Percutaneous endoscopic gastrostomy under conscious sedation in patients with amyotrophic lateral sclerosis is safe

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Percutaneous endoscopic gastrostomy under conscious sedation in patients with amyotrophic lateral sclerosis is safe: an observational study

Denise Strijbos a,b,c, José Hofstede b, Daniel Keszthelyi c, Ad A.M. Masclee c and Lennard P.L. Gilissen a

Objectives Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes muscle weakness with respiratory and swallowing dysfunction, eventually leading to death. Permanent enteral feeding is indicated in almost all patients. A percutaneous endoscopic gastrostomy (PEG) tube is considered the first choice, usually performed under conscious sedation (intravenous midazolam). Guidelines are very cautious with respect to sedation in ALS because of the risk for respiratory complications. In our tertiary referral hospital, conscious sedation has been used for many years. Our aim was to review 30-day complications in PEG performed under conscious sedation in ALS patients (without noninvasive positive pressure ventilation during the procedure).

Patients and methods A retrospective review, including all ALS patients undergoing PEG under conscious sedation from October 2009 to April 2016, was performed.

Results Analysis included 45 (44% men) patients receiving intravenous midazolam sedation (mean dose 5 mg) during PEG placement, age 36–91 years (mean: 68.7 years). Forced vital capacity (FVC) was 24–116% (mean 68%), of which mild to moderate dysfunction (FVC 50–80%) was present in 42.2% of patients and (very) severe dysfunction (FVC <50%) in 8.8%. No respiratory complications (e.g. aspiration pneumonia) were observed. Other complications, for example, infection, bleeding and peritonitis occurred in, respectively, 8.9, 2.2 and 0%. Mean survival after PEG placement was 13.4 months (range: 1–45 months).

Conclusion Conscious sedation during PEG insertion in ALS patients did not lead to respiratory complications or to an increase in other complications. Our data indicate that conscious sedation can be used safely in ALS patients with mild to moderate pulmonary dysfunction. Eur J Gastroenterol Hepatol 29:1303–1308

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes muscle weakness with respiratory and/or swallowing dysfunction, cramps, fasciculations and spasticity, eventually leading to death. In the Netherlands, 300–450 patients per year are diagnosed [1]. A worldwide incidence of 2–3/100 000/year has been reported [2]. The pathophysiology of ALS is still poorly understood. Genetic factors have been identified, with a focus on dysfunction in RNA metabolism and protein homeostasis [2,3]. The gradually progressive course differs among patients. Mostly, muscle weakness and atrophy are the first symptoms, occurring in the arms, legs or the bulbar system (all three in 1/3 of patients), with progression to more central (bulbar) functions, for example, speaking and swallowing. In a very small proportion of patients, dyspnoea is the first symptom, caused by weakness of the respiratory muscles [4,5].

Generally, four phases are distinguished. At the start, symptoms are mostly mild (stage 1, involvement of one region). Stage 2A is the time of diagnosis. The next phases are characterized by progressive muscle weakness and involvement of the second (stage 2b) and third region (stage 3). In stage 4a, a gastrostomy is needed. The last terminal phase (stage 4b) is characterized by progressive weakness of respiratory muscles, with a need for noninvasive positive pressure ventilation (NIPPV) [4]. The median survival at the time of diagnosis is 32 months [6].

Swallowing disturbances, muscle atrophy, upregulation of metabolic activity (hypermetabolism) and a change in metabolism (by a lower activity level and elevated ventilation rate because of respiratory insufficiency), together with exhaustion because of eating, lead to weight loss [3]. This weight loss further deteriorates quality of life and shortens survival [3,7,8]. Thus, prevention of weight loss is an important clinical imperative in ALS. As a result, an indication for permanent enteral feeding arises in almost all patients. Currently, a percutaneous endoscopic gastrostomy (PEG) tube is considered the first-choice method for long-term enteral feeding [5,9,10].

Because of the invasiveness, PEG placement is usually performed under conscious sedation with intravenous midazolam and/or fentanyl.

The risks and complications of procedural sedation for PEG placement on ALS patients have not been substantiated.
The Dutch Guideline ‘PEG in ALS’ states: ‘sedation elevates the risk of respiratory complications, for it changes the normal respiratory response in case obstruction or apnoea occurs and the administration of sedatives results in a higher mortality risk’ [1], but evidence with respect to PEG procedures is lacking. The European Federation of Neurological Societies guideline states that PEG placement before the occurrence of respiratory insufficiency (≤50%) is recommended [5]. A low FVC during PEG placement might increase the risk of mortality because of respiratory insufficiency [11,12].

PEG placement is one of the most invasive and high-risk endoscopic procedures and in addition, ALS patients are very vulnerable. A cautious approach is therefore required. Our department has a dedicated team of gastroenterologists, nurses and dieticians to optimize the care around PEG insertion and follow-up. Long-term results from our centre show a complication rate comparable to that reported in the literature [13]. Historically, sedation has always been provided to ALS patients during PEG placement in our centre. No exceptional PEG-related problems have been observed to date. Our strategy deliberately deviates from that of the Dutch guideline. Therefore, an objective analysis of our data is relevant. We hypothesize that in our hands, the risk on respiratory complications and procedure-related mortality is not elevated when administering conscious sedation (with midazolam) to ALS patients undergoing PEG placement, even in patients with mild to moderate pulmonary dysfunction (FVC 50-70%).

This study describes the results of PEG insertion under conscious sedation in a single tertiary referral centre. Our primary aim was to analyse complications occurring as a result of sedation. The secondary aims were to analyse other complications related to PEG insertion, use of PEG and mortality (30-day and overall).

Patients and methods
A retrospective review was performed to evaluate complications following PEG placement in all ALS patients who underwent PEG under conscious sedation from October 2009 to April 2016 in the Catharina Hospital Eindhoven, a tertiary referral centre. In case of insufficient follow-up data, use of propofol or no sedation, patients were excluded from the analysis.

Procedure
All patients visited the outpatient clinic before PEG insertion. PEG placement was performed according to the standard pull-method [14]. Lidocaine was injected at the insertion site as a local anaesthetic into all the layers of the future PEG tract, including the stomach wall.

No antibiotics were administered before the procedure; instead, an antibacterial gauze was placed around the insertion site immediately after the procedure for three days as described in our recent publication [13]. Oral anticoagulants were paused (preferable international normalized ratio <1.5 in case of vitamin K antagonists) as well as platelet aggregation inhibitors. COX inhibitors were continued.

Sedation was administered to all patients, mostly in a two-step approach (dose titration), with monitoring of blood pressure, heart rate and oxygen saturation by pulse oximetry. No contraindications for referral to an anaesthesiologist were present and service was available in case emergencies or problems occurred. Our department has extended experience with the administration of sedation in endoscopy procedures, also in high-risk procedures.

Patients were observed in the day care unit for at least 2 h.

Data collection
Baseline data collected from medical records were sex, age, interval between diagnosis and PEG insertion, and between insertion and death, comorbidities and forced vital capacity (FVC). Outpatient follow-up data were collected after fourteen days by telephone or outpatient clinic consultation and annotated in patients’ files. Patients or relatives (in case of problems with speaking) were asked whether any complications or adverse events had occurred. All complications were documented and treated if necessary. Retrospectively, all patient files were investigated to determine whether any long-term complications had occurred (with a maximum of 6 years) and survival analysis was carried out.

Outcome measures
The primary outcome was the occurrence of complications, attributable to the procedure (≤30 days), respiratory as well as other complications.

The secondary outcomes were long-term complications, PEG usage (complete or partial enteral feeding), time between placement and start of use, term of use, 30-day mortality and overall survival after PEG.

Statistical methods
Data analysis was carried out using SPSS for Windows, version 23 (IBM Corporation, Armonk, New York, USA). Data are presented as frequencies for categorical variables and as mean±SD for continuous variables. Normal distribution was tested for continuous variables. \( \chi^2 \)-Tests were used to compare categorical data and t-tests for continuous data.

To estimate odds ratios and 95% confidence intervals to identify predictors or risk factors of complications and mortality, \( \chi^2 \)-tests were used. Fisher’s exact tests were used in small sample sizes (if more than one cell or 20% had an expected count <5). No multivariate logistic regression was performed as no comparable significant results were found in the univariate analysis. All statistical tests were two-sided, with a significance level of 0.05.

Ethical considerations
The present study did not require approval, as confirmed by the Medical Research Ethics Committee of the Catharina Hospital Eindhoven. The Medical Research Involving Human Subjects Act was confirmed to not be applicable to this study. The study was carried out in full accordance with the Dutch Codes of Conduct.
Results

A total of 48 ALS patients underwent PEG placement between 2009 and 2016 at our institution. Three patients were excluded from the analyses as they received no sedation (n=1) or propofol sedation (n=2, clinical preference of one gastroenterologist). A total of 45 patients were included in the analysis. Baseline characteristics are listed in Table 1. The technical success rate of PEG placement was 100%.

Sedation

Intravenous midazolam was used for conscious sedation. Dose ranges were 2.5–7.5 mg, but 87% received 5 mg (2.5 mg: 8.6%; 7.5 mg: 4.4%). Five (11%) patients received fentanyl (mean dose 80 µg, range: 50–100 µg) combined with standard midazolam.

At the very beginning of PEG placement in ALS in our hospital, flumazenil (a midazolam antagonist) was administered as a preventive measure, after completion of the insertion, in three patients. No flumazenil was necessary for hypoxaemia or hypoventilation. Short periprocedural hypoxia was found in one patient, with rapid recovery after extra oxygen administration (through a nose sponge).

Forced vital capacity

FVC ranged between 24 and 116% (mean 68.4%). A mild to moderate impairment was found in 42.2% of patients, and severe to very severe impairment (FVC <50%) in 8.8%. In 13.3%, values were unknown. One of these patients was not able to enclose the mouthpiece. In others, no documentation was found.

Complications

No respiratory complications, such as respiratory insufficiency or (aspiration)pneumonia, occurred within 30 days after PEG placement. All other complications are listed in Tables 2 and 3. One patient had bleeding requiring surgical suturing and four patients developed a peristomal infection requiring antibiotic treatment (8.9%). No peritonitis occurred. One patient developed a small bowel ileus, with rapid recovery after interrupting tube feeding for a few days.

Univariate analysis indicated no risk factors for any of the complications that occurred. No significant association was found between sex, FVC, sedation, BMI, age or origin of symptoms compared with any of the early and late complications. Therefore, no multivariate analysis was carried out.

Use of percutaneous endoscopic gastrostomy

In most cases, feeding through PEG was started immediately (64.4%). Six (13.3%) patients started using the PEG only after several weeks to months and three (6.7%) did not use it at all. In seven patients, no data were available.

Mortality

The 30-day mortality was zero. An overall survival rate after PEG placement of 13.4 months (range: 1–45 months) was found. At the end of follow-up (maximum 6 years), 3 (12%) patients were still alive (12, 17.5, 24 months after PEG placement). In two patients, time of death remained unknown because of shifting to another centre for their ALS care and thereby loss to follow-up.

BMI, age, sex, FVC at PEG insertion, amount of midazolam used during the procedure and (start of) use of PEG were not found to be risk factors for mortality in univariate analysis.

Follow-up was recorded in our hospital records (medical and endoscopy unit records) as well as in the records of the revalidation centre. For our primary outcome, 100% of data were complete. In seven (15.6%) patients, data considering long-term use of PEG were missing and in two patients data considering survival were missing. Long-

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Sex</th>
<th>n (%)</th>
<th>(N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>20 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>25 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36–88</td>
<td>68.69 (12.1)</td>
</tr>
<tr>
<td>Range (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>15 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Limb</td>
<td>11 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>11 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>FTD/mixed</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (13.3)*</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤18</td>
<td>2 (4.5)</td>
<td></td>
</tr>
<tr>
<td>20–25</td>
<td>24 (53.3)</td>
<td></td>
</tr>
<tr>
<td>25–30</td>
<td>9 (20)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range (%)</td>
<td>24–116</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>68.4 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Forced vital capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
<td>16 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Mild (60–69)</td>
<td>13 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Moderate (80–59)</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Severe (80–48)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Very severe (≥30)</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>44 (97.8)</td>
<td></td>
</tr>
</tbody>
</table>

*aTotal 99.8% because of round-off.

FTD, frontotemporal Dementia.

Table 2. Early complications (≤30 days)

<table>
<thead>
<tr>
<th>Complication</th>
<th>n (%)</th>
<th>(N=47*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Periprocedural</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Local irritation (wound care)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Infection (antibiotics)</td>
<td>4 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bleeding (requiring sutures)</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Peristomal leak</td>
<td>4 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Ileus</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Dislocation</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Obstruction</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Pain (minor, spontaneous relief)</td>
<td>6 (13.3)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>29 (64.4)</td>
<td></td>
</tr>
</tbody>
</table>

*In some patients more than one complication occurred.
term complications were all registered as patients then returned to our hospital.

Discussion

In this retrospective case series of PEG insertions in ALS patients under conscious sedation, no respiratory complications such as apnoea, hypoxia, (aspiration) pneumonia or laryngospasms were encountered. The frequency of other PEG-related complications was comparable to that in patients with other indications in our own analysis as well as former published data [13,15].

Conscious sedation is often feared in ALS patients and was even advised against in the Dutch National Guideline [1]. The European guideline is very cautious considering sedation as well [5]. These advices are, however, based on scarce and very limited data, with low level of evidence (class III–IV) [1,5]. The AAN guideline does not even mention sedation in PEG placement [16].

A few other studies have reported on safe sedation with midazolam (and one study with propofol) in patients with a FVC less than 50% undergoing PEG placement. However, to date, in all studies, NIPPV was used during the procedure, contrary to our experiences [17–19]. Recently, Dorst et al. [20] reported that PEG could be performed safely even in advanced stages of ALS. In their study, 20 patients received general anaesthesia during PEG placement; in 63 patients, only local anaesthetics were administered. The effect of conscious sedation was not studied [20]. In our study, sedation was used safely, even in patients with mild to moderate respiratory dysfunction. On the basis of these results, we postulate that safe use of conscious sedation during PEG placement in ALS patients is possible and deserves broader evaluation and application in care for ALS patients.

The timing of PEG in ALS patients remains a difficult decision that should be made on the basis of several criteria.

Most importantly, PEG feeding should prevent (further) weight loss as this is a well-known poor prognostic factor [7,16]. Second, safe insertion is a key point in this very frail patient group. Third, patient comfort during PEG insertion should be ensured. Currently, no evidence-based advice on the timing of PEG can be given because of insufficient data [5,16].

Guidelines recommend placement before FVC falls below 50% to decrease the risk [1,5,16]. Evidence is of low level (III–IV) on the basis of few small sample size retrospective studies [10,21–23]. The increasing risk of aspiration pneumonia with progression of the disease is seen as a strong argument in favour of PEG placement [1]. Gastrostomy feeding is believed to reduce the risk of aspiration; however, no convincing evidence to support this belief has been found yet [5,10,24].

In contrast, fear of respiratory complications because of low or declining FVC might result in too early placement, without ever using the PEG. Our results do indicate a low risk for respiratory complications in patients that have been referred in time for PEG placement. Regular evaluation of lung function was part of the follow-up. The counterpart of this careful approach with measuring lung function regularly, and thereby early placement of PEGs, is the fact that six (13.3%) patients started using PEG only after a few months and three (6.7%) patients did not use the PEG at all. Preventive PEG placement is confronting for patients and points towards progression of their disease. It is therefore often experienced as very unpleasant as it points towards progression of their disease. Despite our advice on the risks, patients prefer placement in a later phase of their disease [25].

Although a low or a rapidly declining FVC in ALS patients often determines the timing of PEG insertion, use of FVC as the most important variable is questionable. FVC has proven to be a poor predictor of respiratory failure [26] and of diaphragmatic weakness [27]. Recently, Dorst et al. [20] reported that FVC does not influence the periprocedural survival of patients after PEG. This is in line with the findings obtained by and Kak et al. [28] and Sarfatty et al. [29].

Measurement of lung function through FVC is difficult to perform in ALS patients with bulbar involvement because of trouble with enclosing the mouthpiece. In addition, patients often do not have enough strength to perform a forced expiration. Therefore, forced expiration may not be a representative predictor for the safety of the intervention under conscious sedation. Diffusion capacity, measured by CO2 in expired air, preferably overnight, may prove to be more accurate. In the Netherlands, this procedure is currently only used as a measurement in overnight home ventilation and has not been evaluated as a predictor for the safety of PEG placement.

In general, sedation may result in respiratory side effects, such as hypoxia, hypercapnia, aspiration and related pneumonia. Midazolam might cause pharyngeal dysfunction and a disturbance of breathing coordination. There is a risk of apnoea and hypventilation of up to 15.4%; however, severe events are very rare. The reported overall frequency of respiratory arrest is 0.099% [30,31]. In our series, with midazolam sedation, no pulmonary complications occurred.

Recently, conscious sedation with propofol administered in the endoscopy room by trained personnel, has become more common for invasive endoscopic procedures including PEG. Because of its short time of action and more accurate titration of dose, propofol seems to be a suitable alternative for midazolam sedation. However, a higher risk for assisted ventilation was found in interventional endoscopy procedures when using propofol [32]. In ALS, safe PEG placement with propofol sedation was shown in patients with FVC less than 50%, but with the use of bi-level positive airway pressure ventilation during placement [18].

Possible enteral feeding alternatives for PEG in ALS patients are PRG and surgical gastrostomy or jejunostomy. PRG and PEG are comparable considering the complications and mortality [9,33]. PRG was found to have a higher success rate (100%) compared with PEG (83.6%) in ALS patients [34]. Our data point to a 100% success rate for PEG. In general, no sedation is necessary in PRG.

Table 3. Late complications (>30 days)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n (%)</th>
<th>(N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin deterioration</td>
<td>3 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Buried bumper</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Prolonged pain</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Replacement</td>
<td>1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>38 (84.4)</td>
<td></td>
</tr>
</tbody>
</table>

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It has a comparable procedure-related and 30-day mortality in ALS [11,33,35,36]. However, PRG is not readily available in all centres and is known to have a higher rate of dislocation (40 vs. 6% in PEG) [37]. Surgical gastrostomy and jejunostomy are associated with higher morbidity, up to 29% [38–40], and are therefore (1% of cases) performed very rarely in ALS [33].

Total parenteral nutrition should only be used as a last resort in patients with severe respiratory insufficiency [41–43].

**Survival**

The 30-day survival rate in our group was 100%. The largest prospective trial to date reported a 30-day mortality of 4% [33], but rates of 25% [44] have also been reported. Mathus-Vliegen et al. [45] as well as Kasarskis et al. [22] reported a higher risk of 30-day mortality in patients with an FVC less than 50% (9.6 and 11.5%, respectively). In our group, only four ALS patients had a FVC less than 50%. Mortality at 30 days was zero.

Overall mortality during the entire study interval was 88%, not related to PEG placement or to the use of sedatives. The mean survival after PEG placement was 13.4 months (range: 1–45 months). These data are comparable to previous literature data (varying from 5 to 19 months) [11,12,20,44,46]. The overall survival of an ALS patient starting from diagnosis is 32 months [6].

The major strength of the current study is that it is the first to address safe conscious sedation in ALS patients without using NIPPV during the procedure. Furthermore, our analysis included 45 patients with negligible loss to follow-up, and uniform preinterventional, peri-interventional and postinterventional care. Our data add new information to that from previously published studies on PEG placement and conscious sedation in ALS [17–19].

The limitations of this study relate to its retrospective nature and the lack of a control group. There are missing data for two secondary outcomes (overall mortality and use of PEG for enteral nutrition), and therefore, a risk of bias is present. Our series included a relatively large group of patients with moderately impaired pulmonary function compared with previous reports with patients with more severe impaired pulmonary function.

Nevertheless, other risks of bias are low as all patients referred for PEG were included in the analysis.

We postulate that in a setting with an experienced and dedicated team, conscious sedation is safe and a considerable option during PEG insertion. Our results, hopefully, will open the discussion on this subject in favour of patient comfort, without impairing safety. Because of the retrospective nature of the study and the lack of a control group, our results should ideally be confirmed in randomized-controlled trials.

Future research should also focus on the exact influence of varying sedatives on respiratory muscle in ALS. In addition, comparison of CO₂ diffusion with FVC as a measurement of lung function in ALS could be of interest to determine timing and safe PEG insertion more accurately.

**Conclusion**

We have shown that in experienced hands, the risk of respiratory complications and procedure-related mortality with conscious sedation (with midazolam) in ALS patients undergoing PEG placement is absent, even in patients with mild to moderate pulmonary dysfunction. Confirmation of our results by data from other centres is needed. Here, we contribute towards a discussion on the safety of sedation in a high-risk endoscopic procedure in a group of very frail patients. Although more extensive data are needed, our findings are in favour of revision of guidelines on PEG placement in ALS patients.

**Acknowledgements**

**Conflicts of interest**

There are no conflicts of interest.

**References**

1308 European Journal of Gastroenterology & Hepatology

November 2017 • Volume 29 • Number 11


