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The routine use of a flumazenil infusion following percutaneous endoscopic gastrostomy placement to reduce early post-procedure mortality

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ABSTRACT
Objectives: Percutaneous endoscopic gastrostomy (PEG) insertion offers secure enteral nutrition, but there is a significant mortality associated with the procedure. We reviewed our sedation practice and the effect of yearly protocol changes to establish if the routine reversal of midazolam with a flumazenil infusion improved mortality.
Methods: Since 2003 yearly protocol changes have been introduced, including pre-assessment and sedation reversal. We retrospectively audited one-week and one-month mortality and aspiration rates.
Results: The average one-week mortality rate was 9.2%. The pooled death rates within the first week for patients prior to routine sedation reversal (n=522) was 10.7% and for patients who received routine reversal (n=144) was 5.4% (p=0.087). Within the first month, death rates were 26.3% prior to reversal and 21.4% in the sedation reversal group (p=0.30).
Conclusions: The routine use of flumazenil infusion in appropriate patients is safe. Flumazenil infusion may have a role to play in selected patients at highest risk of aspiration. A prospective, randomised study is warranted.

KEYWORDS Endoscopy, flumazenil, percutaneous endoscopic gastrostomy, sedation, sedation reversal

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is a well-established and commonly practised method to provide a route for enteral feeding. It is a relatively low-risk procedure, is well tolerated[1] and, compared with surgical gastrostomy, is the preferred method of insertion of gastrostomy tube due to a reduced complication rate.[2]

The mortality related to the insertion of PEG tubes, especially in the 30-day post-insertion period, has been shown to be in the range of 4–26%.[3] A significant source of morbidity and mortality is aspiration pneumonia, with the incidence in one study being 2.7% after initiation of PEG feeding.[4]

Safety surrounding endoscopic procedures, particularly PEG insertion, is an important issue and the role of pre-assessment to establish the suitability for PEG insertion was advocated by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report *Scoping our practice*.[5] The 2005 Feed Or Ordinary Diet (FOOD) trial demonstrated increased mortality following early PEG placement (within one week) following cerebrovascular accident, compared with nasogastric (NG) feeding, emphasising the difficulties in the timing of PEG placement.[6]

Many patients who require PEG feeding are frail, have multiple co-morbid conditions and are therefore at risk from both sedation and endoscopic intervention. Patient selection is important and a multidisciplinary assessment framework has been shown to reduce early post-PEG mortality in our unit.[7] In the period 2003–04, when pre-assessment was introduced, we recorded a zero one-week mortality.[7] However, in subsequent years following this study, despite continued pre-assessment, there has been an increase in one-week post-PEG mortality and we considered early post-PEG aspiration as a cause. We also questioned whether the use of sedation was contributing to aspiration in our patients. Intravenous midazolam is the benzodiazepine of choice for sedation in most endoscopy units. Flumazenil (Annexate®, Roche) is a benzodiazepine receptor antagonist which is approved for the reversal of sedation from benzodiazepines used during therapeutic procedures.[8] Importantly, the pharmacokinetics of midazolam are such that it has a longer duration of action than a single bolus of flumazenil, particularly in older patients.[9]

As a result of concerns about the increase in one-week post-PEG mortality, possibly as a result of prolonged sedation in elderly patients, we instigated a change in practice: the routine use of flumazenil as a continuous

TABLE 1 Study population

	No sedation reversal		Routine sedation reversal		
Year (n)	2003–04 (63)	2004–05 (66)	2005–06 (51)	2006–07 (47)	2007–08 (46)
Males	30	32	23	22	22
Females	33	34	28	25	24
Mean age (range)	72 (21–94)	71 (23–93)	77 (50–97)	76 (52–91)	73 (51–90)
Residence prior to admission					
Own home	48	42	39	36	37
Warden-controlled	2	0	0	1	0
Residential home	0	6	2	0	2
Nursing home	13	18	10	10	7
Primary diagnosis which required PEG tube insertion					
Stroke	37	28	24	24	22
Progressive neurological disease	15	16	13	11	10
Cancer	6	4	5	0	5
Other	5	18	9	12	9

TABLE 2 PEG procedure regimen and midazolam dose

Year	Protocol	Mean dose (mg)	Median dose (mg)	Range (mg)
1995–2003	No pre-assessment; Midazolam	Not recorded	Not recorded	Not recorded
2003–04	Pre-assessment introduced; Midazolam and lidocaine throat spray	3.1	3	1–10
2004–05	Pre-assessment; Midazolam and lidocaine throat spray	2.9	3	1–10
2005–06	Pre-assessment; Midazolam only; Flumazenil reversal regimen	3.3	3	0.5–10
2006–07	Pre-assessment; Midazolam only; Flumazenil reversal regimen	3.4	3	1–10
2007–08	Pre-assessment; Midazolam only; Flumazenil reversal regimen	4.0	4	2–10

infusion following a single bolus, to eliminate the effects of midazolam in the post-PEG insertion period. We also postulated that aspiration rates may be increased with the use of local anaesthetic throat spray, therefore we wished to investigate the effect of using midazolam alone, compared with the addition of local anaesthetic throat spray.

PATIENTS/MATERIALS AND METHODS

This paper is a retrospective audit of prospectively collected data for patients accepted for PEG placement in a UK district general hospital. Data were collected for individual years (August to July) and protocols were altered at the beginning of each year. After receiving PEG referral, multidisciplinary pre-assessment was carried out to establish patient suitability to undergo PEG insertion. In an effort to reduce procedure-related confounders, more than 95% of PEG tubes were placed by a single consultant gastroenterologist or specialist registrar under his supervision, assisted by a single clinical nurse specialist. All patients received intra-nasal oxygen therapy and continuous oxygen saturation monitoring during the procedure and recovery. The patient demographics are shown in Table 1.

Patients were given pre-procedure antibiotics as recommended by the British Society of Gastroenterology (BSG).[10] Freka® (Fresenius Kabi) 15-Fr gauge tubes were inserted endoscopically. Specific changes in procedure protocol are outlined in Table 2.

Data for all patients were entered into a database (Microsoft Access) and information regarding mortality at one week and one month as well as clinically apparent aspiration episodes was recorded prospectively by review of patient notes or by telephone.

The regimen used for reversal of sedation was designed so as to ensure antagonism until full benzodiazepine clearance.[11] An initial bolus of 500 μg flumazenil was followed by 1,000 μg made up to a volume of 50 ml, infused over 10 hours intravenously.

Patients under general anaesthetic and those on long-term benzodiazepine therapy were excluded from the study as neither group received flumazenil. We also excluded patients under the age of 50 years as these patients did not receive flumazenil infusion because the risk of benzodiazepine toxicity is low. In the study period 2005 to 2008, 79% of patients undergoing PEG insertion in our unit received the flumazenil regimen. Statistical analysis was performed using Stata Version 10 (StataCorp).

RESULTS

Table 1 shows the demographics of the study population, Table 2 outlines the protocol changes and the doses of sedation administered and Figure 1 documents the mortality data at one week and one month. From 2005, for the purposes of this audit, only those patients who

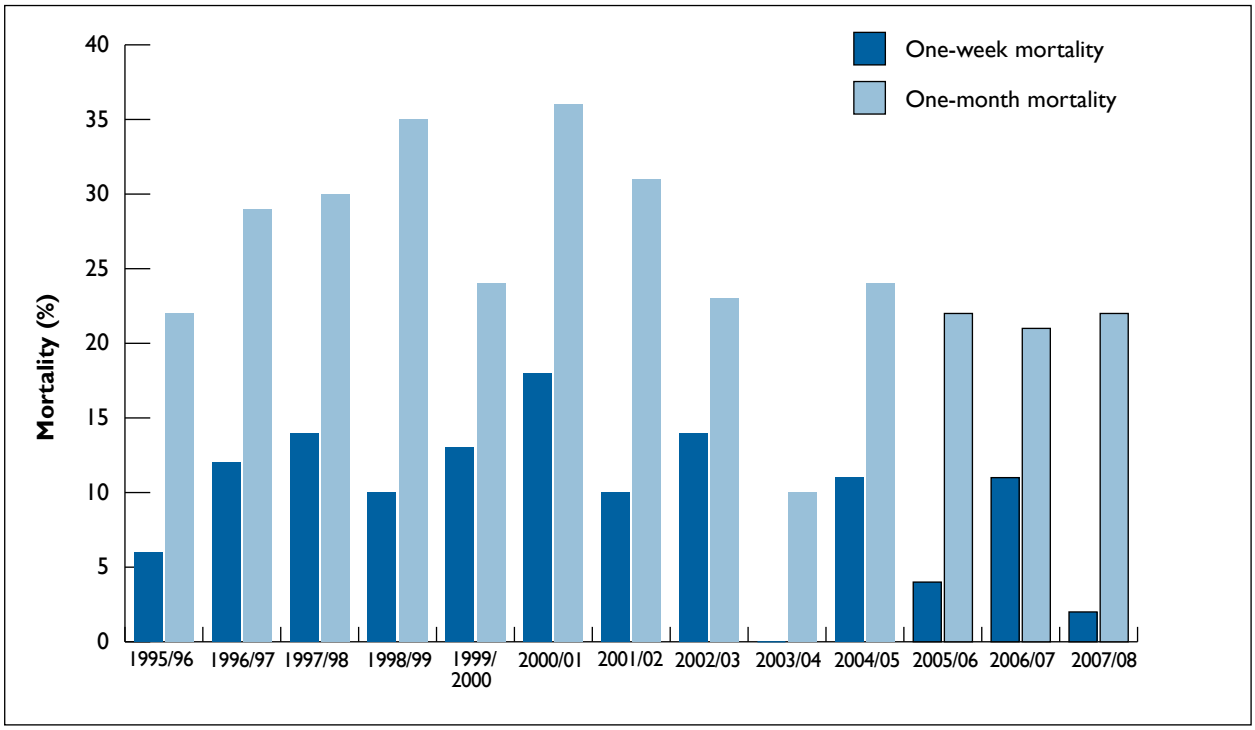

FIGURE 1 Mortality at one week and one month. Bars surrounded by a black line indicate patient groups on the flumazenil regimen.

received benzodiazepine reversal are included. In the study periods from 2005, seven patients were excluded from the analysis if they received a single bolus dose of flumazenil only without infusion (three patients in 2005–06 and four patients in 2007–08). These patients were attending for day-case procedures and were discharged once fully awake.

Across all years, pooled one-week mortality rate is 9.2% (95% confidence interval [CI]: 6.6–12.7%). The pooled death rate prior to the introduction of routine sedation reversal is 10.7% (95% CI: 7.8–14.4%). For the routine reversal cohort, the pooled death rate post-2005 is 5.4% (95% CI: 2.5–11.1%). The difference in mortality between these two groups is 5.3%, which is in favour of routine sedation reversal, but this is not statistically significant (p=0.087).

Regarding mortality at one month, across all years, the average death rate is 25.2% (95% CI: 21.3–29.4%). The pooled death rate pre-2005 is 26.3% (95% CI: 22.1–31.1%) and the pooled death rate post-2005 is 21.4% (95% CI: 14.7–30.0%). The difference in death rates between these two groups is 4.9% in favour of post-2005, but this is not statistically significant (p=0.30).

Aspiration, defined as any clinical or radiological episode of consolidation, hypoxia or dyspnoeic episode were between 5% and 8% for the period from 2003 to 2008, and were not reliably recorded prior to this. For the 144 patients who received routine reversal of sedation, clinically apparent aspiration episodes occurred in 7.6% of patients within one week.

In 2004, lidocaine throat spray was used in conjunction with a titrated dose of midazolam to improve toleration of the procedure and allow as small a dose of sedation as possible to be administered. The changes in protocol outlined in Table 2 show that, when routine reversal of sedation was commenced, the use of lidocaine spray was withdrawn. The dose of midazolam used was still determined by dose titration and procedure tolerance. We show a trend towards using more midazolam (a mean dose of 3.3 mg in 2005–06, 3.4 mg in 2006–07 and 4.0 mg in 2007–08).

Complication summary

In the study period from 2005 to 2008, six procedures failed on account of inability to intubate the oesophagus or anatomical problems preventing safe PEG insertion. There were no identifiable adverse events related to the use of flumazenil; particularly, there were no seizures.

DISCUSSION

The pharmacokinetics of midazolam are altered with age, with evidence that the half-life is prolonged in older patients.[8] A study that analysed patients undergoing minor surgery found the elimination half-life of midazolam to be 2.4 hours for patients aged less than 50 and 4.1 hours for those aged over 50, explained by alterations in clearance and volume of distribution of the drug with advancing age.[11] Drug elimination is likely to be further reduced by the effect of the comorbidities encountered in patients who undergo PEG insertion, for example cardiac failure.

One characteristic of flumazenil's pharmacodynamic profile is a dose-dependent effect with regard to benzodiazepine antagonism. The duration and degree of benzodiazepine reversal is related to the plasma concentrations of both the benzodiazepine involved and flumazenil. Benzodiazepines and their metabolites also undergo a high degree of protein-binding. In disease states, the fraction of unbound drug can be increased, resulting in a toxic condition despite normal serum benzodiazepine levels.[9] In order to ensure complete reversal of the benzodiazepine, multiple dosing or a prolonged infusion of flumazenil is required, particularly in older or dehydrated patients, with prolonged benzodiazepine pharmacokinetics. Continuous infusions of flumazenil, used in benzodiazepine overdose, are safe where bolus injection is insufficient to counter the resedating effect of the benzodiazepine.[9]

We have confirmed that the routine use of flumazenil following benzodiazepine sedation specifically following PEG insertion is safe. This assumes that there is no identified contraindication, such as patients with epilepsy who are taking long-term benzodiazepines or antidepressants, for whom the use of flumazenil may lower seizure threshold. Our aspiration rates in the first week after PEG insertion are similar in the pre- and post-flumazenil datasets and higher than in the published literature,[4] possibly due to the diagnostic threshold used to define an aspiration episode. Our results show a trend towards a rising midazolam dose corresponding to the withdrawal of lidocaine throat spray and postulate that the use of local anaesthetic may allow a lower titrated dose of benzodiazepine to be used.

Our population demographics were comparable year on year, with around 50% of patients being referred for PEG insertion on account of stroke disease. We have shown an overall reduction in post-PEG mortality since 2003, which is likely to be primarily the effect of robust patient selection through pre-assessment, co-ordinated by a dedicated PEG nurse.

This study supports previous data that showed flumazenil infusions to be safe and well tolerated.[9] Although there is a trend to suggest that the routine use of a flumazenil infusion may reduce post-PEG mortality and aspiration, this is not statistically significant and other changes in practice were implemented during the study period. Furthermore, although there may have been a small effect on one-week post-procedure mortality, the one-month post procedure mortality rate remained at 21–24% in the years after routine flumazenil infusion was introduced. This emphasises how severely unwell are patients who require a PEG, particularly older patients with co-morbidity recovering from a stroke.

Although interesting, our results do not clearly demonstrate that the routine use of sedation reversal following PEG insertion confers improvement in mortality, and thus prospective randomised studies would be required to further investigate the potential advantage of this intervention, which may be particularly beneficial for patients who are at the highest risk of aspiration. However, until such studies are performed, the routine use of a flumazenil infusion cannot be justified.

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