vs I-EN on gastrointestinal symptoms or tolerance

Evidence that are related to the impact of C-EN or I-EN on gastrointestinal symptoms or tolerance were reported in 18 of the selected studies (14 RCTs, 3 prospective and 1 retrospective observational studies) that enrolled a total of 1024 patients [18-32, 34-36]. These include: diarrhea, gastric residual volume (GRV), vomiting, changes in gastric pH and in digestive tract colonization, abdominal distension and constipation (Table 3).

The incidence or severity of diarrhea was recorded among the registered outcome measures in 12 studies (10 RCT, 1 retrospective and 1 prospective observational studies) that enrolled a total of 714 patients and reported no differences in the incidence or severity of diarrhea in patients that received C-EN or

I-EN [18, 19, 22, 23, 25, 27, 29-32, 35, 36]. The GRV was evaluated in 12 studies that enrolled a total of 809 patients [19, 22, 23-27, 29, 31, 32, 35, 36]. Nine RCTs showed no difference between the 2 study groups; in 2 studies patients assigned to C-EN achieved earlier the nutrition target as had lower GRV and less interruptions in the administration. One study also demonstrated that patients receiving C-EN required less use of prokinetics (metoclopramide) [29]. Vomiting was evaluated in 5 studies (4 RCTs and 1 prospective observational study) that enrolled a total of 267 patients and reported no difference between C-EN and I-EN treated patients [25, 30, 32, 35, 36]. Changes in gastric pH and in digestive tract colonization were evaluated in 4 studies (3 RCTs and 1 prospective observational study) that enrolled a total of 156 patients [20, 21, 24, 28]. Three studies showed stable pH values in patients receiving C-EN and a decrease in pH values during the interruption of nutrition supply in those receiving I-EN; 1 study reported no difference between C-EN and I-EN treated patients. Digestive tract colonization resulted to be similar between C-EN and I-EN treated patients according 2 studies; 1 RCT report that, at day 6^{th}, the variety and number of digestive colonization microorganism is higher in patients receiving C-EN than in I-EN; 1 RCT proved that both C-EN and I-EN, when administered at gastric level, are associated with the potential for higher pathogenic digestive colonization than jejunal C-EN. Abdominal distention was evaluated in 2 studies that enrolled a total of 68 patients with no difference between C-EN and I-EN treated patients [25, 30]. Constipation was evaluated in 1 RCT that enrolled a total of 30 patients and reported higher incidence of constipation in patients receiving C-EN than in I-EN [31].

C-EN vs I-EN on respiratory tract

Effects of C-EN and I-EN on the respiratory tract was reported in 12 of the selected studies (10 RCTs 1 prospective and 1 retrospective observational studies) that enrolled a total of 708 patients [18-20, 22, 23, 25-31]. These included: presence of EN in tracheobronchial (TBA) secretions, incidence of pneumonia, changes in respiratory tract colonization, length of ICU stay and extubation rate (Table 4).

Presence of EN in TBA secretions was evaluated in 8 studies (7 RCTs and 1 prospective observational study) that enrolled a total of 296 patients [18, 19, 22, 25, 26, 29-31]. Seven studies reported no difference in the rate of EN in TBA secretions between C-EN and I-EN treated patients; 1 RCT reported higher rate of EN in TBA in C-EN than in I-EN patients. Incidence of pneumonia was evaluated in 6 studies (4 RCTs, 1 prospective and 1 retrospective observational studies) that enrolled a total of 480 patients and proved no difference between C-EN or I-EN patients [20, 23, 25, 27, 28, 30]. Changes in respiratory tract colonization was evaluated in 2 RCTs that enrolled a total of 100 patients and reported no difference between C-EN than in I-EN patients [20, 28]. Length of ICU stay were reported in 2 RCTs that enrolled a total of 228 patients with no differences [26, 36]. Extubation rate after 21 days was recorded in 1 RCT that enrolled a total of 107 patients: a lower rate of successful extubation were recorded in C-EN than in I-EN patients [26].

Discussion

This SR summarizes clinical evidence related to safety and efficacy of C-EN or I-EN in ICU patients. Recorded variables address 3 major subsets: effects on nutritional status, gastrointestinal symptoms and tolerance and respiratory tracts.

Evidence on nutritional status are controversial regarding the efficacy in nutrition supplying (i.e. days in whom “caloric prescribed goal” was achieved, amount of delivered feeding volume, time to achieve “caloric prescribed goal”)

Evidence on the effects on gastrointestinal symptoms or tolerance suggest that there are no differences in EN complications (diarrhea, vomiting, abdominal distension) but C-EN associates with lower GRV while I-EN associates with better evidence on digestive tract colonization and constipation.

Evidence on the effects on respiratory tract suggest that there are no differences in EN-related complications (pneumonia, changes in respiratory tract colonization and ICU length of stay). Despite most of the studies showed similar results in the rate of EN in TBA, in 1 study I-EN appears to be superior to C-EN for shorter duration of mechanical ventilation.

Of interest ASPEN and ESPEN suggestions, that address C-EN as possibly preferable, seems not supported by strong available evidence as also mentioned in the original document. The ASPEN report it as “expert consensus” and ESPEN refer to it as “grade B, strong consensus”. [37] In 2014 a SR, intended to report data on the effectiveness of C-EN or I-EN from studies published before January 2011, analyzed data from 5 RCTs and concluded that available evidences were insufficient to favor either C-EN or I-EN mode [38]. Compared to that SR, the present manuscript is more comprehensive and included data from 19 original studies. Still the available evidence is insufficient to define ultimate indications on which nutrition mode is associated with better safety and efficacy profile. The ESPEN guidelines were published in 2019 and were based on dedicated meta-analysis of 4 RCTs that enrolled a total of 236. According to the presented results, C-EN is associated with

lower incidence of diarrhea than I-EN [5]. In this SR we retrieved and presented a total of 12 studies presenting data on the incidence of diarrhea during C-EN or I-EN and the ultimate conclusions led to controversial evidence. Furthermore, several other conflicting results and methodological inconsistencies have now been highlighted.

Among the distinctive results of this SR is the huge difference in methodological approach used throughout the selected studies. More in particular, the study period ranged between 1 and 24 days; I-EN was administered in different modes in terms of times, flow rate and bolus feed administered; the exact amount of calories delivered was not uniform and calculated with different approach; the achievement of “prescribed caloric goal” was accepted as a different percentage to the total (from 75% to 100%); the cutoff used to record GRV (from 75 to 300 ml) was various and distant from the actual guidelines to define these complication (>500 ml)(Table 1). Moreover, most studies did notreport separately symptoms of gastrointestinal intolerance (diarrhea, vomiting, constipations) [37]. Beside these inconsistencies, it is important to note that there is an open controversy on the optimal nutritional composition [39-43].

Among the possible study limitations of this SR is the selective inclusion only of studies that recruited patients treated in ICU. The exclusion of studies in hospitalized patients treated outside the ICU and of studies in non-hospitalized patients, might have excluded evidence that are of potential interest. Despite this limitation, we consider the ICU cohort a unique subset of enterally fed patients, given the severity of their clinical condition. As such, clinical recommendations need to be based on studies carried out within this environment.

Another possible limitation is referable to the design of the selected studies. For this SR, we have considered suitable any study design and included RCTs but also prospective and retrospective observational studies. The Authors acknowledge the difference in the strength of evidence associated with various study design but, in order to present the most possible comprehensive data, have considered appropriate to report not only RCTs.

In conclusion, the evidence collected in this SR is not sufficient to provide clear indications on which nutritional mode, either C-EN or I-EN, should be preferred. Some results favor the use of C-EN (lower GRV and less need for prokinetic) while others support I-EN (better digestive tract colonization, lower constipation and less EN contamination of TBA secretions). Future studies should be dedicated to identify the benefits and limitations of C-EN or I-EN. The present SR can provide a background to design study protocols with an appropriate methodological approach and qualified endpoints.

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Table 1: Studies, number of patients, type of ICU and period of the selected studies

Studies	Type of study	Patients treated in C-EN group	Patients treated in I-EN group	Type of ICU	Study Period (days)	Target Energy supply
Trudy 1982[18]	RCT	8	5	NICU	24	N/A
Kocan 1986 [19]	RCT	17	17	NICU	10	Wilmore nomogram
Bonten 1996[20]	RCT	60	60	ICU, CS-ICU	14	N/A
Spilker 1996[21]	PO	13	13	ICU	5	N/A
Steevens 2002[22]	RCT	9	9	TICU	7	25-30 kcal/kg/day
Rhoney 2002[23]	RO	66	86	NICU	ns	Unit protocol
Gowardman 2003[24]	RCT	26 (12 +14) *	15	ICU	12	30 kcal/kg/day
Serpa 2003[25]	RCT	14	14	ICU	3	25 kcal/kg/day
Chen 2006[26]	RCT	51	56	ICU	7	25 kcal/kg/day
Mac Leod 2007[27]	RCT	81	79	TICU	7	25 kcal/kg/day

Tamowicz 2007[28]	RCT	20	20	ICU	10	N/A
Maurya 2011 [29]	RCT	20	20	NICU	1	30 kcal/kg/day
Abdelsalam 2012 [30]	PO	20	20	ICU	3	25 kcal/kg/day
Kadamani 2014[31]	RCT	15	15	ICU	3	N/A
Tavares De Araujo 2013 [32]	RCT	23	18	ICU	5	25-30 kcal/kg/day
Shahriari 2015 [33]	PO	25	25	ICU	4	Harris-Benedict equation
Evans 2016 [34]	RCT	24	26	ICU	17	N/A
Yagan 2017 [35]	RCT	19	18	ICU	14	Harris-Benedict equation
McNelly 2020 [36]	RCT	59	62	ICU	10	25 kcal/kg/day

Legend to Table 1.- * C-EN through nasogastric tube + C-EN through nasojejunal tube. RCT = randomized clinical trial; PO = prospective observational; RO = retrospective observational. ICU= General Intensive Care Unit; NICU= Neurological/Neurosurgery Intensive Care Unit; CS-ICU= Cardiac Surgery Intensive Care Unit; TICU= Trauma Intensive Care Unit

Table 2: Summery of the effects of C-EN or I-EN on nutritional status

Studies	Days in target nutrition/ total days C-EN vs I-EN	Total amount of delivered feeding volume C-EN vs I-EN	Time necessary to achieve prescribed caloric prescribed goal C-EN vs I-EN***	Serum Prealbumin (mg/dl) C-EN vs I-EN (baseline and final values)	Differences in BGC between C-EN and I-EN	Daily mean caloric intake between C-EN, I-EN and C-EN jejunal	Mean weight loss between C-EN and I-EN	Glucose variability and insulin utilization between C-EN and I-EN	Leptin and ghrelin blood levels between C-EN and I-EN	The RQ and REE between C-EN and I-EN	Patients achieving target of protein and caloric goal C-EN vs I-EN
Kocan 1986 [19]	-	-	4.2 vs 5.2 days 2nd	-	-	-	1.2 vs 1.6 kg 2nd	-	-	-	-
Steeve	0/7	-	-	12 ± 5	-	-	-	-	-	-	-

ns 2002 [22]	vs 2/7 1st			vs 11 ± 3 1st 14 ±10 vs 16 ±9							
Rhooney 2002 [23]	-	-	3.3 vs 4.6 days* 1s	-	-	-	-	-	-	-	-
Gowardman 2003[24]	-	-	-	-	-	553 vs 1173 vs 1461 * 1s	-	-	-	-	-
Serpa 2003 [25]	0/3 vs 1/3 1s	Day 1 614±169 vs 766±55 * 1s	-	-	-	-	-	-	-	-	-
Chen 2006 [26]	-	58% vs 92%** 1s	-	-	-	-	-	-	-	-	-
Mac Leod 2007 [27]	7/10 vs 6/10 1s	-	No difference between the 2 groups 1s	-	-	-	-	-	-	-	-
Maurya 2011 [29]	-	-	-	-	-	-	No differences 1s	-	-	0.8 vs 0.86 / 1527 vs. 1599 kcal/ day 1s	-

Abdelsalam 2012 [30]	-	Day 1 657±43 vs 745±16* 1[s]	-	-	-	-	-	-	-	-	-
Tavares De Araujo 2013 [32]	4.2/5 vs 4.4/5 1[s]	-	-	-	-	-	-	-	-	-	-
Shahriari 2015 [33]	-	-	-	23 vs 22; 25 vs 22* 1[s]	-	-	139 vs 140 and 131 vs 140** 1[s]	-	-	-	-
Evans 2016 [34]	-	No differences	37 h vs 42 h 1[s]	-	-	-	-	No differences 1[s]	-	-	-
Yagan 2017 [35]	-	-	-	9.7 vs 9.9; 10.6 vs 11.4 1[s]	-	-	-	-	5.1±0.5 vs 4.9±0.4 ng and 2787±253 vs 3730±294pg 1[s]	-	-
McNelly 2020 [36]											69,9 % vs 80,3 % and 72,5 % vs 82,4 %

Legend to Table 2

BGC: Blood Glucose Concentrations; ** number of patients with feeding volume administered >1000 ml/day; ***100% (19), 80% (22,34) and 75% (23) of caloric prescribed.

Differences in BGC between C-EN and I-EN: First day and last day values of study period were reported. 1[s] First outcome; 2[nd] Secondary recorded variable

* p<0.05

Table 3 Summary of the effects of C-EN or I-EN on gastrointestinal symptoms or tolerance

Studies	Frequency of stool	Consistence of stool	Amount of stool	Differences between C-EN and I-EN	Cut off of GRV	Times wich GRV was checked	Difference of GRV between C-EN vs I-EN	Patients with at least 1 episode of vomiting (C-EN vs I-EN)	Patients with abdominal distention (C-EN vs I-EN) *****	Patients with constipation (C-EN vs I-EN) ******	Gastric pH between C-EN vs I-EN patients *******
Trudy 1982[18]	2 or more/24 h	Liquid, unformed	N/A	6/8 vs 2/5 1[s]	-	-	-	-	-	-	-
Kocan 1986 [19]	n/24 h	Walike Scale (W.S.)	N/A	1.56/day and 3.69 W.S. vs 1.48/day and 3.97 W.S. 1[s]	>100 ml **	Every 4 h	15.8 ml vs 21.8 ml*** 1[s]	-	-	-	-
Bonten 1996[20]	-	-	-	-	-	-	-	-	-	-	3.2 vs 2.5* (GM) 1[s]
Spilker 1996[21]	-	-	-	-	-	-	-	-	-	-	N/A (GM) 1[s]
Steevens 2002[22]	3 or more/24 h	Liquid	>250 ml	2/9 vs 5/9 1[s]	>300 ml **	Every 4 h or before	33% vs 55%****	-	-	-	-

						start feeding (I-EN)	1[s]				
Rhoney 2002[23]	1-2/24 h	Liquid	N/A	10/66 vs 15/86 1[s]	>75 ml	Every 4 h	40.4% vs 55.6%*** 1[s]	-	-	-	
Goward man 2003[24]	-	-	-	-	>200 ml**	Every 4 h	751 vs 540 vs 866 ml*** 2[nd]	-	-	-	5.2 vs 4* 1[s]
Serpa 2003[25]	n/24 h	N/A	N/A	1/14 vs 4/14 1[s]	>150 ml**	Every 3 h	N/A	2/14 vs 2/14 1[s]	4/14 vs 5/14 1[s]	-	-
Chen 2006[26]	-	-	-	-	>60 ml	Every 4h or before start feeding (I-EN)	19.6% vs 10.7%*** 1[s]	-	-	-	-
Mac Leod 2007[27]	N/A	N/A	N/A	3/81 vs 5/79 2[nd]	>200 ml**	Every 4 h	N/A 2[nd]	-	-	-	-
Tamowicz 2007[28]	-	-	-	-	-	-	-	-	-	-	5.2 vs 4* (GM) 1[s]
Maurya 2011 [29]	N/A	N/A	N/A	0/20 vs 2/20 2[nd]	>200 ml	Every 4 h (C-EN) and every 3 h (I-EN)	37±32 vs 73±32 ml*; *** 2[nd]	-	-	-	-
Abdelsalam 2012 [30]	N/A	N/A	N/A	4/20 vs 3/20 2[nd]	-	-	-	1/20 vs 4/20	N/A	-	-

								2nd			
Kadamani 2014[31]	3 or more/24 h	N/A	N/A	6/23 vs 5/18 1s	>200 ml	Every 4 h	13.3% vs 20% 1s	-	-	10/15 vs 3/15 * 1s	-
Tavares De Araujo 2013 [32]	N/A	N/A	N/A	6/23 vs 5/18 2nd	>250 ml**	Before start feeding	No cases of GRV	7/23 vs 4/18 2nd	-	-	-
Yagan 2017 [35]	N/A	N/A	N/A	2/19 vs 1/18 2nd	>250 ml	Every 4-6 h	10% vs 5% 2nd	0/19 vs 2/18 2nd	-	-	-
McNelly 2020 [36]	N/A	Bristol Stool Chart score	N/A	4/59 vs 0/62 2nd	>300 ml**	-	N/A	-	16/59 vs 5/62 2nd	5/59 vs 0/62 2nd	-

Legend to Table 3.- ** Studies in those GRV was a reason to stop EN; *** Amount of volume over the cut-off of GRV; **** % of patients over the cut-off of GRV of C-EN vs I-EN group. ***** Defined as an abdominal circumference increased 3 cm or more; ****** Defined as absent bowel movement for three consecutive days or more; ******* Administration of I-EN vs interruption; GM= Use of gastric medication (sucralfate, proton pomp inhibitor, ranitidine, etc..); 1s First outcome; 2nd Secondary recorded variable; * p<0.05

Table 4: Summary of the effects of C-EN or I-EN on respiratory tract

Studies	Diagnosis of presence of EN in TBA secretion	Patients with presence of EN in TBA secretion C-EN vs I-EN	Diagnosis of Pneumonia	Patients with pneumonia C-EN vs I-EN	Extubation rate patients C-EN vs I-EN
Trudy 1982[18]	Blue aniline, breath sounds reduction Cyanosis, X-ray	2/8 vs 1/6 1s	-	-	-
Kocan 1986 [19]	Blue aniline	1/9 vs 3/11 1s	-	-	-
Bonten 1996[20]	-	-	X-ray, fever, presence of microorganism in TBA secretions	3/30 vs 5/30 1s	-

Steevens 2002[22]	Blue aniline	0/9 vs 1/9 1[s]	-	-	-
Rhoney 2002[23]	-	-	X-ray, fever leukocytosis and dyspnea	N/A 1[s]	-
Serpa 2003[25]	Blue aniline, symptoms, X-ray	1/14 vs 1/14 1[s]	X-Ray, Symptoms	N/A	-
Chen 2006[26]	Blue aniline, Pulmonary aspiration index: glucose in sputum, wheezing, fever, aspiration pneumonia patchs in x-ray	25, 18,18, 26/51 vs 13, 8, 15, 8/56; * 1[s]	-	-	16/51 vs 34/56* 2[nd]
Mac Leod 2007[27]	-	-	N/A	33/81 vs 38/79 2[nd]	-
Tamowicz 2007[28]	-	-	X-ray, fever, leukocytosis, pO2 reduction	7/20 vs 4/20 1[s]	-
Maurya 2011 [29]	N/A	0/20 vs 0/20 2[nd]	-	-	-
Abdelsalam 2012 [30]	Blue aniline, X-Ray	0/20 vs 0/20	X-ray	0/20 vs 0/20 1[s]	-
Kadamani 2014[31]	Blue aniline, desaturation, cyanosis	0/15 vs 0/15 1[s]	-	-	-

Legend to table 4.- 1[s] First outcome; 2[nd] Secondary recorded variable; * p<0.05

Table 5.- Risk of Bias in RCT

I.D	Sequence generation	Allocation Concealment	Blinding of participants, personnel and outcome assessor	Incomplete outcome data	Selective outcome reporting	Others criteria

Trudy 1982[18]	H	U	U	H	L	U
Kocan 1986 [19]	H	U	U	L	L	H
Bonten 1996[20]	L	L	U	L	L	U
Steevens 2002[22]	L	U	U	L	L	U
Gowardman 2003[24]	L	L	U	L	L	U
Serpa 2003[25]	U	L	U	U	L	H
Chen 2006[26]	U	L	U	L	L	U
Mac Leod 2007[27]	L	L	U	L	L	L
Tamowicz 2007[28]	U	L	U	L	L	U
Maurya 2011 [29]	L	L	U	L	U	L

Kadamani 2014[31]	U	L	U	L	L	H
Tavares De Araujo 2013 [32]	U	L	U	L	L	U
Evans 2016 [34]	L	L	U	L	L	U
Yagan 2017 [35]	L	L	U	L	U	L
McNelly 2020 [36]	L	L	H	U	H	H

Legend to Table 6: L (low risk of bias); H (high risk of bias); U (unclear risk of bias).

Table 6.- Risk of Bias of non RCT

I.D	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Spilker 1996[21]	M	U	L	M	U	L	L
Rhoney 2002[23]	M	L	M	L	M	L	L
Abdelsalam 2012 [30]	L	M	S	L	L	M	L
Shahriari 2015 [33]	M	L	M	M	L	L	L

Legend to Table 7. L (low risk of bias); M (moderate risk of bias); S (serious risk of bias); C (critical risk of bias); U (unclear risk of bias)

Figure 1 PRISMA summary literature search