British Journal of Anaesthesia **113** (S2): ii37–ii47 (2014)
doi:10.1093/bja/aeu378

BJA

Monitoring and delivery of sedation

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Editor's key points

- Depth of sedation monitoring relies on clinical criteria, although neurophysiological approaches are emerging.
- Pulse oximetry is effective for detecting hypoxaemia, but independent monitoring to detect hypoventilation is required given the low margin of safety for sedative drugs.
- Patient- and procedure-dependent factors are critical in selecting optimal monitoring approaches and sedative drugs.

Sedation for medical procedures is provided in a variety of clinical settings by medical personnel with differing levels of education and training. Although generally a safe practice, there is a degree of morbidity and mortality associated with sedation practice. Monitoring standards continue to be refined by professional societies with the goal of improving care. The depth of sedation should be monitored with clinical criteria. Processed electroencephalographic monitors currently do not contribute significantly to sedation care. Monitoring ventilation using pulse oximetry should be abandoned for more direct methods, such as capnography-transcutaneous carbon dioxide, respiratory acoustical and thoracic impedance monitoring could also play a role. Propofol has become widely utilized for sedation, although there are concerns about its margin of safety and synergistic interactions with other agents. Dexmedetomidine and propofol/ketamine also have utility. Patient-controlled sedation pumps and target-controlled infusion devices have been developed to improve patient care and satisfaction. A computer-assisted propofol sedation device to be used by non-anaesthesiologists has been approved in the USA by the Food and Drug Administration. More computer-assisted sedation delivery devices are likely to be developed, but their clinical utility is unclear.

Keywords: computer-assisted infusion; drug interactions; monitoring, depth of anaesthesia; sedation; monitoring, ventilation

While seemingly a straightforward aspect of the anaesthetic practice, the provision of sedation can be challenging. There are many factors to be considered when caring for an individual patient. Patients present with a variety of medical co-morbidities, some procedures require deeper levels of sedation than others, and the degree of noxious stimulation often changes during the course of a procedure. Often the procedure involves the patient's mouth or airway impeding access by the anaesthesia provider. The sedating agents in common use can blunt airway reflexes, cause respiratory depression, and can interact synergistically to potentiate these effects. Procedures requiring sedation are often performed in offices, clinics, or sections of a hospital that are far away from assistance. Ultimately care must be individualized to account for all of these variables.

This review considers our current understanding of monitoring for sedation with examination of emerging technologies. It will discuss some pharmaceutical choices for providing sedation, but it is not meant to be a comprehensive review of anaesthetic pharmacology. Devices and technologies that have been developed to improve delivery of sedation will be discussed. The contentious topic of what degree of education and training should be required to deliver sedation, particularly propofol sedation, will not be addressed.

Monitoring of sedation

Standards and guidelines

Sedation practice is widespread across healthcare systems and is practiced in a wide variety of settings and administered by healthcare providers with a diverse range of education, training, and experience. Administering agents that blunt a patient's sensorium and can compromise their respiratory and cardiovascular function is inherently risky. These risks have been recognized for some time, particularly when sedating medications are combined with opioids.[1] The incidence of significant morbidity or mortality is difficult to ascertain, but it is certainly greater than zero, and appears to have contributed to the recent death of comedienne Joan Rivers after care at an outpatient endoscopy clinic in New York City.[2] Review of monitored anaesthesia care (MAC) cases in the ASA closed-claims database confirms that significant morbidity and mortality can occur: respiratory depression because of an absolute or relative overdose of sedating agents was responsible for 21% of MAC-related claims.[3] Over half of these adverse events were felt to be preventable with better monitoring. In an attempt to minimize patient risk and to standardize practice, organizations of anaesthesiologists have issued guidelines for monitoring during sedation (Table 1).[4–8] The guidelines universally require assessment of the depth of

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sedation and the use of pulse oximetry and non-invasive arterial pressure monitoring. Recommendations concerning the monitoring of ventilation are evolving.

In order to be able to better quantify and analyse sedation-related adverse events, the World Society of Intravenous Anesthesia (WSIVA) international task force has proposed a reporting tool[9] that is unique in that it combines physiologic descriptors, interventions, and outcome measures. One report has already demonstrated that this tool can be utilized and events can be appropriately categorized as being sentinel, moderate, minor, or minimal risk events.[10] Widespread adoption of this tool would certainly improve our ability to identify and better understand the safety issues involved with sedation.

Assessment of depth of sedation

Clinical scales/scores

Administration of sedation medication results in a continuum of effect ranging from anxiolysis to general anaesthesia. The depth of sedation often varies during a procedure, which requires vigilance and ongoing assessment and documentation. Several depth of sedation assessment methods are used in clinical practice and in research protocols; these include the ASA Continuum of Sedation, the Modified Observer's Assessment of Alertness/Sedation Scale (MOASS), and the Ramsay Sedation Scale (RSS) (Table 2).[11–14] Practitioners should assess the depth of sedation periodically throughout a procedure by utilizing one of these scales or by assessing responsiveness to verbal and tactile stimulation. The authors know of no data to demonstrate that one scale or approach is superior to another.

Processed EEG

The above assessment methods require that the patient be periodically stimulated, which can interfere with the procedure and may be difficult during prolonged procedures or where the patient is physically distant. Processed EEG monitors, such as the bispectral index monitor (BIS™, Covidien, Inc., Boulder, CO, USA), have been evaluated to determine their efficacy in monitoring the depth of sedation. Multiple observational studies have correlated processed EEG indices with the MOASS, RSS, or the ASA Continuum of Sedation during sedation in volunteers[15 16] and in patients undergoing sedation in a variety of clinical settings, such as endoscopy suites,[17 18] dental offices,[19] the emergency department,[13 20] and the operating theatre.[21 22] Uniformly, these studies find a significant correlation between the processed EEG index and the sedation scale. However, there is a lack of discrimination of index value associated with each sedation state (Fig. 1): so, a particular index value can herald several different sedation states. In addition, the provision of analgesics can further confound the relationship between processed EEG index and sedation depth. Some authors find that this lack of precision negates the utility

Table 1 Standards and guidelines concerning sedation from national organization

	American Society of Anesthesiologists[4]	The Association of Anaesthetists of Great Britain and Ireland[5]	European Society of Anesthesiologists[6]	Australian and New Zealand College of Anaesthetists[8]
Level of statement	Standards	Standards and guidance	Guidelines	Guidelines
Year written/ updated	2011	2013	2007	2014
Assessment of depth of sedation	Required	Required	Required	Required
Arterial pressure measurement	Required, at least Q 5 min	Required*	Required	Required
Pulse oximetry	Required	Required*	Required	Required
Electrocardiogram	Required	'Conscious sedation' with continuous verbal contact: not required. Deep sedation: required	Required	May be required according to the clinical status of the patient
Capnometry	Moderate and deep sedation: required unless precluded or invalidated by the nature of the patient, procedure, or equipment	'Recommended' for moderate and deep sedation and when (a) ventilation cannot be directly observed, for example MRI/CT, (b) multiple drugs/anaesthetic drug techniques are used, or (c) pre-assessment highlights increased clinical risk	Not required	May be required according to the clinical status of the patient
Notes		* Document states that monitoring for minimal sedation/anxiolysis is 'dictated by co-morbidity'	Guidelines are for non-anaesthesiologists. Taskforce currently updating[7]	

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of processed EEG for sedation monitoring,[20–22] while others accept the limitation and suggest thresholds for processed EEG values.[13 17–19]

Ultimately, the utility of processed EEG index values should be determined through randomized clinical trials that are powered to address meaningful outcome measures and compare standardized care to care guided by EEG-based index values. Studies have been performed in a number of clinical settings with a variety of sedation protocols powered to consider differing outcome measures. In general, shorter procedures, such as flexible bronchoscopy[23] and colonoscopy,[24 25] show no benefit. Several studies of endoscopic retrograde cholangiopancreatography (ERCP) demonstrate lower propofol administration and faster recovery times with care guided by processed EEG index values,[26–28] although no significant safety benefits were described. A recent large observational study in which care was provided by sedation nurses administering midazolam and fentanyl found that titration to processed EEG monitor did not result in lower drug administration compared with standard care, but did result in significantly lower incidence of pronounced desaturation (Sa_{O_2} <90%).[29] Other than this finding, no study to date has demonstrated a meaningful outcome improvement with sedation care guided by processed EEG.

Anaesthesia responsiveness monitoring

The Anesthesia Responsiveness Monitor (Scott Laboratories, Lubbock, TX, USA) was developed to objectively identify a patient's depth of sedation. It consists of an earpiece and a handset containing a button and vibrator. A computerized voice asks the patient to push the button and the handset vibrates up to four times over a 10 s period. The system quantifies how quickly the patient responds, and a lack of response signals a sedation level deeper than moderate sedation.[30] In volunteer studies, subjects always were unresponsive to the monitor before they were clinically unconscious, showing no false positives.[30] The plasma propofol concentrations at which they lost and returned to a responsive state were equivalent, demonstrating good consistency.[31] The monitor is incorporated into the computer-assisted personalized sedation device described below.

Assessment of ventilation

Virtually every medication administered for the purposes of sedation has the ability to suppress central respiratory drive. Drug-induced airway obstruction, aspiration, and respiration depression with hypoventilation, apnoea and hypoxaemia remain principal causes of sedation-related morbidity.[32] During moderate sedation, these risks should be minimized. However, sedated patients have the potential to progress to levels of deeper sedation where respiratory compromise has an increased likelihood.[33] Subhypnotic doses of sedating medications cause significant pharyngeal dysfunction.[34] Electromyographic recordings of the genioglossus nerve demonstrate a marked decrease in activity with the transition from consciousness to unconsciousness.[35] Early detection of inadequate respiratory function is imperative, and allows for initiation of interventions to prevent sedation-related complications. Respiratory monitoring is thus a critical aspect in assuring quality care of the sedated patient. Clinical observation has been shown to be unreliable in assessing respiratory status,[35 36] thus complementary detection methods are desirable. A

Table 2 Sedation scores used in clinical practice and research studies

ASA continuum of sedation[11]	Modified Observer's Assessment of Alertness/Sedation Scale[12]	Modified Ramsay Sedation Scale[13]
Minimal sedation/anxiolysis: a drug-induced state during which patients respond normally to verbal commands	5—Responds readily to name spoken in normal tone	1—Awake and alert, minimal or no cognitive impairment
Moderate sedation/analgesia ('Conscious sedation'): a drug-induced depression of consciousness during which patients respond purposefully* to verbal commands, either alone or accompanied by light tactile stimulation	4—Lethargic response to name spoken in normal tone 3—Responds after name called loudly or repeatedly or both 2—Responds only after mild prodding or mild shaking	2—Awake but tranquil, purposeful responses to verbal commands at a conversational level 3—Appears asleep, purposeful response to verbal commands at a conversational level 4—Appears asleep, purposeful responses to commands but at a louder than conversational level, requiring light glabellar tap, or both
Deep sedation/analgesia—purposeful* response after repeated or painful stimulation	1—Responds only to painful stimulation	5—Asleep, sluggish purposeful responses only to loud verbal commands, strong glabellar tap, or both 6—Asleep, sluggish purposeful responses only to painful stimuli
General anaesthesia—a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation	0—No response to painful stimulation	7—Asleep, reflex withdrawal to painful stimuli only 8—Unresponsive to external stimuli, including pain
Note: *Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.	Note: MOASS is the responsiveness component of the Observer's Assessment of Alertness/Sedation Scale[12]	Original Ramsay Sedation Scale is a 6-item scale developed to assess ICU sedation[14]

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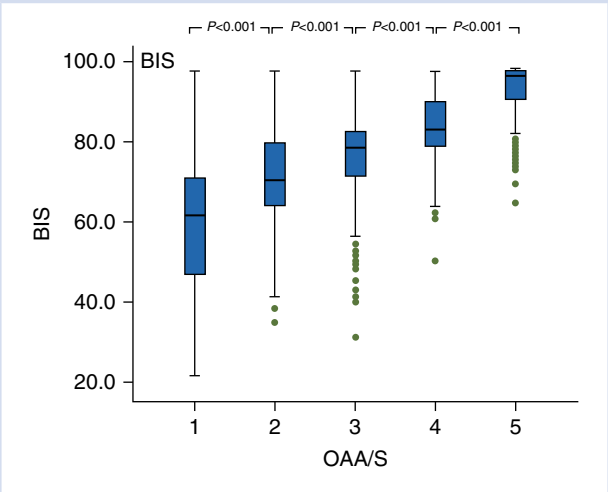

Fig 1 The relationship between the BIS value and MOASS score during sedation. Box plots represent 25–75th percentile, whisker bars represent the 5th and 95th percentiles. There is a significantly different BIS value between each sedation score ($P<0.001$). However, note that a BIS value of 80, for example, is found within the boxplot of an MOASS score or 2, 3, or 4 and within the whisker bars of 1 and 5, indicating a lack of discrimination. Reprinted from von Delius and colleagues,[18] with permission from Macmillan Publishers Ltd.

number of modalities exist for this purpose, including pulse oximetry, capnography, impedance techniques, and acoustic monitoring.

Pulse oximetry

Pulse oximetry is an imperfect monitoring method of ventilation. It accurately detects arterial oxygen saturation, but does not evaluate alveolar ventilation. With administration of supplemental oxygen, pulse oximetry will fail to reflect alveolar hypoventilation in the setting of respiratory depression.[37] This leads to the practice of withholding supplemental oxygen so that falling oxygenation will signal inadequate ventilation. With oxygen administration, pulse oximetry alone may not be sufficient monitoring in patients undergoing sedation because of delays in detecting alveolar hypoventilation.[38] The authors believe that the practice of withholding oxygen to detect hypoventilation is ill-advised and potentially dangerous: logic dictates that while hypoventilation can be detrimental to a patient, hypoventilation plus hypoxaemia is likely to be worse. Adequacy of ventilation during sedation should be assessed by more direct methods.

Capnography

Capnography is another common technique that has increased in popularity in part as a result of technological advancements allowing for less-invasive devices and increasing accuracy in end-tidal carbon dioxide detection.[39] There is evidence to suggest that capnography allows for earlier detection of respiratory depression compared with pulse oximetry in both paediatric[40] and adult[41–43] populations undergoing sedation. Other studies have shown interventions based on capnography compared with standard monitoring with a pulse oximeter result in decreased episodes of apnoea and hypoxaemia (Fig. 2).[41 44 45] These data have also been supported by a recent meta-analysis, concluding that episodes of respiratory depression were 17.6 times more likely to be detected by capnography compared with standard monitoring.[46] Owing to the growing evidence, the ASA amended its Standards for Basic Anesthetic Monitoring effective 2011 to include mandatory end-tidal carbon dioxide monitoring during moderate and deep sedation.[5] Not all studies demonstrate a benefit with capnography, however. A recent investigation of patients not receiving routine supplemental oxygen for minor gynaecological procedures showed no difference in the incidence of hypoxaemia when capnography was utilized.[47] Perhaps the true benefit of capnography is that its use could eliminate the practice of withholding oxygen in order to monitor hypoventilation via hypoxaemia.

Transcutaneous CO_2 monitoring

This is another possible monitoring modality for adequate ventilation. In a comparison with end-tidal side-stream capnography during deep sedation, transcutaneous monitoring correlated better with measured arterial CO_2 and was better at detecting states of hypercarbia.[48] However, transcutaneous monitoring is known to be less effective in detecting apnoea: the authors suggest that an approach that combines transcutaneous with end-tidal monitoring might improve overall efficacy.[48]

Impedance monitoring

Transthoracic impedance pneumography analyses impedance changes across electrodes located on the chest during the respiratory cycle and produces a visual tracing with a corresponding respiratory rate. Traditional impedance monitoring is unable to distinguish between respiratory effort and respiratory flow; in obstructive apnoea, the chest wall will continue to move in the absence of airflow causing the impedance monitoring to interpret a normal respiratory rate.[49] A new impedance-based monitor, the respiratory volume monitor (RVM, Respiratory Motion, Inc., Waltham, MA, USA) has been described that accurately depicts the lack of ventilation with a closed glottis (Fig. 3).[50] In volunteers the RVM is very accurate compared with spirometry with breathing patterns that are fast, slow, and irregular.[50] The role of modern impedance monitoring during sedation warrants further investigation.

Acoustic monitoring

Monitoring turbulent airflow through the larynx is another method to assess ventilation. The rainbow Acoustic Monitor™ (Masimo, Inc., Irvine, CA, USA) has been utilized in several studies. Two studies that compared capnography and acoustic monitoring in patients undergoing sedation showed a similar detection of respiratory pauses. Both studies also showed that acoustic monitoring was associated with a lower frequency of false alarms compared with capnography.[36 51]

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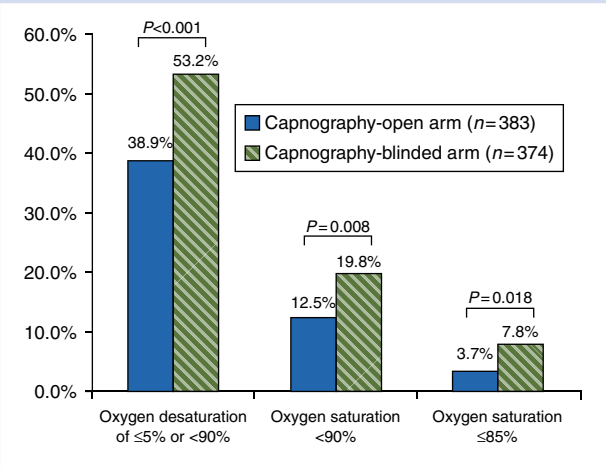

Fig 2 When capnometry monitoring is added to routine clinical care with propofol sedation for colonoscopy, there is significantly less hypoxaemia [defined as Sp_{O_2} decrease of >5% or reading of <90% ($P<0.001$), $Sp_{O_2}<90\%$ ($P=0.008$) or $Sp_{O_2}<85\%$ ($P=0.018$)]. Blue bars represent care with capnometry and green bars represent routine clinical monitoring. Reprinted from Beitz and colleagues,[45] with permission from Macmillan Publishers Ltd.

Another study focused on patients presenting to the post-anaesthesia care unit, and concluded that acoustic monitoring had greater sensitivity in detecting ventilatory pauses compared with capnography.[52] A differing technology utilizing principles of entropy to analyse acoustic signals has also been described.[53] The applications of these studies are restricted because of small sample sizes. Larger studies are required to reliably compare acoustic monitoring to other techniques to discern its role in sedation procedures.

Other respiratory monitoring techniques have been hypothesized, such as humidity monitoring,[54] but have not been adequately studied in clinical practice.

Delivery of sedation

In the delivery of sedation, several choices must be made such as the choice of agent(s) and the intended depth of sedation. A full assessment of the variety of options for agents for sedation is beyond the scope of this review (but see the related review by Mason in this issue).[55] It is clear, however, that there is an increasing interest in using propofol for this purpose because of its favourable pharmacokinetic profile and absence of lingering side-effects. As a single agent administered by careful titration, the literature supports an impressive safety profile.[56] Propofol alone can be inadequate for painful procedures because of its limited analgesic properties necessitating the addition of an opioid. This practice utilizes the profound synergy between these agents, and can result in blunting the response to noxious stimulation.[57] However, it is widely recognized that addition of an opioid to propofol greatly increases the incidence of respiratory depression and its negative consequences.[58] In a volunteer study, investigators found it difficult to find pairs of propofol and remifentanil effect-site concentrations that allowed oesophageal instrumentation while maintaining a state of moderate sedation and avoiding respiratory rates below 4 bpm (Fig. 4).[59] Interestingly, there appears to be genetic elements to consider as well: patients homozygous for a recessive allele of the OPRM1 opioid receptor gene required significantly more remifentanil to tolerate upper endoscopy.[60]

Bolus or continuous propofol delivery

Propofol for sedation is commonly administered either by continuous infusion or by bolus techniques, and there are theoretical advantages to each approach, which have been compared in several studies. During deep sedation for oral surgery, the continuous infusion group received more propofol than the bolus group, but the sedation state was judged to be better; haemodynamic parameters were not different.[61] For short gynaecological procedures, the continuous infusion group received more propofol and experienced a longer induction and emergence than the bolus group.[62] In a large study of patients undergoing flexible bronchoscopy, the continuous infusion group received more propofol and took a longer time to emerge than the bolus group; the incidence of significant morbidity was not different.[63] In a study of endoscopist-directed, nurse-administered propofol for moderate sedation for colonoscopy the continuous infusion group received more propofol and took a longer time to emerge than the bolus infusion group with equivalent patient and physician satisfaction.[64] These data indicate that continuous infusion techniques result in greater propofol delivery compared with intermittent bolus techniques. Careful reading, however, shows that the differences in recovery times are not clinically significant and neither technique is likely to be clinically superior compared with the other.

Dexmedetomidine

Dexmedetomidine (DEX) is another noteworthy agent increasing in popularity because of its combined sedation, anxiolytic and analgesic properties with limited respiratory depression.[65 66] Recent studies comparing two doses of DEX with midazolam/fentanyl have demonstrated its safety and efficacy for a variety of procedures performed under conscious sedation.[67 68] Most studies comparing DEX with propofol or midazolam/fentanyl find lower heart rate and blood pressure during the procedures and longer recovery times in the DEX group, and some studies demonstrate less respiratory depression.[68] Some authors find these properties to be unsuitable for certain procedures such as cataract extraction,[69] colonoscopy,[70] and shock wave lithotripsy.[71] Other authors find that the sedative and haemodynamic properties are well suited to other procedures such as plastic facial surgery,[72] awake craniotomy,[73] and third molar extraction.[74] Another potential advantage is that DEX can be delivered by intranasal spray.[74]

Ketamine

Ketamine has been used as a sedation agent because of its dissociative properties, analgesia, and limited respiratory

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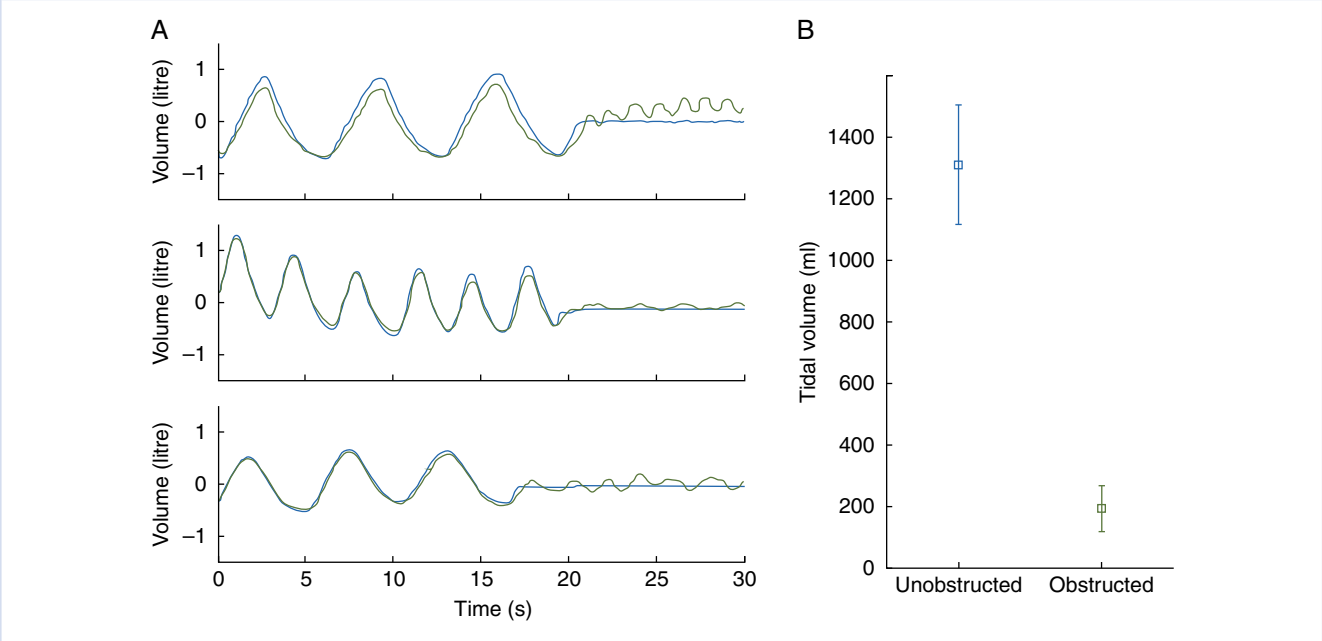

Fig 3 The respiratory volume monitor (see text) and obstructed breathing. (A) Three subjects were instructed to simulate an upper airway obstruction by closing their glottis for ~15 s after the beginning of each trial and to continue to attempt to breathe. The Morgan spirometer (blue trace) shows the halted air exchange after the obstruction is introduced. The respiratory volume monitor (green trace) measures the breathing attempts, registering small breath-like excursions. (B) Average tidal volumes (TVs) measured in 10 subjects during normal breathing (blue) and segments of obstructed breathing (green). Error bars show 95% confidence interval (2 × SEM). The average TV decreases significantly from 1310 ± 190 to 192 ± 7 ml ($P<10^{-6}$). This is in the range of the calculated anatomic dead space for this cohort (166 ml). From Voscopoulos and colleagues.[50] Reprinted with permission.

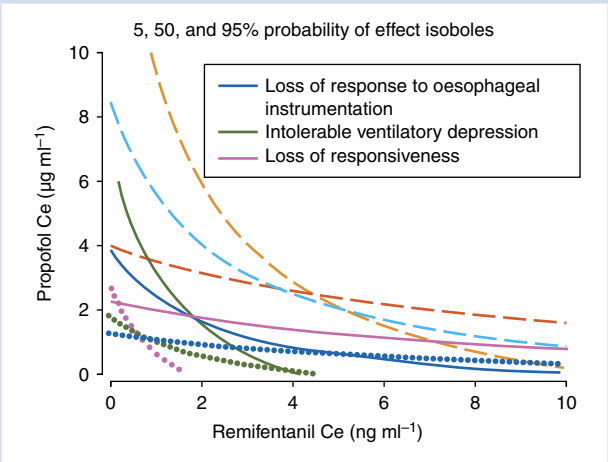

Fig 4 The 5, 50, and 95% probability of effect isoboles for the interaction of propofol with remifentanil during oesophageal instrumentation. Note at the 50% isobole there are no propofol/remifentanil pairs that would allow oesophageal instrumentation (right side of blue line) while not experiencing both loss of responsiveness to verbal stimulation and a respiratory rate <4 bpm (left side of pink and green lines, respectively). From LaPierre and colleagues.[59] Reprinted with permission.

depression; however, it is plagued by major adverse effects such as emesis and recovery agitation.[75] Administration of a combination of propofol and ketamine might be advantageous as each agent could theoretically counteract the other's undesirable effects. Propofol lacks analgesic properties that potentially could be provided by ketamine.[76] Propofol causes hypotension that could be ameliorated by the sympathomimetic nature of ketamine, and the respiratory depression seen with propofol and opioids could be averted by the substitution of ketamine for opioid as the analgesic agent.[76] Ketamine's adverse effects of emesis and agitation might also be alleviated by the anti-emetic and hypnotic properties of propofol.[76] When mixed in a single syringe, a combination of these agents has chemical and physical stability for up to 3 h, allowing for convenient administration.[77] Combinations of propofol and ketamine have been studied primarily in the emergency department setting[78–80] but have also been described in other settings.[81–83] One combination that is frequently utilized is a 1:1 mixture of 1% propofol and 1% ketamine, referred to as 'ketofol'.

Although effective and theoretically promising, the question remains whether combining propofol with ketamine provides improved clinical outcomes compared with established single-agent sedation techniques. In two recent studies, the combined agents did not reduce the incidence of respiratory depression[79] or adverse respiratory events[80] but did result in better sedation conditions than propofol alone. In addition, it is not clear if a different ratio of agents is superior to the 1:1 ratio of ketofol. Additional studies are required to further clarify the role of combinations of propofol and ketamine for procedural sedation.

Given the potential difficulties of safely providing sedation, a number of devices and strategies have been developed.

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Patient-controlled sedation

Patient-controlled sedation (PCS) is an anaesthetic technique comparable with patient-controlled analgesia that allows patients to self-titrate sedative, analgesic or both medications during the course of uncomfortable procedures.[84] This allows patients to minimize discomfort while accounting for intra-patient pharmacodynamic differences and differing levels of tolerance of discomfort. PCS has been studied primarily in endoscopy procedures, but has also been demonstrated to be an effective sedation method in other clinical contexts, including dental,[85] ophthalmological,[86] orthopaedic,[87] gynaecological,[88] and emergency department[89] procedures.

PCS during ERCP has been investigated in a number of studies and proven to be an effective method of sedation administration.[90–93] One randomized control trial that utilized propofol/remifentanil PCS for ERCP showed similar procedural success rate and decreased recovery time when compared with anaesthesiologist-managed sedation. In addition, the PCS group received less propofol and experienced fewer episodes of deep sedation.[90]

It has been hypothesized that an advantage of PCS is greater patient satisfaction because of the autonomy associated with self-administration and sense of control for the patients.[86] Some PCS studies have included patient satisfaction as a primary or secondary outcome. These data are conflicting with PCS resulting in less,[94] comparable,[90 95 89] or greater[96 97] satisfaction compared with a standard sedation practice. It is difficult to directly compare these studies as they contain a wide range of procedures, assessment methods, and sedative agent(s). PCS does not appear to universally increase patient satisfaction, which is likely contingent on the clinical setting and individual patient preference.

Target-controlled infusion

Target-controlled infusions (TCI) have been utilized for sedation. Propofol TCI has been used in a variety of settings, including endoscopy,[98] bronchoscopy,[99] and dental procedures.[100] Opioid TCI has been utilized in various settings as well, including sufentanil for burn dressing changes,[101] and remifentanil for awake intubation,[102] and colonoscopy.[103]

Whether sedation with TCI is superior to manually controlled sedation is not clear. A Cochrane Collaboration review from 2008 considering both general anaesthesia and sedation concluded that there was 'insufficient evidence to make firm recommendations', but only 2 of the 20 extracted studies were of sedation practice.[104] More recent studies illustrate potential advantages of TCI. For dental procedures in patients with intellectual disability, propofol TCI titrated to BIS™ resulted in less propofol usage and faster times to eye opening compared with manual administration titrated to clinical signs.[105] Propofol TCI administered for deep sedation ERCP resulted in faster emergence and less-frequent oxygen desaturations compared with a manual-controlled group.[106] Remifentanil TCI compared with manual administration for colonoscopy showed less concomitant propofol delivery and a lower incidence of apnoea and respiratory depression.[103] Sedation with TCI is advantageous in these settings, but whether sedation with TCI is superior to manually controlled sedation in other procedures requires further study.

A logical combination would be to add TCI to PCS; this has been reported in several pilot and 'proof of concept' studies demonstrating feasibility.[107–110] A study comparing propofol PCS/TCI to manual control for colonoscopy showed a slower onset time and less hypotension with equivalent satisfaction scores.[111] Another study compared propofol PCS/TCI with Entonox for colonoscopy and demonstrated equivalent conditions during the procedure and outcomes.[112] Finally, a study compared PCS with anaesthesiologist-controlled TCI during ERCP and demonstrated both TCI and PCS to be effective sedation methods with similar success rates and adverse event profiles.[93] This study did show statistically significant decreases in recovery time and propofol consumption in the PCS arm. It is not clear that adding TCI to PCS significantly improves clinical effectiveness or safety.

Computer-assisted personalized sedation (CAPS)

The SEDASYS® (Ethicon Endo-Surgery, Cincinnati, OH, USA) is the first computer-assisted personalized sedation system to receive US FDA approval. It was developed to allow mild-to-moderate propofol sedation to be delivered by non-anaesthesiologists.[113] It consists of a full monitoring array (electrocardiography, non-invasive blood pressure, pulse oximetry, capnography) and also the aforementioned ARM. In addition, there is a propofol infusion pump, with the infusion rate selected by the proceduralist. The system is designed to stop propofol delivery if monitoring detects apnoea or an unresponsive ARM. It has been studied in a small trial of upper endoscopy and colonoscopy patients showing very fast recovery times after the procedure ($<$30 s) with high satisfaction scores.[114] However, a significant proportion of patients had recall of the procedure. A large, multicentre study comparing SEDASYS® to benzodiazepine/opioid for upper endoscopy and colonoscopy demonstrated less oxygen desaturation, greater patient satisfaction, and faster recovery with the CAPS system (Fig. 5).[115] A more appropriate comparator group would have been anaesthesiologist-administered propofol sedation.[113] It should be noted that, by protocol, all SEDASYS® patients receive fentanyl, up to 100 μg, which exposes these patients to the risks of opioid/propofol ventilatory depression discussed above. It should also be noted that patient selection is likely to be important for patient safety: the FDA has approved the device only for ASA physical status class I and II undergoing routine colonoscopy and oesophagogastroduodenoscopy procedures, and only for sedation levels, at deepest, of moderate sedation. In the name of patient safety, anaesthesiologists should be vigilant to prevent 'off-label' uses.

Other computer-based devices

Closed-loop delivery systems for sedation have been described that deliver propofol based on a computer algorithm titrating to a BIS™ value.[116 117] These have not been investigated beyond the 'proof of concept' stage. Computer-based modelling of the interaction of propofol and remifentanil might

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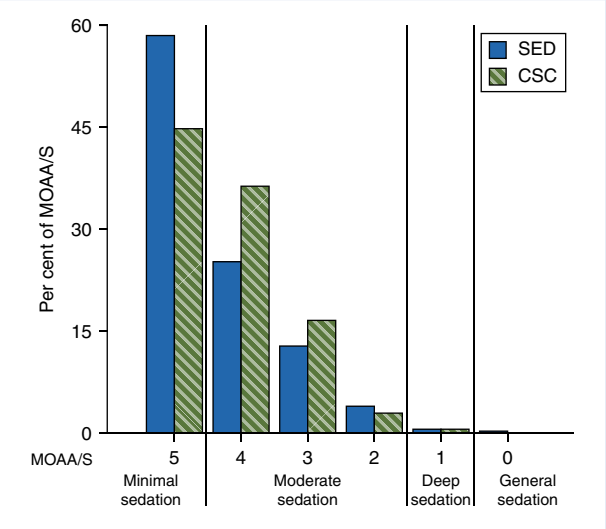

Fig 5 The range of sedation scores during colonoscopy with a dose of fentanyl followed by propofol delivered with the SEDASYS system (blue bars) and nurse-administered opioid and midazolam (green bars). Note the high percentage of minimally sedated patients in the SEDASYS® group. Despite this observation, the overall satisfaction scores were higher in the SEDASYS® group. Reprinted from Pambianco and colleagues,[115] with permission from Elsevier.

have value in guiding care. An 'adaptive neuro fuzzy inference system' has been recently described that can predict which effect-site concentration pairs of propofol and remifentanil result in a particular range of processed EEG values and a desired level of sedation without applying stimulation to the patient.[118] The noxious stimulation response index has been described which, using the propofol and remifentanil effect-site concentrations, predicts who will respond to noxious stimulation with more accuracy than physiologic or electroencephalographic parameters.[119] Commercial monitors such as the Navigator Applications Suite™ (GE Healthcare, Little Chalfont, Buckinghamshire, UK) and SmartPilot® View (Dräger, Lübeck, Germany) display propofol/opioid interaction and associated isoboles, and might allow anaesthesiologists to administer more effective combinations of agents. Whether any of these technologies improves sedation care remains to be determined.

Conclusions

With continued improvements in monitoring, understanding of drug interactions, and development of new delivery technologies, the practice of administering sedation will hopefully become safer and more effective.

Authors' contributions

C.G.S. wrote significant portions of the manuscript. D.M.M. wrote significant portions of the manuscript and oversaw its production.

Declaration of interest

D.M.M. receives financial support for investigator-initiated research from Covidien, Inc. and Masimo, Inc., and supplies for investigator-initiated research from Respiratory Motion, Inc. He is a member of Masimo's scientific advisory board and receives an honorarium.

Funding

Support for this paper was provided solely by Departmental funds.

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