



RESEARCH

Risk factors for endoscopic sedation reversal events: a five-year retrospective study

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ABSTRACT

Objective Conscious sedation is widely used in endoscopic practice but is not without risk. We aimed to determine the frequency of sedation complications requiring reversal, and to identify potential patient and procedural risk factors.

Design A retrospective study of all gastrointestinal endoscopic procedures performed under conscious sedation, in a large three-campus tertiary referral endoscopic centre, between 12 October 2007 and 31 December 2012 (n=52 553). Flumazenil or naloxone administration was used as a marker of sedation complications requiring reversal. Reversal cases were analysed for associations with sedation dose, patient American Society of Anesthesiologists (ASA) grade, age and type of procedure undertaken.

Results In total, 149 sedation reversals occurred, representing 0.28% of all sedated endoscopic procedures carried out. Endoscopic Retrograde Cholangiopancreatography (ERCP) and increasing patient ASA grade were positively associated with sedation reversal ($p<0.05$). Mean midazolam dose was highest for ERCP (4.9 ± 2.9 mg) and lowest for flexible sigmoidoscopy (1.7 ± 0.6 mg; $p<0.01$). Mean opioid dose (calculated as pethidine equivalent) was highest for ERCP (62.9 ± 38.7 mg) and lowest for gastroscopy (6.9 ± 13.5 mg; $p<0.01$). Maximum doses of midazolam or opioid recommended by the British Society of Gastroenterology were exceeded in 7.4% and 14.1% of reversals, respectively.

Conclusions ERCP procedures and higher patient ASA grade were associated with an increased risk of conscious sedation-related complications requiring reversal. In these high-risk groups, alternative sedation strategies should be considered and tested. Prospective studies are needed to further explore risk factors that may help predict adverse sedation outcomes.

INTRODUCTION

While sedation plays an integral role in endoscopic practice, it is not without risk. Most gastrointestinal (GI) endoscopic procedures are performed under ‘conscious sedation’, a drug-induced depression of consciousness during which patients are able to maintain purposeful responses to verbal or tactile stimulation, and cardiorespiratory function remains intact.¹

Over the past decade, there has been a significant increase in awareness of the potential hazards of endoscopic sedation. Synergistic action between benzodiazepines and opioids further increases this risk. In a nationwide study from the USA, 96.9% of all endoscopic procedures were performed under conscious sedation. Complications occurred in 1.4% of cases, of which 0.9% were cardiorespiratory events.² Safe sedation guidelines produced by the British Society of Gastroenterology (BSG) and the American Society for Gastrointestinal Endoscopy highlight the need for accurate patient risk stratification, close procedural monitoring and minimisation of sedation doses.^{3 4}

A UK National Confidential Enquiry into Patient Outcome and Death (2004) evaluated inpatient deaths occurring within 30 days of therapeutic GI endoscopic procedures. In 14% of cases, the sedation doses were judged to be inappropriate.⁵ Serious harm or death resulting from midazolam or opioid overdose during conscious sedation is now a UK Department of Health ‘Never Event’ (2012–2013).⁶

Establishing risk factors to help predict adverse responses to conscious sedation may help reduce the incidence of

sedation-related complications. In this study, we retrospectively analysed GI endoscopic procedures performed under conscious sedation (midazolam \pm opioid) over a 5-year period. Our objective was to assess the frequency of sedation complications requiring reversal, and to identify potential patient and procedure related risk factors.

METHODS

Study population

Imperial College Healthcare NHS Trust, London, UK, comprises a large three-campus tertiary referral endoscopic centre, with an estimated catchment population of 650 000.⁷ The three endoscopic units based at Charing Cross, St Mary's and Hammersmith hospitals, undertake around 17 000 endoscopic procedures per annum.⁷ We performed a retrospective analysis of endoscopic procedures carried out in the Trust between 12 October 2007 and 31 December 2012. All endoscopic procedures performed under conscious sedation (midazolam \pm opioid), excluding propofol administration, were included in the study. We compared our results with a previous two-site Trust audit conducted by our group between 1 January 2000 and 31 December 2005 (unpublished data).

Endoscopic data collection

The Trust endoscopy reporting software and database system 'Scorpio' (Ascribe, UK), was analysed to identify all sedation reversal events that occurred between 12 October 2007 and 31 December 2012. Flumazenil or naloxone administration was used as a marker of sedation complications requiring reversal treatment. Only reversal events that occurred during or immediately after the procedure, in the endoscopy room, were included in our study.

Patient and procedure related risk factors for sedation reversals

The endoscopic records for all patients who received sedation reversal drugs, flumazenil or naloxone, during their endoscopic procedure were analysed to identify patient age, the documented American Society of Anesthesiologists (ASA) grade, type of procedure undertaken, type of sedation used and the total doses of midazolam \pm opioids administered.

All opioid doses were converted to pethidine equivalent doses to allow comparison. We note that there are differences in the literature regarding opioid conversion ratios and the published experience is limited. We used the conversion ratio of 100 μ g fentanyl being approximately equivalent to 75 mg pethidine based on their equivalent analgesic activity, and 1 mg alfentanil being approximately equivalent to 150 mg pethidine.^{8–11} Conversion calculations are detailed in online supplementary appendix 1.

30 day mortality rate following endoscopic procedures

All cases where patients died within 30 days of their endoscopic procedure were identified. Individual case notes for these patients were obtained from medical records to assess the rationale for the endoscopy, type and doses of sedation used, documented reason for sedation reversal, the patient's medical history, ASA grade, and whether the sedation used during the endoscopic procedure may potentially have contributed to the mortality.

Statistical analysis

Results were expressed as mean \pm SD for continuous variables and frequency (%) for categorical variables. Statistical analysis was carried out using χ^2 test and the linear regression model. All tests were performed using Origin (OriginLab Corporation, USA). In all cases, the null hypothesis tested was that there was no association between the variables, and a p value of <0.05 was considered statistically significant.

RESULTS

A total of 73 989 endoscopic procedures were performed across the three endoscopic units over the study period. Conscious sedation (midazolam \pm opioid) was used in 52 553 procedures. Flumazenil or naloxone was required in 149 endoscopic cases, representing 0.28% of all sedated endoscopic procedures carried out. This was comparable with our previous audit, 2000–2005, with a sedation reversal rate of 0.27%. No significant difference was noted in the overall sedation reversal rate between the two study periods (0.28% vs 0.27%; $p>0.79$).

Endoscopic Retrograde Cholangiopancreatography (ERCP) was the procedure type most commonly associated with sedation reversal, with a sedation reversal rate of 1.0% ($p<0.05$) (figure 1A). This was followed by enteroscopy (0.40% reversal rate), gastroscopy (0.27%), colonoscopy (0.22%), flexible sigmoidoscopy (0.21%) and endoscopic ultrasound (0.09%).

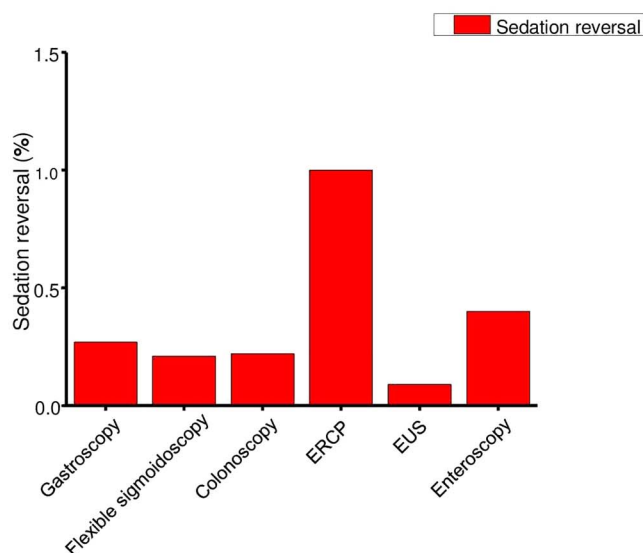
Patient demographics for sedation reversal events are presented in table 1. There was a positive association with sedation reversal and increasing patient ASA grade ($p<0.05$) (figure 1B). No significant association was found between patient age (\leq or >70 years) and the frequency of sedation reversal events.

The mean dose of midazolam used in reversal events was 3.0 mg (range 0.5–14 mg). The mean dose of midazolam varied by procedure type and was highest for ERCP (4.9 ± 2.9 mg) and lowest for flexible sigmoidoscopy (1.7 ± 0.6 mg; $p<0.01$) (see online supplementary appendix 2). Midazolam doses exceeding 5 mg were administered in 7.4% of reversal cases (11/149 procedures, nine of which were ERCP procedures).

Opioids were used in 55.7% of reversal cases (83/149 procedures) and included pethidine, fentanyl or alfentanil. All opioid doses were converted to a

A Sedation reversal and type of procedure

Bar graphs showing the association between the percentage of sedation reversal events and type of endoscopic procedure.



B Sedation reversal rate and ASA grade

Bar graphs showing the positive association between the percentage of sedation reversal events and patient ASA grade. ASA grade: (1) fit; (2) mild systemic; (3) severe systemic; (4) life-threatening systemic.

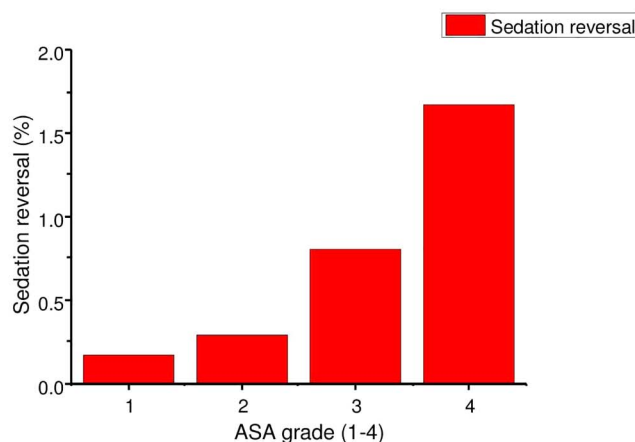


Figure 1 (A) Sedation reversal and type of procedure. Bar graph showing the association between the percentage of sedation reversal events and type of endoscopic procedure. (B) Sedation reversal rate and ASA grade. Bar graph showing the positive association between the percentage of sedation reversal events and patient ASA grade. ASA grade: (1) fit; (2) mild systemic; (3) severe systemic; (4) life-threatening systemic. ASA, American Society of Anesthesiologists; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound.

pethidine equivalent dose. The mean pethidine equivalent dose of opioid used was 47.9 mg (range 12.5–150 mg). The mean dose of opioid varied according to the procedure-type and was highest for ERCP (62.9 ± 38.7 mg) and lowest for gastroscopy (6.9 ± 13.5 mg; $p < 0.01$) (see online supplementary appendix 2). One enteroscopy procedure used a pethidine equivalent dose of 75 mg, however, given that this was the only enteroscopy reversal to occur, we have taken the highest statistically significant mean dose of opioid to remain for ERCP. Pethidine

equivalent doses exceeding 50 mg were administered in 25.3% of reversal cases where an opioid had been used (21/83 procedures, 18 of which were ERCP procedures), representing 14.1% of the total number of sedation reversal events.

No significant association was found between the mean dose of midazolam or opioid used in sedation reversal events and patient age (\leq or > 70 years).

The main reasons for sedation reversal were: hypoxia, hypotension, bradycardia, a reduced level of responsiveness and risk of aspiration from food

Table 1 Patient demographics in sedation-reversal events

Patient demographics	Number of patients (% of total)
Age	
≤70	79 (53.0)
>70	70 (47.0)
Sex	
Male	66 (44.3)
Female	83 (56.7)
ASA grade	
1 Fit	45 (30.2)
2 Mild systemic disease	53 (35.6)
3 Severe systemic disease	43 (28.9)
4 Severe systemic disease with a constant Threat to life	6 (4.0)
Not specified	2 (1.3)

ASA, American Society of Anesthesiologists.¹²

residue (table 2). In 56 procedures (37.6% of reversal cases), the rationale for the use of reversal agents had not been specified.

Ten patients died within 30 days of their endoscopic procedure being carried out. These patients' case notes were obtained from the medical records department (under the Data Protection Act 1998). Details of the 10 cases are presented (table 3). Four patients underwent upper GI endoscopies for percutaneous endoscopic gastrostomy placement, three patients required ERCPs for stent insertion, and three upper GI endoscopies were performed for haematemesis or melaena. Interestingly, on more detailed analysis, we found that the ASA grades documented for five patients had been underestimated. Overall, seven out of the ten patients were deemed to be ASA Grade 3 (severe systemic illness) and three patients ASA Grade 4 (severe systemic illness with a constant threat to life). Although these patients all experienced sedation-related complications requiring reversal, on review, the sedation did not appear to be a likely factor contributing to mortality.

Table 2 Documented rationale for sedation-reversal events

Indication for sedation reversal	Number of reversal events (% of total)
Hypoxia	28 (18.8)
Hypotension	26 (17.4)
Bradycardia	1 (0.7)
Respiratory depression	2 (1.3)
Reduced responsiveness	24 (16.1)
Risk of aspiration	12 (8.1)
Procedure abandoned due to poor bowel preparation	2 (1.3)
Patient discomfort/agitation	2 (1.3)
Drug induced ileus	1 (0.7)
Chest pain	1 (0.7)
Not specified	56 (37.6)

DISCUSSION

Conscious sedation remains the most commonly used endoscopic sedation strategy; improving patient comfort and overall endoscopist satisfaction.¹³ With increasing numbers of endoscopic procedures performed each year, patient safety is of vital importance. Serious harm or death resulting from midazolam or opioid overdose during conscious sedation is now a UK Department of Health 'Never Event'.⁶ However, data reporting endoscopic sedation-related complications varies widely, and few studies have explored the risk factors behind these adverse events. In this study, we focus on sedation-related complications significant enough to necessitate sedation reversal.

To the best of our knowledge, only one previously published study has specifically examined predictive factors for reversal agent use in GI endoscopy, however, this study from the USA was confined to ERCP procedures only.¹⁴ Our study is the first to examine sedation reversal events in detail across the full spectrum of GI endoscopic procedure types. We also believe it to be the largest retrospective study of endoscopic sedation reversal events in Europe. Our 5-year analysis, across a three-campus tertiary referral endoscopic centre, has revealed a subset of patients and procedures that may carry an increased risk of developing sedation-related complications requiring reversal. Identifying such risk factors may enable more accurate risk stratification prior to endoscopy and allow consideration, where necessary, of alternative sedation techniques.

First, our results suggest that patients with a higher ASA grade may be more likely to incur sedation-related complications requiring reversal. In support of this, a review of 324 737 endoscopic procedures by Sharma *et al* reported higher ASA grades to be a significant independent risk factor for cardiorespiratory unplanned events.² Old age (>60 years) and inpatient status were also identified as potential patient risk factors for endoscopic cardiopulmonary complications.² Since inpatients tend to be more unwell than outpatients, ASA grade may be a potential confounder for an inpatient association. Interestingly, in our study, we did not find a significant association between the frequency of sedation reversal events and patient age (less than vs greater than 70 years). We hypothesise that this may be due to more gradual increments of sedation being used in elderly patients, although prospective studies will be required to substantiate this.

Our data suggest that ERCP procedures may be associated with a higher rate of sedation complications requiring reversal compared with other endoscopic procedure types. Chawla *et al* reported the grade of difficulty of cannulation in ERCPs as a variable significantly associated with failure of gastroenterologist-directed conscious sedation.¹⁵ Furthermore, we found that ERCP procedures involved higher mean sedation doses. Despite synergistic effects between benzodiazepines and

Table 3 Cases of mortality within 30 days of the endoscopic procedure

Procedure type	Patient age (years)	Indication for procedure	ASA grade documented	Sedation used	Reason for reversal	Factors contributing to mortality
ERCP	80	Obstructive jaundice	Severe systemic	Midazolam 2 mg, Fentanyl 75 µg	Persistent hypoxia	Intracranial event, sepsis secondary to pneumonia, acute renal failure
OGD	81	Melaena	Fit (*Severe systemic)	Midazolam 1 mg	Hypotension	Recurrent GI bleed with no bleeding source identifiable. Pulmonary oedema, aspiration pneumonia, cellulitis
ERCP	59	Stent insertion (pancreatic cancer with gastric outlet obstruction)	Severe systemic (*Life-threatening)	Midazolam 3 mg, Fentanyl 50 µg	Deep sedation and food residue in stomach (risk of aspiration in recovery)	Metastatic pancreatic adenocarcinoma
OGD	85	PEG placement (unsafe swallow)	Severe systemic	Midazolam 2 mg	Hypoxia, reduced responsiveness	Aspiration pneumonia, acute mesenteric ischaemia likely embolic in origin secondary to AF
ERCP	45	CBD stricture, stent insertion	Severe systemic (*Life-threatening)	Midazolam 4 mg, Fentanyl 50 µg	Low respiratory rate	Advanced metastatic breast carcinoma
OGD	66	PEG placement (unsafe swallow)	Mild systemic (*Severe systemic)	Midazolam 2 mg, Pethidine 50 mg	Reduced responsiveness, not rousable postprocedure	Pneumonia, poor compliance with treatment secondary to dementia
OGD	76	Haematemesis	Mild systemic (*Life-threatening)	Midazolam 4 mg	Food residue in stomach (aspiration risk)	Advanced metastatic oesophageal cancer, persisting GI bleed (patient refused further intervention)
OGD	56	PEG placement	Severe systemic	Pethidine 50 mg	Reduced responsiveness postprocedure	HIV-associated progressive multifocal leucoencephalopathy
OGD	86	Melaena	Severe systemic	Midazolam 2.5 mg	Hypoxia	GI bleed with no bleeding source identifiable, pulmonary oedema, worsening acute on chronic renal failure
OGD	90	PEG placement	Severe systemic	Midazolam 1 mg	Hypoxia	Hospital-acquired pneumonia, <i>Clostridium difficile</i> infection, GI bleeding, congestive cardiac failure

*Pre-endoscopy patient ASA grade deemed to be different after review of individual patient medical case notes.

ASA, American Society of Anesthesiologists; AF, atrial fibrillation; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; GI, gastrointestinal; OGD, oesophago-gastro-duodenoscopy; PEG, percutaneous endoscopic gastrostomy.

opioids, higher doses of midazolam were frequently coupled with higher doses of opioids in ERCP procedures, providing a potential explanation for the increased rate of sedation complications in this group.

More than 48 000 ERCP procedures are performed in the UK each year.¹⁶ Due to their complex and often prolonged nature, ERCP procedures tend to require sedation for longer periods of time, leading to higher total sedation doses compared with routine upper or lower GI endoscopy. In view of this, a number of studies have explored different sedation combinations for these higher risk procedures.^{1 4 17 18}

Propofol is a rapid-onset, short-acting anaesthetic agent used to achieve deep sedation. Its use in endoscopic procedures in the UK remains limited, requiring the presence of a trained anaesthetist due to an increased risk of respiratory depression.¹⁹ Routine use of propofol incurs greater staffing demands, procedure time and costs and is, therefore, unrealistic. However, increasingly, studies have shown that with appropriate caution, propofol may be an

appropriate alternative sedation strategy for certain endoscopic procedures, particularly in high-risk groups.^{1 17 18 20}

A systematic review of studies comparing conscious sedation with deep sedation (propofol) in ERCP procedures found no significant difference in sedation-related complications between patient groups. Moreover, propofol administration was associated with faster patient recovery and higher patient satisfaction.¹⁸ Similarly, a randomised controlled trial comparing conscious sedation with propofol in high-risk patient groups (patients over the age of 80 years, with an ASA grade of 3 or above) found similar procedure tolerability in both groups, while propofol was associated with shorter recovery times and fewer oxygen desaturation events.²⁰ This suggests that in select patients, propofol administration may be a safe and feasible option when administered by trained personnel.

The overall frequency of sedation complications necessitating reversal in our study was 0.28%.

By comparison, a study of 21 011 endoscopic procedures by Arrowsmith *et al* reported serious cardiopulmonary complications in 0.54% of procedures using midazolam or diazepam.²¹ Sharma *et al*² reported a complication rate of around 1.4% of endoscopic procedures performed under conscious sedation. Of note, our study only included endoscopic cases where sedation complications necessitated reversal, therefore, the total frequency of sedation-related complications, including those not significant enough to require reversal, is likely to be higher than 0.28%.

The majority of sedation complications encountered in our study were cardiorespiratory events. In over a third of reversal cases, the specific nature of the complications necessitating reversal had not been documented on the endoscopy report. This information is valuable to help with future patient risk factor stratification and decisions regarding sedation strategies, therefore, more detailed documentation of sedation reversal events on endoscopic records should be provided.

The range of sedation doses used in our study was broad, with a midazolam dose range between 0.5 and 14 mg, and a pethidine equivalent dose range between 12.5 and 150 mg. The majority of endoscopic procedures requiring sedation reversal did not, however, involve excessively high sedation doses. Indeed, the mean dose of midazolam used in reversal events was 3.0 mg and the mean opioid dose (pethidine equivalent) was 47.9 mg, both within the maximum recommended doses specified by BSG safe sedation guidelines (ie, midazolam 5 mg, pethidine 50 mg).³ Overall, higher doses of midazolam or opioid than those recommended by the BSG were used in a total of 7.4% and 14.1% of all reversal cases retrospectively; this predominantly occurring during ERCP procedures. Arrowsmith *et al*²¹ found that in all cases of cardiopulmonary complications, no patients had received more than 10 mg midazolam. These observations suggest that sedation-related complications may still occur at relatively lower doses of sedation and may be influenced by multiple factors including ASA grade and a patient's inherent sensitivity to sedation, rather than by high sedation doses alone.

Our study is a retrospective analysis and is, therefore, limited by reliance on accurate documentation by endoscopists, particularly regarding the sedation doses given, the use of reversal agents and accurate patient ASA grade classifications. The ASA grades for five (out of 10) patients who died within 30 days of their procedure, had been underestimated, suggesting that ASA grades documented on endoscopy reports may not always have been accurately assessed prior to endoscopy. Only reversal agents administered in the endoscopy room were recorded in our study, therefore, any reversal events occurring postprocedure, in recovery areas, were not included.

Using endoscopy records retrospectively, the required data was not available to ascertain whether

sedation increments or boluses had been given. We hypothesise that in some cases where complications occurred with low sedation doses, boluses of sedation may have been given rather than increments titrated to effect. We plan on investigating this further with prospective studies, comparing reversal rates in endoscopic procedures where sedation boluses versus increments are given.

Interestingly, no significant difference occurred in the frequency of sedation reversal events in our current study (2007–2012) compared with our previous audit (2000–2005). This is likely to be due, at least in part, to suboptimal adherence to sedation guidelines. Several published studies demonstrate that, in general, adherence to guidelines in clinical practice remains inadequate. A systematic review by McGlynn *et al*²² identified that patients in the USA received 54.9% of guideline-recommended care. Furthermore, a systematic review by Ebben *et al*²³ showed a wide variation of adherence to clinical guidelines, between 7.8% and 95% in a prehospital setting, and 0% and 98% in the emergency department. Responsible factors identified included lack of evidence or applicability, lack of knowledge of the recommendations and organisational constraints.^{22 23}

Despite the introduction of sedation guidelines emphasising patient stratification, we have shown that errors are persisting in assigning accurate ASA grades to patients prior to endoscopy. This may influence the degree of caution endoscopists apply to sedation. Furthermore, in view of resources restricting the use of deep sedation, we suspect that ERCP sedation practices have not significantly changed between the two study periods in our Trust. We, therefore, propose that more stringent preprocedural patient stratification, as well as more frequent application of anaesthetist-supported deep sedation for ERCP procedures, may help to reduce our stationary sedation reversal rates. Additional tailored interventions are needed to improve awareness and adherence to sedation guidelines in our Trust.

In conclusion, to the best of our knowledge, this study is the first to examine sedation reversal events in detail across a full spectrum of GI endoscopic procedure types. Our data suggest that ERCP procedures and higher patient ASA grade may help predict an increased risk of conscious sedation-related complications requiring reversal. In these high-risk groups, alternative sedation strategies should be considered. Well-powered prospective studies are needed to compare the use of propofol to conscious sedation in ERCP procedures and patients with higher ASA grades to assess for an impact on the frequency of sedation reversal events. Prospective studies are urgently awaited to explore and further determine potential risk factors in order to accurately predict adverse sedation outcomes.

Significance of the study

What is already known on this topic?

- ▶ Endoscopic sedation-related complications remain a major concern.
- ▶ Serious harm or death resulting from midazolam or opioid overdose during conscious sedation is a UK Department of Health 'Never Event'.
- ▶ Safe sedation guidelines encourage patient risk stratification, close procedural monitoring and minimisation of sedation doses.

What this study adds?

- ▶ ERCP procedures and higher patient ASA grade appear to be associated with higher rates of conscious sedation-related complications requiring reversal.
- ▶ ERCP procedures appear to be associated with higher doses of both midazolam and opioids in sedation reversal events.

How might it impact on clinical practice in the foreseeable future?

- ▶ In prolonged therapeutic ERCP procedures and high risk patient groups, alternative sedation strategies, including the use of propofol, may help to reduce the frequency of adverse sedation events.
- ▶ Prospective studies are needed to further establish variables that may help predict adverse responses to conscious sedation in endoscopy.

Contributors NZ performed the data collection, data analysis, and drafted and revised the paper. NZ is the guarantor. SC performed all the statistical data analysis, contributed to data interpretation, and revised the draft paper. SW monitored data collection, contributed to data interpretation and revised the draft paper. WH contributed to data interpretation and revised the draft paper. AVT initiated the study, analysed the data and revised the draft paper.

Competing interests None.

Ethics approval Imperial College Healthcare NHS Trust Ethics Committee.

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