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Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005489.
DOI: 10.1002/14651858.CD005489.pub2.

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[Intervention Review]

Early versus delayed enteral nutrition support for burn injuries

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Editorial group: Cochrane Injuries Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Wasiak J, Cleland H, Jeffery R. Early versus delayed enteral nutrition support for burn injuries. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005489. DOI: 10.1002/14651858.CD005489.pub2.

ABSTRACT

Background

A burn injury increases the body's metabolic demands, and therefore nutritional requirements. Provision of an adequate supply of nutrients is believed to lower the incidence of metabolic abnormalities, thus reducing septic morbidity, improving survival rates, and decreasing hospital length of stay. Enteral nutrition support is the best feeding method for patients who are unable to achieve an adequate oral intake to maintain gastrointestinal functioning, however, its timing (i.e. early versus late) needs to be established.

Objectives

To assess the effectiveness and safety of early versus late enteral nutrition support in adults with burn injury.

Search methods

We searched Cochrane Injuries Group's Specialised Register (Dec 2007), CENTRAL (*The Cochrane Library,* issue 4, 2007), MEDLINE (1966 to December, 2007), EMBASE (1980 to December 2007) and CINAHL (1982 to May, 2006).

Selection criteria

We included all randomised controlled trials comparing early enteral nutrition support (within 24 hours of injury) versus delayed enteral support (greater than 24 hours).

Data collection and analysis

Two authors used standardised forms to independently extract the data. Each trial was assessed for internal validity with differences resolved by discussion.

Main results

A total of three randomised controlled trials were eligible for inclusion in this review. Results of the studies indicate that evidence about the benefit of early enteral nutritional support on standardised clinical outcomes such as length of hospital stay and mortality, remains inconclusive. Similarly, the question of whether early enteral feeding influenced or decreased metabolic rate as documented in part by our included studies, remains uncertain.

Authors' conclusions

This systematic review has not found sufficient evidence to support or refute the effectiveness of early versus late enteral nutrition support in adults with burn injury. The trials showed some promising results that would suggest early enteral nutrition support may blunt the hypermetabolic response to thermal injury, but this is insufficient to provide clear guidelines for practice. Further research incorporating larger sample sizes and rigorous methodology that utilises valid and reliable outcome measures, is essential.

PLAIN LANGUAGE SUMMARY

Do burns patients who receive early (within 24 hours) nutritional support have better outcomes than those whose nutritional support is delayed (after 24 hours)?

Adult patients with large burns have increased nutrition and energy requirements. If such requirements are not met, it is associated with worse health outcomes including increased infection rates and poorer healing. Patients are often not able to meet the increased requirements through oral feeding alone, thus enteral feeding is often used. Enteral nutrition is provided by inserting a feeding tube via the nose or mouth, into the stomach or small intestine. The feeding tube delivers a liquid formula (enteral nutrition) containing the required nutrients. Enteral feeding is continued until sufficient oral intake is established to meet the patient's need.

Enteral nutrition is essential for the successful management of the burns patient, however there is debate regarding the optimal method and timing of feeding. It is unclear whether providing enteral nutrition from an early stage after injury is preferable to delaying such support. The authors of this review attempted to resolve this uncertainty by examining all high quality trials comparing the effectiveness of initiating enteral nutrition in the early stages after injury (within 24 hours), with delayed (after 24 hours) enteral nutrition, in burns patients over the age of 16 years.

The authors found three studies involving 70 adult burn patients. The results of the studies provide no conclusive evidence for the benefit of early enteral nutritional support compared to delayed support, on outcomes such as length of hospital stay and mortality.

The trials involved a small number of participants and were limited by methodological weaknesses. There is a need for larger, high quality research into the use of early versus delayed feeding in burn patients.

Overall, the authors conclude that there is currently little evidence to support the use of early nutritional support, but more trials are needed.

BACKGROUND

The type of formula and the timing of enteral nutrition support in patients with thermal injuries has long been debated. What is known is that burn injury can result in profound metabolic abnormalities, and that malnourishment is associated with increased infection risks, decreased healing rates, and altered cell function. The rapid removal of devitalized burn tissue, combined with early nutritional support, appears to significantly attenuate this auto-destructive process (Demling 2000).

After the thermal injury has occurred a cascade of events are set in motion. An initial "Ebb" phase occurs immediately after the thermal injury, and corresponds to a period of hypovolaemia and tissue hypoxia, poor cardiac output and increased oxygen consumption. The "Flow" phase occurs within 12 to 24 hours post initial insult as the patient is fluid resuscitated and a return of an adequate oxygen transport occurs. At this stage an increase in glucose production and free fatty acid release takes place (Mahan 1996). The metabolic response to burns is complex and is illustrated by an accelerated catabolism leading to a negative nitrogen balance and loss of lean body tissue (primarily skeletal muscle).

Patients with large burns have significant energy requirements. Basal metabolic rates can double when burns are greater than 50% total body surface area (TBSA). These patients, as well as those with inhalation injury who require mechanical ventilation, are not able to meet their requirements for macro- and micronutrients and fluids via the oral route. Under these circumstances, enteral nutrition support is indicated.

Enteral nutrition is provided by placing a flexible feeding tube via the nose, mouth or a formed tract (i.e. gastrostomy) into the stomach or proximal small intestine. The feeding tube delivers liquid nutritional formula (enteral nutrition), which contains macro- and micronutrients. Enteral nutrition will be provided until sufficient oral intake is established to meet the patient's requirements.

The Eastern Association for the Surgery of Trauma (EAST) group (EAST 2001) recommends that enteral nutrition should ideally begin during resuscitation in a patient with severe burns, but because delays (>18 hours) result in a high risk of gastroparesis and need for intravenous nutrition, a fear of complications normally delays enteral support until after the resuscitation period has transpired (McDonald 1991).

Although providing nutrition is clearly essential in the successful management of the burn injured patient, there are several conflicting findings amongst research groups regarding the optimal method and timing of enteral nutritional support. Although providing early nutritional support has a number of advantages including increased caloric intake (Gottschlich 2002) and improving bowl mucosal integrity (Peng 2001), it has remained unclear whether early enteral nutritional support has any beneficial impact on a diverse field of nutritional, metabolic and biochemical outcomes and clinical indicators such as length of stay, infection rates and mortality (Peck 2004). In addition, it has been suggested that more complications occur with early enteral support than late enteral support, including the risk of intestinal necrosis (Gottschlich 2002).

As suggested by Peck 2004 the result of these and other studies reveal that the clinical efficacy of early enteral nutrition and its effect on metabolic, and hormonal and biochemical markers, remains unresolved. While the provision of enteral nutritional support in patients with major burn injuries continues to be an accepted therapeutic modality, there is an urgent need to review the evidence regarding its safety and efficacy, optimal timing and formulation.

OBJECTIVES

The objective of this review was to establish the relative safety and effectiveness of early versus delayed enteral nutrition support in patients with burn injuries.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) that evaluated the safety and effectiveness of early versus delayed nutritional support in patients with burn injury.

Types of participants

We focused on adults (>16 years) with any burn injury to the epidermis, subcutaneous tissues, vessels, nerve, tendons, or bone.

Types of interventions

Trials comparing early enteral nutritional support (within 24 hours of injury) versus late enteral nutritional support (greater than 25 hours). In this instance, enteral nutrition (EN) was defined as the delivery of a liquid nutritional formula, which contains macro- and micronutrients such as carbohydrates, fat, protein, vitamins, mineral and trace elements that passes any part of the digestive tract, regardless of the method of deliver (e.g. nasogastric, naso-jejunal, naso-enteric, oro-gastric, PEG or jejunal feeding tubes). Studies examining combined enteral and oral supplementation feeding regimes were also included.

Types of outcome measures

Clinically important measures of effectiveness were selected as follows:

Primary outcomes

1. All cause mortality at end of follow-up
2. Length of hospital stay
3. Frequency of infection
4. Number of adverse events such as bowel necrosis, acute respiratory distress syndrome, renal failure, multisystem organ failure

Secondary outcomes

1. Weight
2. Biochemical markers such as albumin, white cell count and C-reactive protein

(Secondary parameters such as those listed above were considered if reported in the studies.)

Search methods for identification of studies

The searches were not restricted by date, language or publication status.

Electronic searches

We searched:

Cochrane Injuries Group's Specialised Register (Dec 2007),
CENTRAL (*The Cochrane Library,* issue 4, 2007),
MEDLINE (1966 to December, 2007),
EMBASE (1980 to December, 2007),
CINAHL (1982 to May, 2006),
Zetoc (searched 4th December 2007).

Details of the search strategies can be found in Appendix 1.

Searching other resources

In addition, we contacted experts in the field of burns and nutrition and contacted authors of relevant trials to identify any unpublished or ongoing studies.

Data collection and analysis

Selection of studies

Records retrieved by the initial search were scanned by JW, RJ and HC to exclude obviously irrelevant studies, and then two authors (JW and RJ) identified trials that may have met the inclusion criteria. Full-text articles were retrieved and reviewed by two authors (JW and RJ) for the purpose of applying inclusion criteria independently. In all instances, differences of opinion were resolved by discussion among the authors.

Data extraction and management

Data from the studies were extracted independently by two authors (JW and RJ) using standardised forms. The author of one primary study was contacted to provide information when missing or incomplete data was encountered. All differences were resolved by discussion among the review authors.

Assessment of risk of bias in included studies

Study quality was assessed using an adaptation of the method outlined in Schulz 1995. Results from the study quality are presented in a descriptive manner. The following characteristics were assessed:

- Method of randomisation;
- Allocation concealment;
  - A) *Adequate* - measures to conceal allocations such as central randomisation; serially numbered, opaque sealed envelopes; or other description that contained convincing elements of concealment;
  - B) *Unclear* - in which the author either did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories in A);
  - C) *Inadequate* - such as alternation methods or use of case record numbers;
- Patient baseline characteristics;
- Blinding (of treatment provider, patient, outcome assessor);
- Intention-to-treat analysis;
- Loss to follow-up.

Assessment of heterogeneity

We used a fixed-effect model where there was no evidence of significant heterogeneity between studies and planned to use a random-effects model when such heterogeneity was likely (DerSimonian 1986). Consideration was to be given to the appropriateness of meta-analysis in the presence of significant clinical or statistical heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic and consideration was given to the appropriateness of pooling and meta-analysis. Heterogeneity was to be explored and subgroup analyses performed, if appropriate.

Assessment of reporting biases

Publication bias was to be tested using funnel plots; however, this was not appropriate given the small number of studies located.

Data synthesis

For proportions (dichotomous outcomes), relative risk (RR) was used. Continuous data were converted to the mean difference (MD) using the inverse variance method and an overall MD calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned based on method of feeing i.e. jejunal versus gastric, nasogastric versus naso-jejunal by calculation of RR or MD in each subgroup and examination of the 95% confidence intervals (CI). Non-overlap in intervals were planned to be taken to indicate a statistically significant difference between subgroups; however, no subgroup analysis was appropriate with the data available. An intention-to-treat analysis was to be performed where possible.

RESULTS

Description of studies

A total of 192 references have been identified (to Dec 2007). Independent scrutiny of the titles and abstracts identified 18 potentially relevant articles. Of the 18 articles assessed in full text form, 15 were excluded because they used: feeds other than enteral alone i.e. total parenteral nutrition (Enzi 1990; Taylor 1999; Chen 2006), explored immediate feeding only (McArdle 1984), examined mixed populations such as paediatric or adults populations, or both (Engelhardt 1994; Gottschlich 2002; Hart 2003; McDonald 1991), study designs such as case reports, case series (Andel 2001; Chiarelli 1990; Garrel 1991; Hansbrough 1993; Kaufman 1986; Koller 1994; Noordenbos 2000). The remaining three studies by Peck 2004; Peng 2001 and Wang 1997 formed the basis of the review.

In Peck 2004, 27 patients (19 men) between 18 and 50 years of age admitted within 24 hours burn injury with at least 20% injuries total body surface area (TBSA) were randomised to either early enteral feeding (within 24 hours) or delayed enteral feeding (between 24 hours and seven days). A commercial feeding formula was used with the rate of the infusion increased every six hours as tolerated until the goal rate was achieved. Patients were allowed oral intake as tolerated, stressing complex carbohydrates and protein-containing fluids and foods, minimizing fluids with simple sugars. All patients were treated according to practice guidelines set out by the American Burn Association protocols; fluid resuscitation, topical wound care with silver sulphadiazine cream during the

first week, and active physical and occupational therapy. This trial reported on a series of clinical outcome measures such as number of infections, number of antibiotic days, length of stay and mortality and energy balance such as resting energy expenditure and basal energy expenditure.

In Peng 2001, 22 patients (15 men) with burns ranging from 50% to 80% TBSA were randomised to either early enteral feeding (within 24 hours) or delayed enteral feeding (after 48 hours). A commercial feeding formula was given via a nasogastric tube or orally as early as possible in the early enteral group (70-80ml/3h in the first 24 hour post-burn, 0.75 kcal/ml, and 100-150 ml/2h in the second 24 hour post-burn, 0.75-1 kcal/ml). The delayed enteral feeding group was given an orally administered liquid diet after 48 hour post-burn. The trial reported on a series of secondary outcome measures such as plasma endotoxin, tumour necrosis factor - alpha (TNF-a) and tumour necrosis factor - interleukin 8 (TNF-IL8) levels.

In Wang 1997, 21 patients (18 males) between 18 and 51 years of age with burns equal to or more than 30% TBSA were randomly assigned to either early enteral feeding (within 12 hours) and delayed enteral feeding (between 12 and 72 hours). Patients allocated to early enteral feeding received a commercial feeding formula given via the oral route or nasoduodenal tube. The trial reported on a series of metabolic and biochemical markers such as resting energy expenditure (REE) and TNF-a and TNF-IL8 levels.

Risk of bias in included studies

Randomisation

Randomisation procedures were not reported in any of the three studies.

Allocation concealment

Allocation concealment was unclear in all of the studies.

Patient baseline characteristics

Burn depth was not described in any of the studies, although estimates of burn size were provided by all three studies. Within the studies, patients were generally well matched for sex, age, and size of burn injury.

Blinding

None of the trials described blinding of investigators or outcome assessors.

Intention-to-treat analysis

None of the studies reported any violation of the allocated treatment.

Loss to follow-up

One study (Peck 2004) reported on losses to follow-up. None of the remaining studies suffered any losses to follow-up.

Effects of interventions

Primary outcomes

1. All cause mortality at end of follow-up

Only one trial contributed results to this outcome (Peck 2004) involving nine subjects (33% of the total study population), four (28%) were randomised to early enteral nutritional support and five (38%) to late enteral nutritional support. There was no difference in all cause mortality between the two groups (RR 0.74; 95% CI 0.25 to 2.18; P=0.59).

2. Length of stay

Only one trial contributed results to this outcome (Peck 2004). There was no difference in overall length of stay (P=1.00) and number of days in intensive care (WMD 3.00 days; 95% CI -21.55 to 27.55; P=0.81) between those receiving early enteral nutritional support and those receiving late enteral nutritional support.

3. Frequency of infection

Only one trial contributed results to this outcome (Peck 2004). There was no difference in number of infections or number of antibiotic days between those receiving early enteral nutritional support and those receiving late enteral nutritional support (P=1.00).

4. Number of adverse events

Only one trial contributed results to this outcome (Peck 2004). There was no significant difference between those receiving early enteral nutritional support and those receiving late enteral nutritional support with respect to tube feeding tolerance (P=1.0), incidence and duration of diarrhoea, (WMD 4.00 days; 95% CI -12.22 to 4.22; P=0.34) aspiration events (RR 0.19; 95% CI 0.01 to 3.56, P=0.26), or the need for TPN (RR 2.32; 95% CI 0.54 to 9.95; P=0.26).

Secondary outcomes

1. Weight

Only one trial contributed results to this outcome (Peck 2004). Data represented as an 'average change per week' showed no significant difference in body weight between those receiving early enteral nutritional support and those receiving late enteral nutritional support (-1.3kg with early enteral support versus -1.2kg with late enteral support; P=0.9).

2. Nutritional markers

Only one trial contributed results to this outcome (Peck 2004). Data represented as an 'average change per week' showed no significant difference in transthyretin (1.3mg/dL with early enteral support versus 1mg/dlL with late enteral support; P=0.5), transferrin (2.0mg/dL with early enteral support versus 5mg/dlL with late enteral support; P=0.2), and urine urea nitrogen (-383mg/24hrs with early enteral support versus 12mg/24hrs with late enteral support; P=0.2) levels in those receiving early enteral nutritional support and those receiving late enteral nutritional support.

3. Metabolic markers

Resting energy expenditure (REE) was reported in one trial (Wang 1997). The authors noted a decrease, on average of 27%, on post burn day four, eight, and 14 respectively in those receiving early enteral nutritional support than those receiving late enteral nutritional support (P<0.05). A second study by Peck 2004 adjusted REE by standardizing basal energy expenditure using the Harris-Benedict equation and reported on daily energy expenditure (DEE) instead. Result showed no significant trend for DEE in either group, although the estimated DEE in the early group tended to be higher rather than lower than the estimated mean DEE in the late group

(1.56 versus 1.42, representing a difference of 0.14; P=0.23). When adjusted for %TBSA, inhalation injury and age, the trend for a higher estimated mean DEE in the early group compared with the late group persisted (mean difference 0.17; P=0.07).

4. Biochemical markers

Two studies (Peng 2001; Wang 1997) examined the effects of early enteral nutrition using biochemical markers such as plasma endotoxin and tumour necrosis factor - alpha and interleukin 8 (TNF-a, TNF-IL8) levels. However, the data from these studies could not be pooled as there were variations in the monitoring and recording of these results. One study (Peng 2001) examined changes in endotoxin and TNF levels and the other study (Wang 1997) examined the content of endotoxin and TNF in plasma.

Wang 1997 showed that serum endotoxin levels in the early nutritional support group were lower on post burn days four, eight and 14 than those who received late enteral nutritional support (P<0.05). Similar reports of endotoxin levels being lower in those receiving early nutritional support group were also noted by Peng 2001 in a series of different time points (i.e. one to six hours, seven to 12 hours, 24 hours, 36 hours, three and five days).

Markers such as TNF-a and TNF-IL8 was seen to be significantly elevated after burn injury in both studies. In Peng 2001, the serum TNF-a levels in both groups were significantly higher than in normal controls (P<0.001). The serum TNF-a levels in those receiving late enteral nutritional support continued to rise after burn injury and reached their highest level at 24 hours post-burn. Following a small decline at day three post-burn, the serum TNF-a levels increased gradually and reached another highest level at day five post-burn. The serum TNF-a level in those receiving early enteral nutritional support increased slower after burn injury (P<0.001). In Wang 1997, TNF-IL8 was lower in those receiving early enteral nutritional support during various time points (P <0.05 to 0.01).

5. Hormonal markers

Only one trial contributed results to this outcome (Wang 1997). Plasma glucagon, cortisol and urinary catecholamine levels were reportedly lower in those receiving early enteral nutritional support (P<0.05 to 0.01).

DISCUSSION

This systematic review summarises the best available evidence relating to safety and effectiveness of early versus delayed nutritional support in adult patients with burn injury. After an extensive search of the literature, we found three RCTs.

Our results highlighted the need for high level, good quality research into the safety and effectiveness of early versus delayed enteral nutritional support in adults with burn injury. There was wide variation amongst the studies in the timing of the initiation of both early and late enteral nutritional support and the type of clinical, metabolic and hormonal outcome measures used to determine effectiveness. All of the trials were prone to a number of methodological shortcomings including a lack of power to detect useful clinical differences between intervention groups. More importantly, the small sample sizes in all three studies may have precluded any definitive statement on definition, safety or frequency of adverse events.

The evidence regarding the benefit of early enteral nutritional support on standard clinical outcomes such as number of infections, length of hospital stay and mortality, remains inconclusive. Similarly, the question of whether early enteral feeding influenced or decreased hyper-metabolism, remains uncertain. This uncertainty is coupled with a number of previously published studies which showed little or no improvement in the reduction of burn hypermetabolism. For example, it was Eyer 1993 who first suggested that enteral nutrition did not attenuate the hyper-metabolic response to injury and Gottschlich 2002 who reported that although early enteral feeding reduced caloric deficits, it did not show a reduction in morbidity, mortality, hyper-metabolism, hospital stay or endocrine status. More so, Hart 2003 suggested that those who underwent late enteral feeding and burn wound excision had a decreased metabolic rate compared with the early feeding and excision group, but this effect was eliminated once delayed group patients were fed and underwent excision. Although there was a suggestion of fewer infections in the early group, no difference was reported between groups in regards to body mass index, length of stay or mortality. More recently with our included study by Peck 2004, early enteral feeding did not reduce post-burn hyper-metabolism nor did it show any difference between groups in regards to number of infections, antibiotic and ventilator days, overall length of stay and mortality.

Peck 2004 would suggest that the ambiguity surrounding this clinical phenomenon could be due to a lack of understanding surrounding the molecular mechanism of the hypermetabolic response to burn injury. It appears that approximately 60% of the increased metabolic response to burn injury is attributable to an increased protein synthesis, gluconeogenesis, urea production, and substrate cycling (Yu 1999). The remaining 40% may be attributable to Na+-K+- ATPase activity and proton leakage across the mitochondrial membrane. This understanding, coupled with recent data on the beneficial effect of beta-blockade (Herdon 2001) and oxandrolone (Wolf 2003) on reversing skeletal muscle catabolism would therefore suggest that the reversal of post-burn hyper-metabolism would require more than early enteral nutritional support alone (Peck 2004).

Additionally, the frequency of monitoring the metabolic, hormonal and biochemical markers differed between the studies. In some studies monitoring was observed at day one, four, eight and 14 post burn injury, whilst in others monitoring was done on a weekly basis. This could have led to either early detection and possible treatment or possibly an inflated incidence in some cases leading to no treatment or insufficient time for the treatment to take effect.

The ambiguity surrounding the reduction in hyper-metabolism was still over-shadowed by gaps in knowledge surrounding when early nutritional support (i.e. timeliness of initiation of support) must be started to achieve benefit. Classic animal studies (Dominnioni 1984; Mochizuki 1984) revealed impressive findings such as decreases in the hyper-metabolic response to tissue injury, lower levels of circulating stress hormones (i.e. glucagons, cortisol and norepinephrine), increased gastrointestinal blood flow, and the ongoing preservation of intestinal mucosal integrity when animals were fed within two hours of burn injury. Although we hoped our systematic review would help clarify this issue in humans, optimal timing for the initiation of enteral nutrition support still represented an important, unresolved issue. The time to initiate feeding varied from within 24 hours (Peng 2001) and up to seven

days post burn injury for late enteral nutritional support (Peck 2004). These variations suggest that early feeding may be difficult to achieve in burn injured patients given the transport and emergency and resuscitation measures required to stabilise a patient with a severe burn.

A number of complications were noted by Peck 2004 although these were not seen to be significant. This was in direct contrast to other studies in the literature that suggested early enteral nutrition support could lead to devastating complications such as bowel necrosis (Gottschlich 2002).

Overall, the evidence would suggest that a degree of vigilance be taken when commencing an early feeding regime, although this is tempered with authors such as Gottschlich 2002 who believe that the provision of enteral nutrition is an important intervention that can be started within a few hours. Peck 2004 purports if this is to be done, it should be done with the knowledge that there appears to be no obvious metabolic or clinical benefit. As a result, current wisdom would then propose that the need for ongoing future research that includes conducting large multi-centre, randomised, double-blind studies, determining precise feeding implementation times, rate of feeding progression, consistent feeding practices (i.e. polymeric versus elemental, fibre enriched, immune-enhancing) coupled with a number of key outcome measures is needed which in turn would allow for pooling of data in a meta-analysis.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review suggest that early feeding may be associated with blunting the hypermetabolic response to burn injury, but the trials were small and prone to a number of methodological shortcomings. More RCTs are needed.

Implications for research

This systematic review highlights the need for further high level, good quality research into the use of early versus delayed feeding burned injured patients. Suggestions for future research include precise feeding implementation times, conducting appropriately powered studies, and selecting uniform and objective outcome measures which will allow for pooling of data in a meta-analysis.

ACKNOWLEDGEMENTS

Doris Lam for help with translation.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Peck 2004

Methods	Randomised controlled trial with patients assigned to one of two groups (i.e. early vs. late enteral nutritional support). Randomisation, allocation concealment , blinding of subjects and investigators (including outcome assessors) not reported.
Participants	27 patients (19 men) between 18 and 50 years of age admitted within 24 hours of burn injuries of 20% TBSA.
Interventions	Early enteral feeding (fed within 24 hours) or late enteral feeding (fed within 7 days) of a commercial feeding formula. Oral intake as tolerated.
Outcomes	Weight, calorie consumption, number of infections, number of antibiotic days, length of acute stay days, number of ICU days, mortality and basic laboratory markers such as transthyretin, transferrin, urine urea nitrogen.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Peng 2001

Methods	Randomised controlled trial with patients assigned to one of two groups (i.e. early vs. late enteral nutritional support). Randomisation, allocation concealment , blinding of subjects and investigators (including outcome assessors) not reported.
Participants	22 patients (15 men) with burn injuries of 50% to 80% TBSA with non-inhalation injuries and gastrointestinal tract disease.
Interventions	Early enteral feeding (fed within 24 hours) or late enteral feeding (fed after 48 hours) of a commercial feeding formula. Oral intake as tolerated.
Outcomes	Biochemical markers such as endotoxin and tumour necrosis factor - alpha and interleukin 8 (TNF - a; TNF - IL8) levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wang 1997

Methods	Randomised controlled trial with patients assigned to one of two groups (i.e. early vs. late enteral nutritional support). Randomisation, allocation concealment , blinding of subjects and investigators (including outcome assessors) not reported.
Participants	21 patients (18 males) between 18 and 51 years of age with burns equal to or more than 30% TBSA.
Interventions	Early enteral feeding (fed within 12 hours) or late enteral feeding (fed within 72 hours) of a commercial feeding formula. Oral intake as tolerated.
Outcomes	Resting energy expenditure and basic laboratory markers such as plasma glucagon, cortisol and urinary catecholamines. Biochemical markers such as endotoxin and tumour necrosis factor - alpha and interleukin 8 (TNF - a; TNF - IL8) levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

TBSA: Total burn surface area

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andel 2001	Case series rather than an RCT.

Study	Reason for exclusion
Chen 2006	1. It had feeds other than enteral nutrition alone (i.e. parenteral nutrition). 2. Timing of late enteral nutritional support not defined. Appears only to address early enteral support.
Chiarelli 1990	Case control rather than an RCT.
Engelhardt 1994	Mixed populations (i.e. adult or paediatric participants, or both).
Enzi 1990	Feeds other than enteral nutrition alone (i.e. parenteral nutrition).
Garrel 1991	Case series rather than an RCT.
Gottschlich 2002	Mixed populations (i.e. adult or paediatric participants, or both).
Hansbrough 1993	Case series rather than an RCT.
Hart 2003	Mixed populations (i.e. adult or paediatric participants, or both).
Kaufman 1986	Case series rather than an RCT.
Koller 1994	Case series rather than an RCT.
McArdle 1984	Immediate enteral nutrition, no comparator.
McDonald 1991	Case series plus mixed populations (i.e. adult or paediatric participants, or both).
Noordenbos 2000	Case series rather than an RCT.
Taylor 1999	Mixed populations (i.e. adult or paediatric participants, or both).

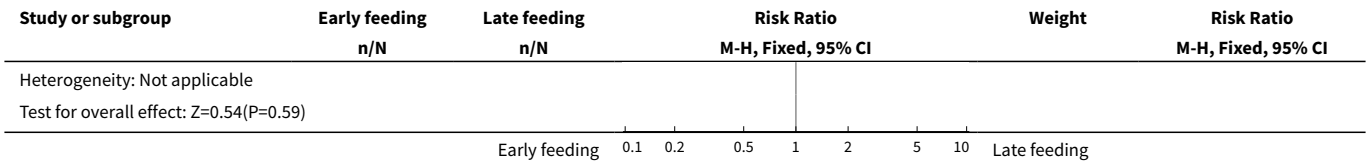
DATA AND ANALYSES

Comparison 1. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cause mortality at end of follow-up	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.25, 2.18]

Analysis 1.1. Comparison 1 Death, Outcome 1 All cause mortality at end of follow-up.

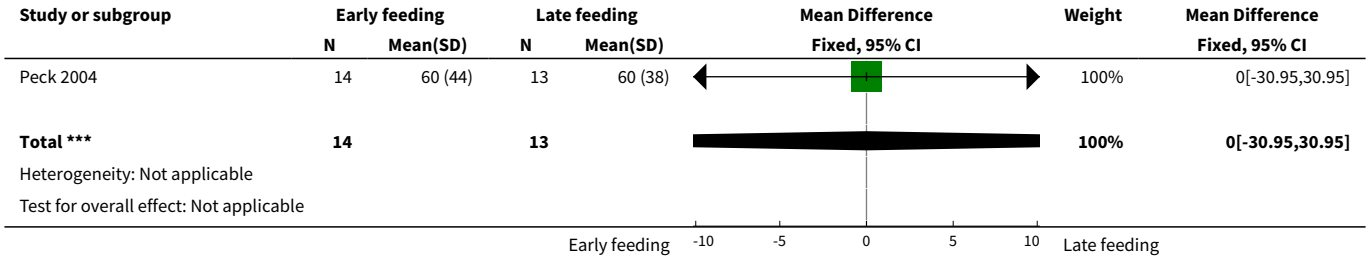
Study or subgroup	Early feeding n/N	Late feeding n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Peck 2004	4/14	5/13		100%	0.74[0.25,2.18]
Total (95% CI)	**14**	**13**		**100%**	**0.74[0.25,2.18]**
Total events: 4 (Early feeding), 5 (Late feeding)					



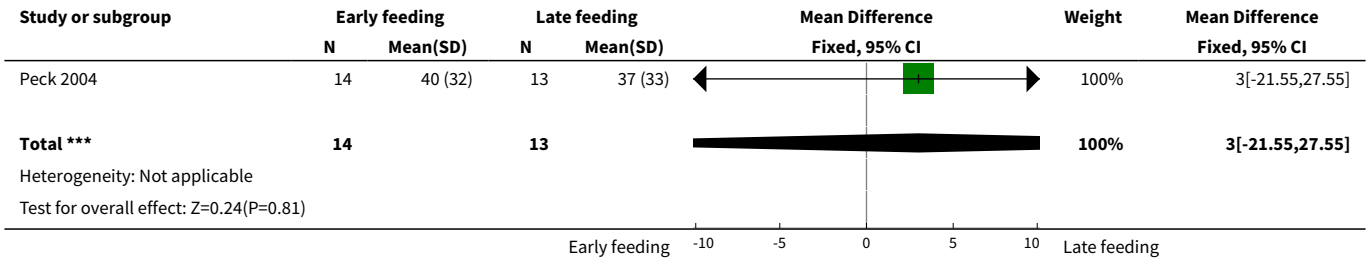
Comparison 2. Overall length of stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of acute stay days	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-30.95, 30.95]
2 Number of ICU days	1	27	Mean Difference (IV, Fixed, 95% CI)	3.0 [-21.55, 27.55]

Analysis 2.1. Comparison 2 Overall length of stay, Outcome 1 Length of acute stay days.



Analysis 2.2. Comparison 2 Overall length of stay, Outcome 2 Number of ICU days.



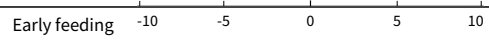
Comparison 3. Frequency of infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of infections	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.94, 1.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of antibiotic days	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-19.67, 19.67]

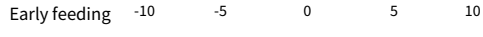
Analysis 3.1. Comparison 3 Frequency of infection, Outcome 1 Number of infections.

Study or subgroup	Early feeding N	Mean(SD)	Late feeding N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Peck 2004	14	3 (2)	13	3 (3)		100%	0[-1.94,1.94]
Total ***	**14**		**13**			**100%**	**0[-1.94,1.94]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Analysis 3.2. Comparison 3 Frequency of infection, Outcome 2 Number of antibiotic days.

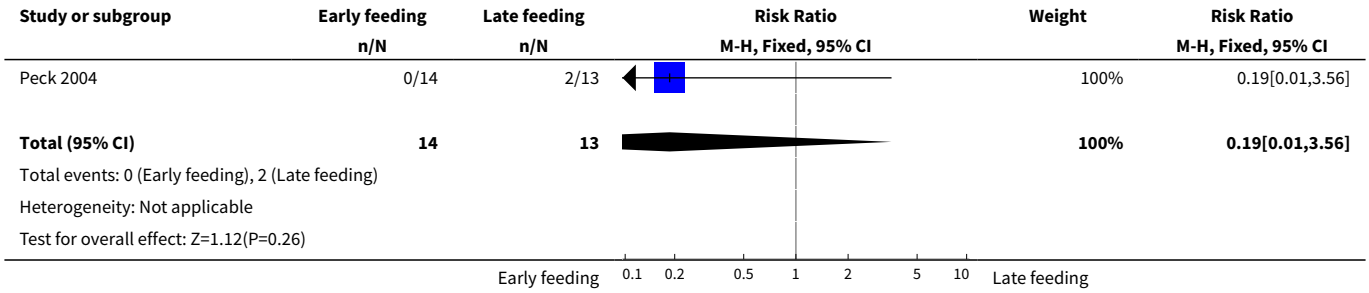
Study or subgroup	Early feeding N	Mean(SD)	Late feeding N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Peck 2004	14	28 (25)	13	28 (27)		100%	0[-19.67,19.67]
Total ***	**14**		**13**			**100%**	**0[-19.67,19.67]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



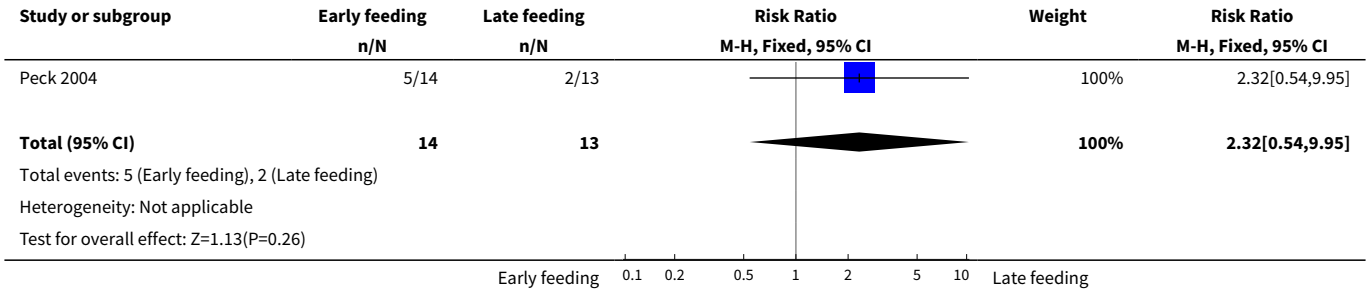
Comparison 4. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Aspiration events	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.56]
2 Commencement of TPN	1	27	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.54, 9.95]
3 Unplanned days without feeds	1	27	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.68, 2.68]
4 Perctange (%) of days with diarrhoea	1	27	Mean Difference (IV, Fixed, 95% CI)	-4.0 [-12.22, 4.22]

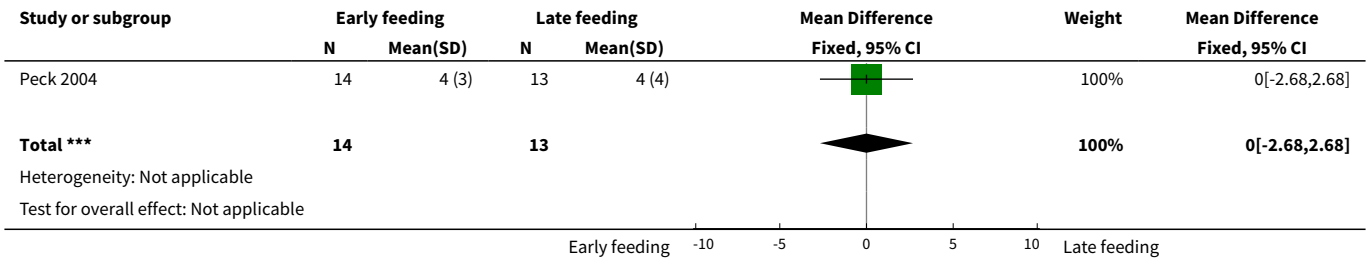
Analysis 4.1. Comparison 4 Adverse events, Outcome 1 Aspiration events.



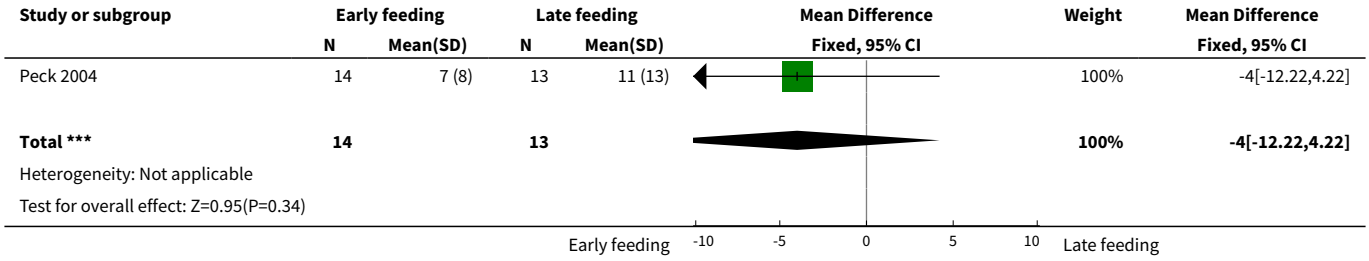
Analysis 4.2. Comparison 4 Adverse events, Outcome 2 Commencement of TPN.



Analysis 4.3. Comparison 4 Adverse events, Outcome 3 Unplanned days without feeds.



Analysis 4.4. Comparison 4 Adverse events, Outcome 4 Perctange (%) of days with diarrhoea.



APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Group's Specialised Register (searched 4th December 2007)
(Burn* or (thermal and injur*)) and (nutrition* or feed*)

MEDLINE 1966 to December 2007
1. exp Burns/
2. burn$.ab,ti.
3. (thermal adj3 injur$).ab,ti.
4. 1 or 2 or 3
5. ((alimentary canal or gastrointestinal or enteral or enteric or oral$ or sip or gastric or tube$ or method$) adj3 (nutrition$ or feed$)).ab,ti.
6. exp Enteral Nutrition/
7. exp Feeding Methods/
8. (PEG or percutaneous endoscopic gastrostomy).ab,ti.
9. ((nasogastric or gastrostomy or jejunostomy or gastric or orogastric or nasoenteric or nasojejunal or feed$) adj3 tube$).ab,ti.
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
13. clinical trial.pt.
14. 12 or 13
15. exp models, animal/
16. exp Animals/
17. exp Animal Experimentation/
18. exp Disease Models, Animal/
19. exp Animals, Laboratory/
20. or/15-19
21. Humans/
22. 20 not 21
23. 14 not 22
24. 11 and 23

EMBASE 1980 to December 2007
1. exp Burns/
2. burn$.ab,ti.
3. (thermal adj3 injur$).ab,ti.
4. 1 or 2 or 3
5. exp Enteric Feeding/
6. exp Nose Feeding/
7. exp Tube Feeding/
8. ((alimentary canal or intestinal$ or intraintestinal$ or gastrointestinal or enteral or enteric or oral$ or sip or gastric or tube$ or method $) adj3 (feed$ or nutrition$)).ab,ti.
9. ((feed$ or nasogastric or orogastric or nasoenteric or nasojejunal or gastrostomy or jejunostomy or gastric) adj3 tube$).ab,ti.
10. (percutaneous endoscopic gastrostomy or PEG).ab,ti.
11. 5 or 6 or 7 or 8 or 9 or 10
12. 4 and 11
13. exp animal model/
14. Animal Experiment/
15. exp ANIMAL/
16. exp Experimental Animal/
17. 13 or 14 or 15 or 16
18. Human/
19. 17 not 18
20. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial$).tw,hw.
21. exp clinical trial/
22. 20 or 21
23. 22 not 19
24. 12 and 23

CENTRAL (*The Cochrane Library,* issue 4, 2007)
#1 MeSH descriptor Burns explode all trees
#2 burn*
#3 thermal near3 injur*
#4 (#1 OR #2 OR #3)
#5 ((alimentary next canal) or gastrointestinal or enteral or enteric or oral* or sip or gastric or tube* or method*) near3 (nutrition* or feed*)
#6 ((percutaneous next endoscopic next gastrostomy) or PEG)
#7 ((nasogastric or gastrostomy or jejunostomy or gastric or orogastric or nasoenteric or nasojejunal or feed*) near3 (tube*))
#8 MeSH descriptor Enteral Nutrition explode all trees
#9 MeSH descriptor Feeding Methods explode all trees
#10 (#5 OR #6 OR #7 OR #8 OR #9)
#11 (#4 AND #10)

Zetoc (searched 4th December 2007)
nutrition* burn* delay*

WHAT'S NEW

Date	Event	Description
8 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jason Wasiak: conception of review, literature searching, study selection, review development and drafting of written submissions.
Heather Cleland: drafting of protocol, review development and drafting of written submissions.
Rachel Jeffery: literature searching, conception of background.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Burns [metabolism] [*therapy]; Enteral Nutrition [*methods]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adult; Humans