Cochrane
Library

Cochrane Database of Systematic Reviews

Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease (Review)

Katzberg HD, Benatar M

Katzberg HD, Benatar M.
Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease.
Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004030.
DOI: [10.1002/14651858.CD004030.pub3](https://doi.org/10.1002/14651858.CD004030.pub3).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	4
AUTHORS' CONCLUSIONS	6
ACKNOWLEDGEMENTS	7
REFERENCES	8
ADDITIONAL TABLES	9
APPENDICES	11
WHAT'S NEW	11
HISTORY	11
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	12
INDEX TERMS	12

[Intervention Review]

Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease

Hans Dieter Katzberg¹, Michael Benatar²

¹University of Toronto Toronto General Hospital / UHN, 5EC-306 Toronto, Canada. ²Department of Neurology, University of Miami, Miami, Florida, USA

Contact address: Hans Dieter Katzberg, University of Toronto Toronto General Hospital / UHN, 200 Elizabeth Street, 5EC-306 Toronto, ON M5G 2C4, Canada. hans.katzberg@utoronto.ca.

Editorial group: Cochrane Neuromuscular Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2011.

Citation: Katzberg HD, Benatar M. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD004030. DOI: [10.1002/14651858.CD004030.pub3](https://doi.org/10.1002/14651858.CD004030.pub3).

Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Enteral feeding (tube feeding) is offered to many people with amyotrophic lateral sclerosis/motor neuron disease experiencing difficulty swallowing (dysphagia) and maintaining adequate nutritional intake leading to weight loss.

Objectives

To examine the efficacy of percutaneous endoscopic gastrostomy placement or other tube feeding placement on:

- (1) survival;
- (2) nutritional status;
- (3) quality of life;
- (4) minor and major complications of percutaneous endoscopic gastrostomy.

Search methods

We searched the Cochrane Neuromuscular Disease Group Trials Register (24 November 2009), MEDLINE (from January 1966 to September 2009), and EMBASE (from January 1980 to September 2009) for all papers on enteral tube feeding in amyotrophic lateral sclerosis/motor neuron disease. The results were screened to identify randomised controlled trials and to identify non-randomized studies that might be worthy of review and discussion. We checked references in published articles and enlisted personal communications to identify any additional references.

Selection criteria

A priori selection criteria included randomised and quasi-randomized controlled trials evaluating the efficacy of percutaneous endoscopic gastrostomy or other feeding tube placement. Since no such trials were discovered, all prospective and retrospective controlled studies were reviewed in the 'Background' or 'Discussion' sections of the review.

Data collection and analysis

We independently assessed study design and extracted data. We considered the following outcomes: (1) survival rate in months (of primary interest), (2) nutritional status measured by weight change, change in body mass index, or other quantitative index of nutritional status,

(3) self-perceived quality of life and (4) safety of the procedure as indicated by minor and major complications of surgical or radiological guided PEG tube insertion.

Main results

We found no randomised controlled trials comparing the efficacy of enteral tube feeding with those people who continued to eat orally, without enteral feeding. We summarized the results of retrospective and prospective studies in the 'Discussion' section.

Authors' conclusions

There are no randomised controlled trials to indicate whether enteral tube feeding is beneficial compared to continuation of oral feeding for any of the outcome measures. The 'best' evidence to date suggests a survival advantage for some people with amyotrophic lateral sclerosis/motor neuron disease, but these conclusions are tentative. Evidence for improved nutrition is also incomplete but tentatively favorable.

Quality of life has been addressed in studies and needs more attention. Based on a number of recent non-randomized studies comparing surgical and radiographic approaches to feeding tube insertion these two procedures for PEG tube insertion appear to be equivalent.

PLAIN LANGUAGE SUMMARY

Enteral feeding (tube feeding) in people with amyotrophic lateral sclerosis, also known as motor neuron disease

Amyotrophic lateral sclerosis/motor neuron disease is a progressive neuromuscular disease causing muscle weakness resulting in paralysis. It is usually fatal. At some stage in the disease, most people have difficulty chewing and swallowing (dysphagia). This can cause significant weight loss. At this stage enteral feeding, or the placing of a feeding tube through the abdominal wall into the stomach (also known as percutaneous endoscopic gastrostomy), may be recommended to maintain adequate nutrition. This review looked for evidence from randomized clinical trials in which patients who underwent tube feeding were compared with patients not on tube feeding with regards to survival, maintaining adequate nutrition and quality of life and complications of feeding tube placement. No randomized controlled trials were found. Non-randomized evidence suggested a benefit from enteral feeding but this needs to be confirmed in a large randomized controlled trial.

BACKGROUND

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a fatal progressive neurodegenerative disease of unknown etiology, characterized by death of both upper and lower motor neurons (Karitzky 2001). Initial symptoms of ALS/MND are typically related to progressive weakness of the arms and legs, but about 25 to 30% of all patients have bulbar symptoms (difficulty chewing, swallowing, dealing with saliva, and speech or voice changes) as the presenting complaint (Beghi 2008). Respiratory insufficiency is usually a later symptom and is the primary cause of death in these patients. However, aspiration pneumonia, malnutrition, and dehydration are complications that result from difficulty swallowing, and can also be fatal. The median survival from symptom onset in a contemporary group of patients with ALS (1999 to 2004) has been estimated at 4.32 years (95% confidence interval 3.81 to 4.84) (Czaplinski 2006).

Nutrition is of great concern in ALS/MND as weight loss, malnutrition and dehydration may aggravate muscle weakness, contribute to respiratory weakness, and perhaps shorten life span. Dysphagia, or difficulty swallowing, may contribute to weight loss, but poor appetite and reduced ability to feed oneself may also lead to reduced oral intake and subsequent malnutrition/dehydration. Dietary changes are warranted when chewing and swallowing problems are observed in order to maintain appropriate caloric intake and prevent aspiration. When the dysphagia becomes severe, percutaneous endoscopic gastrostomy (PEG) tubes or other feeding tubes (nasogastric tubes, surgical gastrostomy, jejunostomy tubes) may provide a safer and more reliable route for nutrition. Other than the nasogastric feeding tube, all other feeding tubes require surgical insertion of a tube directly into the patient's stomach or intestine. These procedures are performed either as an outpatient or inpatient procedure in the endoscopy suite, the radiologic suite, or the operating room. After placement, food and liquid can be delivered directly through the tube, bypassing normal oral entry.

Rates of PEG tube insertion in patients with ALS vary from study to study as well as across different countries. The following usage figures have been reported: Canada = 20% (Strong 1999), Great Britain = 14 to 38% (Allison 2000; Neudert 2001), Germany = 27% (Silani 1998); Italy = 11 to 24% (Boitano 2001; Chiò 2002; Mazzini 1995); Japan = 21 to 60% (Seki 2000; Yanagisawa 1996), Norway = 22% (Bak 1994), USA = 13 to 40% (Bradley 2004; Lechtzin 2001). In general, the overall use of PEG has seen a remarkable growth over the years. To illustrate this, a study done in Finland in 1977 (Jokelainen 1977) reported the usage of feeding tubes, including gastrostomy, to be only 2.7%, much lower than contemporary rates of PEG insertion.

Practice guidelines from the American Academy of Neurology (AAN) were disseminated in 1999 and again in 2009, stating that PEG should be offered and placed when there is symptomatic dysphagia and accelerated weight loss (Miller 1999; Miller 2009). In 2004, data gathered from over 1000 ALS patients in the USA who were cared for prior to the publication of the Practice Parameters in 1999 were compared to an equivalent number of patients cared for after 1999 (Bradley 2004). Data showed that the proportion of patients receiving PEG had risen after 1999, especially in those patients with forced vital capacity (FVC) < 50% of predicted. Of the patients studied after 1999, 48% of patients met the Practice

Parameter criteria for enteral support. Of those, 46% had a PEG recommended and of those, 43% actually had it inserted. Thus, only 20% of those who met criteria for enteral support according to current practice guidelines actually received a feeding tube. It appears that both physicians and patients are ambivalent about the value of a gastrostomy. The benefits of PEG in maintaining adequate nutritional intake and weight stabilization has been shown in uncontrolled studies, but has not been tested rigorously (Kasarskis 1999; Klor 1999). Some researchers have suggested that PEG will increase survival time (Mazzini 1995), but this benefit is equivocal and not uniformly reported.

This review sought randomized clinical trials to provide the best evidence of the efficacy of enteral feeding in patients with ALS/MND.

OBJECTIVES

The objective of this review was to provide the best evidence from randomized controlled trials (RCTs) or quasi-RCTs on the efficacy of enteral feeding in patients with MND/ALS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs irrespective of whether allocation was concealed, (for example alternate allocation) were to have been selected. All non-randomized controlled studies included in the 'Background' and 'Discussion' section of this review were identified using the same search strategy without the RCT filter.

Types of participants

We accepted studies with participants diagnosed with definite, possible, or probable ALS, according to the El Escorial (Brooks 1994) or revised El Escorial criteria (Brooks 2000).

Types of interventions

The primary intervention of interest was placement of PEG or other form of feeding tube at any time during the course of ALS/MND, in comparison with other patients with ALS/MND who had no feeding tube and continued oral intake. Patients who received a PEG could still continue to consume some food or liquid orally. Other studies of interest were those that evaluated the safety and timing of different types or methods of feeding tubes placed in patients with ALS/MND, in particular radiographic-guided gastrostomy tube insertion.

Types of outcome measures

Primary outcomes

Survival time in months either from onset of the disease, time of diagnosis, or placement of the feeding tube.

Secondary outcomes

1. Quantitative index of change in nutritional status such as weight change, change in body mass index (BMI), or other nutritional marker such as pre-albumin level or insulin like growth factor I (IGF-I) level. If different measures of nutritional status were used

in different studies, they could be compared if the scores could be normalized.

2. Self-perceived quality of life (QOL), rated using an ordinal or interval scale that addressed quality of life issues.
3. Safety of PEG was also of interest in this review. We looked for frequency of adverse events related to the PEG procedure or use of a feeding tube, as indicated by minor and major complications of PEG. Examples of minor complications include transient laryngeal spasm, localized infections or failure to place PEG due to technical difficulties; examples of major complications include gastric hemorrhage, death due to respiratory arrest during the procedure, or aspiration pneumonia.

Search methods for identification of studies

We searched the Cochrane Neuromuscular Disease Group Specialized Register (14 November 2009), MEDLINE (January 1966 to September 2009), EMBASE (January 1980 to September 2009) for all trials of motor neuron disease or amyotrophic lateral sclerosis published, using 'gastrostomy', 'percutaneous endoscopic gastrostomy', 'enteric feeding', 'enteral nutrition', 'enteral feeding', 'nasogastric tube', 'PEG', 'feeding tube', 'intubation, gastrointestinal' as search terms. The results were screened to identify randomized controlled trials to be included in the review and identify non-randomized studies that might be worthy of review and discussion. We also checked references in published articles and enlisted personal communication to identify any additional references.

The MEDLINE and EMBASE search strategies are in [Appendix 1](#) and [Appendix 2](#).

Data collection and analysis

All randomized or quasi-randomized clinical trials that met our inclusion criteria would have been selected. If RCTs had been found, the primary author would have performed data extraction and this would have been checked by the second author. Missing data or other relevant information would have been obtained by directly contacting trial authors whenever necessary. A meta-analysis would have been done, whereby survival results would have been analyzed and compared using the Parmar method ([Parmar 1998](#)), and a weighted treatment effect (using a fixed-effect model) calculated across trials using the Cochrane statistical package, Review Manager (RevMan) Version 5. Results would have been expressed as risk ratios (RRs) with 95% confidence intervals (CIs) and risk differences (RDs) with 95% CIs for dichotomous outcomes and mean differences (MDs) and 95% CIs for continuous outcomes. Similar analyses would have been performed for all secondary outcomes under consideration. We would have analyzed subgroups of interest if sample size were sufficient in one or more studies. These predefined subgroups were chosen because of their prognostic importance in previous prospective studies and trials.

1. Younger adults (under 60 years) and older adults (> 60 years).
2. FVC < 50% and FVC > 50%.
3. Bulbar onset and limb-onset.
4. Time from onset of symptoms to placement of the feeding tube (< 3 years and > 3 years duration from onset of first symptom).

In the absence of RCTs, cohort and case-control studies were identified and their results summarized in the Discussion.

Assessment of risk of bias in included studies

No RCT studies were identified. Risk of bias would have been assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2008](#)), taking into account the domains: adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias. Risk of bias for randomized studies would have been reported as 'high' 'low' or 'unclear', where 'yes' indicates a low risk of bias, 'no' a high risk of bias and 'unclear' if there were insufficient detail to make a judgement.

RESULTS

Description of studies

The literature search for the first version of this review identified a total of 242 references, from which nine non-randomized studies comparing ALS/MND patients with and without PEG were compared and one additional case control study comparing two different gastrostomy procedures were reviewed.

For this update we re-ran the searches and identified a total of 178 MEDLINE references, 230 EMBASE references and 5 references from the Cochrane Neuromuscular Disease Group Specialized Register. After deleting duplicate, irrelevant, and manuscripts with no methodology, there were a total of 119 articles that were worthy of consideration, but no RCTs that met the selection criteria. Of the remaining articles, 182 did not contain relevant information, and 112 evaluated PEG tube insertion but did not meet our selection criteria or had a design which was not controlled (case report, case series, opinion). There were 11 non-randomized controlled studies in which in which ALS/MND patients with and without PEG were compared for outcomes of interest. Four additional case control studies compared the safety of two different gastrostomy procedures performed in ALS/MND patients.

Risk of bias in included studies

No RCT studies were identified.

Effects of interventions

We found no RCTs or quasi-RCTs of the efficacy of PEG in patients with ALS/MND that compared outcomes in patients with and without tube feeding. Controlled studies that addressed the outcomes of interest are discussed in the following section.

DISCUSSION

Survival outcomes of enteral nutrition

Prospective studies

There were three prospective studies of PEG insertion that looked at a survival advantage, including 531 participants. Two were positive and one was negative.

Two ALS patient cohorts followed prospectively showed a significant survival advantage in patients using PEG compared to those who did not. Mazzini et al ([Mazzini 1995](#)) showed a survival of 38 months versus 30 months ($P < 0.03$) in 31 patients undergoing PEG insertion compared to 35 control patients who refused the procedure, however, multivariate regression to assess possible confounders was not performed. Chio et al ([Chio 2002](#); [Chio 2006](#)) prospectively followed 221 patients with ALS/MND across

26 neurology departments in northwestern Italy. Multivariate regression analysis with Cox proportional hazard model including PEG use as a time dependent variable found that the 169 patients not using PEG tube had a hazard ratio (HR) of 3.38 ($P = 0.0006$) for death compared to the 52 patients using PEG. One prospective study did not show a survival advantage from PEG tube. Murphy *et al.* identified 244 patients from 1985 to 2006 in North Canterbury, New Zealand with a confirmed diagnosis of ALS. In this cohort, they did not observe a survival benefit in the 57 patients undergoing PEG insertion compared to those who continued oral feeding. They report a total median survival from onset of symptoms of 26 months in the PEG group (range 5 to 88 months), which was similar to the entire group (27.6 months) (Murphy 2008).

Retrospective studies

There were eight retrospective studies of PEG insertion that looked at a survival advantage, including 3289 participants. Two were positive and six were negative.

Two retrospective studies demonstrated a survival advantage in ALS patients undergoing PEG insertion compared to patients without PEG. In a cohort of 1041 patients followed from 1984 to 2004, Czaplinski *et al* showed that patients who underwent PEG tube insertion at some point showed a significantly improved survival in a multivariate model accounting for possible confounders (HR 0.75, CI 0.63 to 0.90, $P = 0.003$) (Czaplinski 2006). Chio *et al* (Chiò 1999) matched 50 ALS/MND patients undergoing PEG with 100 historical controls without PEG for age, FVC, severity of disease, and site of onset. Multivariate analyses showed patients with PEG to have significantly increased survival in the whole patient cohort (OR = 1.55, $P = 0.02$) and in bulbar-onset patients (HR = 1.83, $P = 0.02$) but not in spinal-onset patients.

Six retrospective studies failed to find a significant survival advantage in ALS patients undergoing PEG insertion compared to those not receiving PEG. Mitchell *et al* conducted a retrospective analysis of the effects of riluzole on outcomes in 475 patients diagnosed with MND from 1980 to 2003. A Cox regression analysis including PEG tube use as a variable found a non-significant protective effect of PEG tube use compared to no use (OR = 0.59, 95% CI 0.22 to 1.61, $P = 0.30$) (Mitchell 2006). Two additional studies evaluating outcomes in small ALS cohorts (< 60 patients) found no survival advantage in those undergoing PEG compared to unmatched oral feed patients (Desport 2000; Sorenson 2007). Strong *et al* (Strong 1999) looked at a slightly larger group of 73 patients undergoing PEG feeding versus 293 oral feeders and found a survival advantage (mean of 22 months versus 30 months; $P < 0.001$) only in the bulbar onset patients but not the entire cohort or the patients with limb onset. Two large ALS patient registries, the Scottish Motor Neurone Disease Register (Forbes 2004), and the ALS-CARE database in the USA (Mitsumoto 2003), attempted to eliminate single center bias by evaluating survival in PEG versus non-PEG patients across multiple ALS clinics. Unmatched analysis of all 1226 patients in the Scottish Motor Neurone Disease Register and 324 patients with ALSFR scores of five or less in the ALS-CARE database did not show a survival advantage from PEG tube feeding. Patients with bulbar symptoms in both cohorts also did not appear to have a specific survival advantage with PEG.

Nutritional outcomes of PEG

The major purpose of a feeding tube is to deliver nutrition, however, the evidence for a nutritional advantage of PEG in the ALS population is weak. We looked at the evidence for weight gain or other measures of improved nutrition after patients received a PEG (or other feeding tube). Data for this outcome measure is available from only two controlled studies. In their retrospective case control study, Desport *et al* (Desport 2000) reported a significant advantage in the patients undergoing PEG. They had a weight gain of 8% after PEG, and body mass index (BMI) and triceps skinfold thickness (TSF) were also increased significantly compared to a non-enteral control group. The prospective cohort study by Mazzini *et al* (Mazzini 1995) found that BMI significantly increased by 0.5 points after PEG and decreased by 4.5 points in the non-PEG patients over a period of 12 months.

Quality of life outcomes of enteral nutrition

Only two of the controlled studies considered changes in quality of life (QOL) after enteral nutrition. Neither of these showed evidence for improved QOL after PEG. Mazzini (Mazzini 1995) related anecdotal impressions from patients that their QOL improved after PEG but report no concrete data. Mitsumoto (Mitsumoto 2003) reported quantitative results, based on percent of patients who responded affirmatively or negatively to specific questions about QOL after PEG. A majority of the patients (79%) reported that stabilized nutritional and hydrational status was the most positive effect of PEG. A minority of PEG patients (17%) reported improved psychological well being with regard to nutrition and 28% listed less fatigue or less time spent on meals and medications.

Safety and timing of PEG insertion

Safety and timing of PEG placement was another issue that was of interest in this review. In the studies discussed above, complication rates were usually noted. Minor complications included tube displacement, tube obstruction, and infection at the site of tube (2 to 16%). Major complications included PEG failure (8 to 45%), gastric hemorrhage (3%), procedural deaths (2%), and death within 30 days (4 to 16%) (Chiò 1999; Desport 2000; Mazzini 1995; Sorenson 2007; Strong 1999).

The issue of timing of PEG tube insertion is an important topic but has not been well studied in clinical trials. The 2009 AAN Practice Parameter (Miller 2009) stated that there was insufficient evidence to support or refute specific timing of PEG insertion in patients with ALS, but did quote a study by Kasarskis *et al* (Kasarskis 1999) which found that the risk of PEG insertion increased when patient FVC declined to < 50% in an uncontrolled series of ALS patients. In the studies we identified, Chio *et al* (Chiò 2006) showed that rate of respiratory decline was the most important prognostic factor for longer survival time. Mazzini 1995, Chiò 1999, and Desport 2000 reported that longer survival was associated with higher FVC at time of PEG, however these observations do not take into account that patients with higher FVC may have less advanced disease at the time of PEG which would serve as a confounder on the survival analysis. In 2001 and 2002, two uncontrolled retrospective studies reported on PEGs that were placed in ALS/MND patients with low vital capacity (Boitano 2001; Gregory 2002). Both of these reported few complications when they used non-invasive ventilation (NIV) to support respiration during PEG placement. Boitano's series of five patients all did well, with

FVC ranging from 21 to 44%. In Gregory's series, 29/33 (88%) PEG tubes were successfully placed with NIV support in patients whose FVCs ranged from 7 to 52%.

Method of PEG tube Insertion

An alternative method of placing feeding tubes has become more common in the past few years, percutaneous radiological gastrostomy (PRG), sometimes called radiologically inserted gastrostomy (RIG). There have been four case control studies that specifically compared safety and outcome in ALS patients after having a traditional PEG versus PRG/ RIG.

Two of these studies attempted to control for potential confounders in comparing PEG and PRG/RIG groups by using multi-variable regression to evaluate efficacy and hazards. Shaw et al retrospectively evaluated survival in 98 patients at an ALS clinic undergoing PEG (n = 18), RIG (n = 72), or NG (n = 8) tube insertion and found that median survival was not significantly different in the PEG (7.1 months) versus RIG groups (6.8 months) (Shaw 2004). Desport et al assessed survival and complications in 30 patients undergoing PEG tube insertion and 20 patients undergoing RIG tube insertion; multivariate analysis did not show a significant difference in survival or overall complications between the two groups (Desport 2000). There was a lower frequency of tube blockages/migration in the RIG group (35% versus 10.4%, $P = 0.003$), however, the RIG group did have a higher incidence of post-procedure pain (39.4% versus 10%, $P = 0.003$).

Two additional studies assessed outcome and complications based on the method of feeding tube insertion. Thornton et al (Thornton 2002) compared 20 PEG to 16 PRG procedures in ALS/MND patients and reported no survival difference between the two groups. However, many of the PRG procedures had been done in patients failing traditional PEG surgical insertion. They experienced one death with each procedure and one case of peritonitis with PEG. In a retrospective case control study, Chio (Chio 2004) found improved survival in 25 PRG patients compared to 25 similar but unmatched PEG patients (204 versus 85 days; $P = 0.004$). However, in this cohort, all the comparison PEG patients underwent the procedure prior to October 2000, when the standard of care likely was significantly poorer than for the PRG patients, who all had insertions after this date. Rate of minor complications and major complications in both groups were similar to studies mentioned previously. Neither of these studies accounted for potential confounders.

Summary

Results of these 11 controlled studies comparing PEG tube feeding to oral feeding are summarized in Table 1.

All of these 11 studies tested for a possible survival advantage. Two prospective and two retrospective studies reported a longer survival in ALS patients after PEG compared to oral feeders, even when controlling for possible confounders in multivariate analysis. One prospective and six retrospective studies failed to find a survival advantage with PEG; however, these studies had multiple design flaws, the major one being lack of control for confounders. Survival advantage in the positive studies was not limited to patients with either limb or bulbar onset.

Nutrition was not studied as rigorously, with only three of eleven studies reporting relevant statistics. The results all suggested a

positive outcome of PEG, and this was supported by the single prospective study that measured nutritional parameters.

QOL is clearly understudied. Only two studies addressed QOL and only one measured QOL in the group receiving PEG.

The frequency of minor complications of PEG tube insertion ranges from 2 to 16% and major complications, mostly comprise PEG tube failure, occur in up to 45% of patients. Complications during the procedure including procedural death are infrequent. There is no consensus about the best timing for PEG tube insertion. Although there is some evidence that PEG tube insertion may be more risky in patients with $FVC < 50\%$, there also is evidence that even patients with low FVC may still benefit from PEG tube placement, particularly when NIV is used during the procedure.

PRG/RIG feeding tube insertion appears to be equally effective and have similar complication rates according to four studies comparing this procedure to surgical PEG insertion.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials to indicate whether enteral feeding is beneficial compared to continuation of oral feeding for survival. The 2009 AAN Practice Parameter's recommendation that patients undergo PEG placement if there is significant dysphagia or weight loss is weakly supported by this review. There continues to be no direct evidence addressing the adequate timing of PEG tube insertion. RIG procedure is increasingly utilized particularly when FVC is low, and appears to be not significantly different in efficacy or complication rates to standard surgical PEG insertion. Nutritional advantages of PEG have not been studied systematically, however there is some suggestion of their benefit in a few studies. The effect on quality of life has not been shown.

Implications for research

The evidence for a survival advantage after PEG is weakly positive, with three large prospective cohort studies showing longer survival in patients with a gastrostomy tube than in those without feeding tubes. More research is urgently needed to guide practitioners and patients in this area. There are likely several factors other than PEG that affect survival and only a large RCT can tease out these other important factors. The possible survival advantage of RIG has also shown promise and should be investigated further.

The best time to undergo PEG placement has not been determined. An assessment of the safety and effectiveness of PEG insertion in those with ALS within the context of a prospective clinical trial is required, with proper adjustment for possible confounders, most importantly severity of disease.

The evidence for a nutritional advantage of PEG is weak but positive. The use of prospective cohort studies is needed to compare outcomes in patients who have a PEG placed at different levels of nutrition or malnutrition.

The effects of PEG placement on patients and their caretakers as well as on quality of life need to be evaluated in a controlled fashion. This critical area remains untested and yet, it is one of the most

important arguments for having a PEG placed. There are several QOL Instruments that could be applied to this area of study.

review. Dr Edward Kasarskis, Dr Richard Olney and Dr Maria Laura Manca were co-authors on the original draft of this manuscript.

ACKNOWLEDGEMENTS

To Kate Jewitt for her guidance and help throughout the endeavor. Dr Susan Langmore wrote the first draft of the original version of the

REFERENCES

Additional references

Allison 2000

Allison SP, Rawlings J, Field J, Bean N, Stephen AD. Nutrition in the elderly hospital patient - Nottingham studies. *Journal of Nutrition, Health & Aging* 2000;**4**(1):54-7.

Bak 1994

Bak S, Bak L. Symptomatic treatment of amyotrophic lateral sclerosis [Symptomatisk behandling af amyotrofisk lateralsklerose]. *Ugeskr Laeger* 1994;**156**(28):4138-40.

Beghi 2008

Beghi E, Millul A, Logroscino G, Vitelli E, Micheli A. SLALOM Group. Outcome measures and prognostic indicators in patients with amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 2008;**9**(3):163-7.

Boitano 2001

Boitano LJ, Jordan T, Benditt JO. Noninvasive ventilation allows gastrostomy tube placement in patients with advanced ALS. *Neurology* 2001;**56**(3):413-4. [MEDLINE: 21106697]

Bradley 2004

Bradley WG, Anderson F, Gowda N, Miller RG, ALS CARE Study Group. Changes in the management of ALS since the publication of the AAN ALS Practice Parameter 1999. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 2004;**5**(4):240-4.

Brooks 1994

Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on motor neuron diseases/amyotrophic lateral sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial 'Clinical limits of ALS' Workshop Contributors. *Journal of the Neurological Sciences* 1994 Suppl;**124**:96-107. [MEDLINE: 95105875]

Brooks 2000

Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Disease. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 2000;**1**:293-9. [MEDLINE: 21357372]

Chiò 1999

Chiò A, Finocchiaro E, Meineri P, Bottacchi E, Schiffer D. Safety and factors related to survival after percutaneous endoscopic gastrostomy in ALS. ALS Percutaneous Endoscopic Gastrostomy Study Group. *Neurology* 1999;**53**(5):1123-5. [MEDLINE: 99424597]

Chiò 2002

Chiò A, Mora G, Leone M, Mazzini L, Cocito D, Giordana MT, et al. Early symptom progression rate is related to ALS outcome: a prospective population based study. *Neurology* 2002;**59**(1):99-103.

Chiò 2004

Chiò A, Galletti R, Finocchiaro C, Righi D, Ruffino MA, Calvo A, et al. Percutaneous radiological gastrostomy: a safe and effective method of nutritional tube placement in advanced ALS. *Journal of Neurology, Neurosurgery and Psychiatry* 2004;**75**(4):645-7.

Chiò 2006

Chiò A, Bottacchi E, Buffa C, Mutani R, Mora G, PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. *Journal of Neurology, Neurosurgery and Psychiatry* 2006;**77**(8):948-50.

Czaplinski 2006

Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower disease progression and prolonged survival in contemporary patients with amyotrophic lateral sclerosis: is the natural history of amyotrophic lateral sclerosis changing?. *Archives of Neurology* 2006;**63**(8):1139-43.

Desport 2000

Desport JC, Preux PM, Truong CT, Courat L, Vallat JM, Couratier P. Nutritional assessment and survival in ALS patients. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 2000;**1**(2):91-6. [MEDLINE: 21360689]

Forbes 2004

Forbes RB, Colville S, Swingler RJ, Scottish Motor Neurone Disease Research Group. Frequency, timing and outcome of gastrostomy tubes for amyotrophic lateral sclerosis/motor neurone disease - a record linkage study from the Scottish Motor Neurone Disease Register. *Journal of Neurology* 2004;**251**(7):813-7.

Gregory 2002

Gregory S, Siderowf A, Golaszewski AL, McCluskey L. Gastrostomy insertion in ALS patients with low vital capacity: respiratory support and survival. *Neurology* 2002;**58**(3):485-7. [MEDLINE: 21829351]

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Jokelainen 1977

Jokelainen M. Amyotrophic lateral sclerosis in Finland II: Clinical characteristics. *Acta Neurologica Scandinavica* 1977;**56**(3):191-204.

Karitzky 2001

Karitzky J, Ludolph AC. Imaging and neurochemical markers for diagnosis and disease progression in ALS. *Journal of the Neurological Sciences* 2001;**191**(1-2):35-41. [MEDLINE: 21534785]

Kasarskis 1999

Kasarskis EJ, Scarlata D, Hill R, Fuller C, Stambler N, Cedarbaum JM. A retrospective study of percutaneous

endoscopic gastrostomy in ALS patients during the BDNF and CNTF trials. *Journal of the Neurological Sciences* 1999;**169**(1-2):118-25. [MEDLINE: 20009711]

Klor 1999

Klor BM, Milianti FJ. Rehabilitation of neurogenic dysphagia with percutaneous endoscopic gastrostomy. *Dysphagia* 1999;**14**(3):162-4. [MEDLINE: 99287766]

Lechtzin 2001

Lechtzin N, Wiener CM, Clawson L, Chaudhry V, Diette GB. Hospitalization in amyotrophic lateral sclerosis: causes, costs and outcomes. *Neurology* 2001;**56**(6):753-7.

Mazzini 1995

Mazzini L, Corra T, Zaccala M, Mora G, Del Piano M, Galante M. Percutaneous endoscopic gastrostomy and enteral nutrition in amyotrophic lateral sclerosis. *Journal of Neurology* 1995;**242**(10):695-8. [MEDLINE: 96122579]

Miller 1999

Miller RG, Rosenberg JA, Gelinas DF, Mitsumoto H, Newman D, Sufit R, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. *Neurology* 1999;**52**(7):1311-23. [MEDLINE: 99242151]

Miller 2009

Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009;**73**(15):1218-26.

Mitchell 2006

Mitchell JD, O'Brien MR, Joshi M. Audit of outcomes in motor neuron disease (MND) patients treated with riluzole. *Amyotrophic Lateral Sclerosis* 2006;**7**(2):67-71.

Mitsumoto 2003

Mitsumoto H, Davidson M, Moore D, Gad N, Brandis M, Ringel S, et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 2003;**4**(3):177-85.

Murphy 2008

Murphy M, Quinn S, Young J, Parkin P, Taylor B. Increasing incidence of ALS in Canterbury, New Zealand: a 22-year study. *Neurology* 2008;**71**(23):1889-95.

Neudert 2001

Neudert C, Oliver D, Wasner M, Borasio GD. The course of the terminal phase in patients with amyotrophic lateral sclerosis. *Journal of Neurology* 2001;**248**(7):612-6.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24):2815-34. [MEDLINE: 99120172]

Seki 2000

Seki H, Kameya T, Kimura I. A survey of current nutrition therapy for the ALS patients in Japanese national sanatoriums. *Rinsho Shinkeigaku - Clinical Neurology* 2000;**40**(11):1083-9.

Shaw 2004

Shaw AS, Ampong MA, Rio A, McClure J, Leigh PN, Sidhu PS. Entristar skin-level gastrostomy tube: primary placement with radiologic guidance in patients with amyotrophic lateral sclerosis. *Radiology* 2004;**233**(2):392-9.

Silani 1998

Silani V, Kasarskis EJ, Yanagisawa N. Nutritional management in amyotrophic lateral sclerosis: a worldwide perspective. *Journal of Neurology* 1998;**245**(Suppl 2):S13-9.

Sorenson 2007

Sorenson EJ, Crum B, Stevens JC. Incidence of aspiration pneumonia in ALS in Olmsted County, MN. *Amyotrophic Lateral Sclerosis* 2007;**8**(2):87-9.

Strong 1999

Strong MJ, Rowe A, Rankin RN. Percutaneous gastrojejunostomy in amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* 1999;**169**(1-2):128-32.

Thornton 2002

Thornton FJ, Fotheringham T, Alexander M, Hardiman O, McGrath FP, Lee MJ. Amyotrophic lateral sclerosis: enteral nutrition provision - endoscopic or radiologic gastrostomy?. *Radiology* 2002;**224**(3):713-7.

Yanagisawa 1996

Yanagisawa N, Shindo M. Nationwide study on the natural course of amyotrophic lateral sclerosis in Japan. Annual report of the Research Committee of CNS Degenerative Diseases, Ministry of Health and Welfare in Japan for the year 1995. *Matsumoto* 1996:253-5.

ADDITIONAL TABLES

Table 1. Controlled studies assessing survival in ALS patients using PEG versus oral feeding alone

Author and date of publication	Number of patients in each group	Survival advantage from PEG	Nutritional advantage from PEG	Quality of life (QOL) advantage from PEG	Study type	Control for confounders
--------------------------------	----------------------------------	-----------------------------	--------------------------------	--	------------	-------------------------

Table 1. Controlled studies assessing survival in ALS patients using PEG versus oral feeding alone (Continued)

Mazzini 1995	31 PEG ^a vs 35 PO ^b	Yes; 38 vs 30 month survival; P = 0.03	Yes	Anecdotal advantages only	Prospective cohort	No matching or regression analysis performed
Strong 1999	73 PEG vs 293 PO	No for entire cohort	Not reported	Not reported	Case control	No matching or regression performed
Chiò 1999	50 PEG vs 100 PO	Yes; protective OR 1.55, P = 0.02	Yes, observation only	Not reported	Case control	Matched on age, FVC ^e , site of onset, severity of disease (Norris Score)
Desport 2000	30 PEG vs 30 PO	No	Not reported	Not reported	Case control	Multivariate regression used
Mitsumoto 2003	137 PEG vs 187 PO	No; 47 months vs 58 months; P = 0.33	Yes; observation only	17% with improved psychological wellbeing and 28% with less fatigue and less time spent on meals/medications	Case control	Patients with bulbar scores of 5 or less selected and adjustment for bulbar subscore performed in analysis.
Forbes 2004	142 PEG vs 1084 PO	No; 25.0 vs 24.7 months; P = 0.52	Not reported	Not reported	Case control	No matching or regression performed
Czaplinski 2006	275 PEG vs 766 PO	Yes; protective OR ^c 0.75, P = 0.003	Not reported	Not reported	Retropective cohort	Multivariate regression performed
Chiò 2002 / Chiò 2006	52 PEG vs 169 PO	Yes; protective HR ^d 3.38, P = 0.0006	Not reported	Not reported	Prospective cohort	Multivariate regression performed
Murphy 2008	57 PEG vs 187 PO	No; 26 vs 27 month survival	Not reported	Not reported	Prospective cohort	No matching or multivariate regression performed
Mitchell 2006	127 PEG vs 348 PO	No; protective OR 0.59, P = 0.30	Not reported	Not reported	Case control	Multivariate regression performed controlling for age, sex, onset site, riluzole use
Sorenson 2007	12 PEG vs 28 PO	No	Not reported	Not reported	Case control	No matching or regression performed

^aPEG = percutaneous enteral gastrostomy.

^bPO = per os (oral).

^cOR = odds ratio.

^dHR = hazard ratio.

^eFVC = forced vital capacity.

APPENDICES

Appendix 1. Medline OvidSP search strategy

1 exp Motor Neuron Disease/
2 amyotrophic lateral sclerosis/
3 (amyotroph\$ lateral\$ sclerosis\$ or motor\$ neuron\$1 disease\$1 or motoneuron\$1 disease\$1).tw.
4 lou gehrig\$.mp.
5 or/1-4
6 GASTROSTOMY/ or gastrostomy.tw.
7 Enteral Nutrition/ or enteral nutrition.tw. or enteral feeding.mp. or enteric feeding.mp.
8 feeding tube.mp.
9 nasogastric tube.mp.
10 Intubation, Gastrointestinal/ or gastrointestinal intubation.mp. or digestive tract intubation.mp.
11 peg.mp.
12 or/5-11
13 5 and 12

Appendix 2. Embase OvidSP search strategy

1 exp Motor Neuron Disease/
2 amyotrophic lateral sclerosis/
3 (amyotroph\$ lateral\$ sclerosis\$ or motor\$ neuron\$1 disease\$1 or motoneuron\$1 disease\$1).tw.
4 lou gehrig\$.tw.
5 or/1-4
6 GASTROSTOMY/ or percutaneous endoscopic gastrostomy/ or gastrostomy.tw.
7 Enteric feeding/ or enteral nutrition.mp. or enteral feeding.mp. or enteric feeding.tw.
8 feeding tube.mp.
9 Nasogastric tube/ or nasogastric tube.tw.
10 digestive tract intubation/ or gastrointestinal intubation.mp. or digestive tract intubation.tw.
11 peg.mp.
12 or/6-11
13 5 and 12

WHAT'S NEW

Date	Event	Description
4 August 2010	New citation required but conclusions have not changed	New team of authors.
4 June 2010	New search has been performed	Searches updated to September 2009. No studies identified for inclusion. Additional studies considered in the Discussion.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2006

Date	Event	Description
9 July 2008	Amended	Converted to new review format.
1 June 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All authors reviewed and rated articles for this project. Dr Katzberg wrote the first draft of the current update and Dr Michael Benatar participated in the literature search and review as well as drafting and editing the manuscript. Both current authors agreed on the final text.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2010 update, the methods section was revised to incorporate updated risk of bias methodology and the Background section has been partially rewritten.

INDEX TERMS

Medical Subject Headings (MeSH)

*Enteral Nutrition; Amyotrophic Lateral Sclerosis [therapy]; Deglutition Disorders [complications]; Gastrostomy; Motor Neuron Disease [*therapy]; Prospective Studies; Retrospective Studies

MeSH check words

Humans