Best anaesthetic drug strategy for morbidly obese patients

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Purpose of review
The purpose of this review is to describe an evidence-based drug strategy applicable to any obese patient, rather than to present one standard 'ideal' anaesthetic drug combination. The ultimate choice of specific drugs in any given situation will depend upon clinician experience, patient specifics, and drug availability. The fundamental principle in anaesthesia for the obese patient is to use the shortest acting, least fat soluble agents to ensure rapid recovery to safe levels of alertness and mobility.

Recent findings
No new drugs have been introduced over the past few years, but we have seen an introduction of enhanced recovery after surgery-based protocols into bariatric surgery. Our understanding of how obesity affects pharmacokinetics/dynamics of our drugs is improving, with new and better use of established drugs. Allometric scaling is being tested in the different pharmacokinetic/dynamic models used in target controlled infusion devices, with improved performance as a result. Obstructive sleep apnoea has a significant impact upon outcome and utilization of clinical resources, including critical care beds. If an improved drug dosing strategy will reduce this impact, then this would be a step forward.

Summary
This review introduces newer findings to help us use anaesthetic and analgesic drugs more safely in the morbidly obese. However, there remain many areas of uncertainty with a lack of consensus on many issues.

Keywords
dosing scalars, enhanced recovery after bariatric surgery, multimodal analgesia

INTRODUCTION

Scope of the review

Although the worldwide epidemic of obesity has impacted upon our anaesthetic practice for some decades by now, there is currently still a relative lack of pharmacological guidance in the anaesthetic management of this patient group. There have been initiatives to formulate guidelines on key issues from several national and international societies (e.g. European Society of Anesthesiology, Association of Anaesthetists of Great Britain and Ireland, Society for Obesity and Bariatric Anesthesia, European and International Societies for Perioperative Care of the Obese Patient, Society of Anesthesia and Sleep Medicine). These advisories can be consulted on the webpages of these societies. Often much clinical detail needs to be filled in by the clinicians.

Furthermore, many departments of anaesthesia are facing the implementation of accreditation programs designed to focus on quality and safety throughout all aspects of patient care including medication management. As a consequence, there is a drive to develop standardized anaesthesia care protocols for the morbidly obese patient. Unfortunately, there is probably no such thing as 'the ideal anaesthesia technique' or 'the ideal drug combination' for the obese patient.

For some drug classes, with wide safety margins and a relatively high-therapeutic index, dose adjustment in obesity is less critical (e.g. antiemetics), and for many drugs the target effect will be measured and dosing based on that endpoint (muscle relaxation). However, understanding the principles of dosing scalars is essential to safe anaesthetic

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KEY POINTS

- ERAS protocols have been introduced into obesity and bariatric surgery with great success.
- Most of our anaesthetics drugs should be administered based upon lean body mass – Suxamethonium (Succinylcholine) is the main exception and should be dosed on TBW.
- Maintenance of anaesthesia with propofol infusions must be based upon an adjusted body weight, as the fat sink of the morbidly obese will lead to reduced plasma levels with a risk of accidental awareness.
- Allometric scaling principles partially explain and can increase performance of many pharmacokinetic models, but do not correct for the changed body composition.
- Multimodal analgesia plays a vital role in reducing opioid consumption and improving postoperative analgesia and outcome.

practice, to ensure efficacy but at the same time to prevent over-dosage.

We have not seen the introduction of any new drugs the past 18 months. We have, however, seen the introduction of enhanced recovery after surgery (ERAS) protocols into bariatric surgery (Fig. 1). This has in part resulted from an improved understanding of how obesity affects pharmacokinetics/dynamics of our drugs, and thus a better use of established drugs. The use of allometric scaling in pharmacokinetic/dynamic models holds the promise of improving target controlled infusion (TCI) applications of several drugs in the obese.

Premedication

There is no clear consensus on the routine use of aspiration prophylaxis in morbidly obese patients undergoing elective surgery. A recent study on gastric volume and pH levels in morbidly obese patients advised the routine prescribing of ranitidine and metoclopramide [2]. Others have suggested a similar approach with the use of H_2-antagonists or proton pump inhibitors combined with metoclopramide in the obese patient at risk [3]. Ultrasonography of the stomach has been proposed as a tool for clinicians to select the obese patient at risk for aspiration. If the gastric volume is less than 1.5 ml/kg, then the risk of aspiration can be considered as low [4]. We do know that those patients with a recent gastric banding [5,6] are identified as at increased risk for pulmonary aspiration of oesophageal contents.

When practicing strict adherence to ERAS protocols, sedative premedication should be avoided [7,8▪▪,9]. However, examining studies on the safety of nonsurgical procedures in morbidly obese patients (e.g. for gastroscopy, transoesophageal echocardiography, or placement of intra-gastric balloon) one can only surmise that sedation with all sorts of benzodiazepines is commonly used in high-risk morbidly obese patients and considered well tolerated [10–12]!

Should the clinician wish to premedicate an anxious obese patient, several options are available. The use of a small bolus of intravenous midazolam

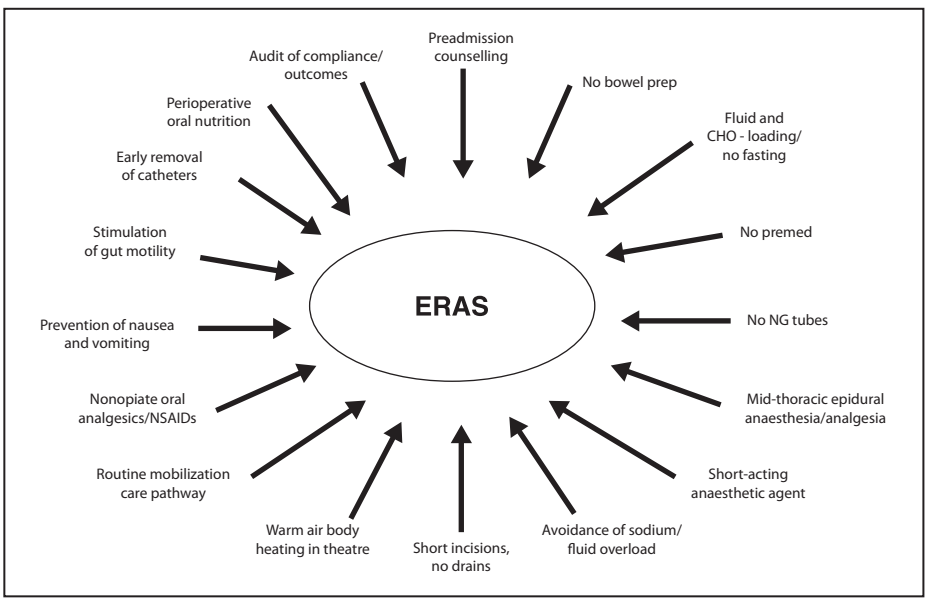

FIGURE 1. Elements of an enhanced recovery after surgery protocol. Adapted with permission from [1].

in the obese in monitored conditions prior to the moment of induction has been studied extensively. With an unchanged systemic clearance but an increased distribution volume, lower midazolam concentrations and sedative effects may be expected in obese compared to normal weight, when injecting an intravenous bolus of midazolam [13▪]. A slow infusion of clonidine-ketamine before induction [14] or intranasal dexmedetomidine [15], are alternatives in obstructive sleep apnoea (OSA) patients, who may be extremely sensitive to hypnotics.

As part of the analgesic strategy, the pre-emptive use of paracetamol (acetaminophen) [16], NSAIDs [17] and oral doses of gabapentin [18,19▪] and pregabalin [20] before bariatric surgery can reduce pain after surgery.

Thromboprophylaxis

Thromboprophylaxis is mandatory (especially so in the older obese patient with hypertension and diabetes) and because most venous thromboembolism episodes after bariatric surgery occur within 30 days of discharge from the hospital, extended administration might be indicated [21]. We do not have clear studies in the literature to make definitive suggestions on dosing strategies, duration of prophylaxis and dose adjustments for different weight categories. The American College of Chest Physicians suggests using a higher dose of low molecular weight heparin (LMWH) without specifying exactly by how much [22].

For unfractionated heparin, a dose of 7500 IU given three times daily in patients weighing more than 100 kg has been suggested to be both well tolerated and effective [23▪]. Intravenous administration of unfractionated heparin in morbidly obese and obese critically ill patients can be based on total body weight (TBW) but with a reduced initial dose [24].

For LMWH, different strategies can be found in the literature. The use of a fixed dose enoxaparin can lead to ineffective anti-Xa activity in overweight patients [25▪]. Dose can be increased by 30% in patients with a BMI less than 40 [26] or the frequency of administration can be increased to twice daily, with a LMWH dose of anti-Xa 40–75 IU/kg TBW [27]. Ideally, anti-Xa activity should be monitored and doses adjusted to keep that activity within the prophylactic range (0.2–0.5 IU/ml 4 h after administration). Dose reduction is required in patients with significant renal impairment. For prophylactic use of enoxaparin, a once daily dose of 0.5 mg/kg, calculated on TBW without capping the dose was found to be feasible and resulted in effective anti-Xa levels. It should, however, be noted that current opinion would not support dosing heparins on TBW because of the risks of overshoot and excessive postoperative bleeding [28].

A population-based pharmacodynamic model for Nadroparin to predict anti-Xa activity after 5700 IU subcutaneously used TBW for determining clearance and lean body mass (LBM) to account for volume of distribution [29▪].

A suggested dosing regimen for LMWH thromoboprohylaxis across a wide range of bodyweights is appended (Table 1). This is based upon the recommendations of the Haemostasis, Anticoagulation and Thrombosis Committee of the UK Clinical Pharmacy Association, Quality assurance assisted by UKMi is appended (Table 2).

Concerning the new oral anticoagulants, the manufacturers propose fixed doses with no weight adjustments. The studies to confirm that fixed doses are adequate in the obese are lacking, more clinical

Table 1. Dosing scalars

IBW Broca	Men: height (cm) – 100 Women: height (cm) – 105
IBW Lemmens and Brodsky	$IBW = 22 \times height^2$ (m)
IBW Devine	Men: $49.9 + 0.89 \times$ [height (cm) – 152.4] Women: $45.4 + 0.89 \times$ [height (cm) – 152.4]
Adjusted body weight	$IBW_{Devine} + 0.4$ (TBW–IBW)
Corrected body weight (Servin)	IBW + percentage overweight (20–40%)
LBM James equation	Men: $[1.10 \times weight] - [128 \times (weight/height)^2]$ Women:$[1.07 \times weight] - [148 \times (weight/height)^2]$
LBM Janmahasatian	Men: $9270 \times TBW/(6680 + 216 \times BMI)$ Women: $9270 \times TBW/(8780 + 244 \times BMI)$
PNWT	Men: $0.57 \times TBW - 0.0183 \times BMI \times TBW - 10.5$
PNWT = LBW + fraction excess fat	Women: $1.75 \times TBW - 0.0242 \times BMI \times TBW - 12.6$

IBW, ideal body weight; TBW, total body weight; PNWT, predicted normal weight; LBM, lean body mass.

experience and investigation is required before firm recommendations can be made. Again dosing to TBW would seem excessive at the extremes of weight, but the correct scalar to use for these agents, is not yet clear [30].

Induction/maintenance of anaesthesia

Early and full recovery of consciousness and protective reflexes in the morbidly obese patient is of the utmost importance and should improve outcome after surgery [31▪▪]. To achieve this goal, utilization of short acting agents with prompt onset and recovery may be obvious to most of us: its importance needs to be underlined. Multimodal analgesia and multimodal anaesthesia are central to this process and should be initiated from the moment of induction. It is not just the choice of drug that counts, but also the use of an appropriate dosing strategy.

Dosage recommendations of drugs developed and studied in normal weight patients cannot be simply extrapolated to morbidly obese patients. The relationship between dose and body weight is not a linear one. We do not give a person of 210 kg three times as much drug as a 70 kg person.

Obesity affects volume of distribution, clearance and elimination of most drugs in a complicated manner, which is dependent on water/fat solubility of the drug in question. One approach to overcome this dosing issue is to give fewer drugs per kg TBW, but the more appropriate response is to use normal weight dosage recommendation and make use of dosing scalars, that is, use lean or ideal body weight, or some other adjusted weight scalar, rather than a TBW. Both have the same effect: we give fewer drugs than recommended by the package insert. Several dosing scalars have been introduced in an attempt to correct for body composition, but each of them has limitations. (Table 2)

The use of TBW is definitely dangerous and might easily lead to over-dosage. The use of ideal body weight as a dosing scalar is very popular and can be useful up to a range of BMI 40 or less for many water-soluble drugs. Yet its use is also illogical and might lead to under-dosing of some of our patients; obese patients with the same height all get the same dosage, irrespective of their TBW and excess weight.

The use of dosing techniques based on LBM is more logical. Most of the metabolic processes involved in pharmacokinetics and dynamics occur in the lean body mass. Lean body mass changes with sex, height, and TBW. Important pharmacokinetic variables such as volumes of distribution and clearance can be related to LBM. Cardiac output, an important factor in early distribution of drugs, correlates with BMI but in a nonlinear fashion [32].

Infusion rates for maintenance agents typically use the James's equation, but this is flawed and cannot be used if a TBW much above 120 kg is input. The formula of Janmahasatian is an appropriate equation that provides lean body mass across a much wider range of patient weights [33] (Fig. 2). However it has not yet been implemented into any commercial infusion pumps.

Allometric scaling

Allometry is the study of the relation between body characteristics/properties and body size. This is of particular interest when considering drug dosing in the obese, because allometric scaling helps explain the differences in pharmacokinetic/dynamic properties amongst individuals with body sizes outside the normal ranges. In the general allometric formula $y = ß \times x^a$, the biological descriptor y can be predicted from the body size descriptor x raised to the exponential power a (known as the allometric coefficient) times a constant ß. The classical body size descriptor is TBW. Clearance of drugs (≈ metabolism) is important in calculating infusion rates to maintain steady state concentrations and can be scaled to TBW, using an allometric coefficient of 0.75. Volumes of distribution are important to calculate loading dose and are generally directly proportional to TBW (the allometric coefficient is 1.00) [35]

Allometric scaling informs understanding, but is not directly applicable to the morbidly obese, as it is only half the issue. In obesity, drug dosing is not simply a problem of size, but of changed body

Table 2. Suggested doses of LMWH for thromboprophylaxis in the high-risk patient undergoing general surgery (dose reduction in renal impaired patients).

	<50 kg	50–100 kg	100–150 kg	>150 kg
Enoxaparin	20 mg daily	40 mg daily	40 mg BD	60 mg BD
Dalteparin	2500 U daily	5000 U daily	5000 U BD	7500 U BD
Tinzaparin	3500 U daily	4500 U daily	4500 U BD	6750 U BD
Nadroparin	2850 U daily	3800 U daily	5700 U daily	5700 U daily

Adapted from UK Haemostasis and Thrombosis Committee, 2012 BD, twice daily.

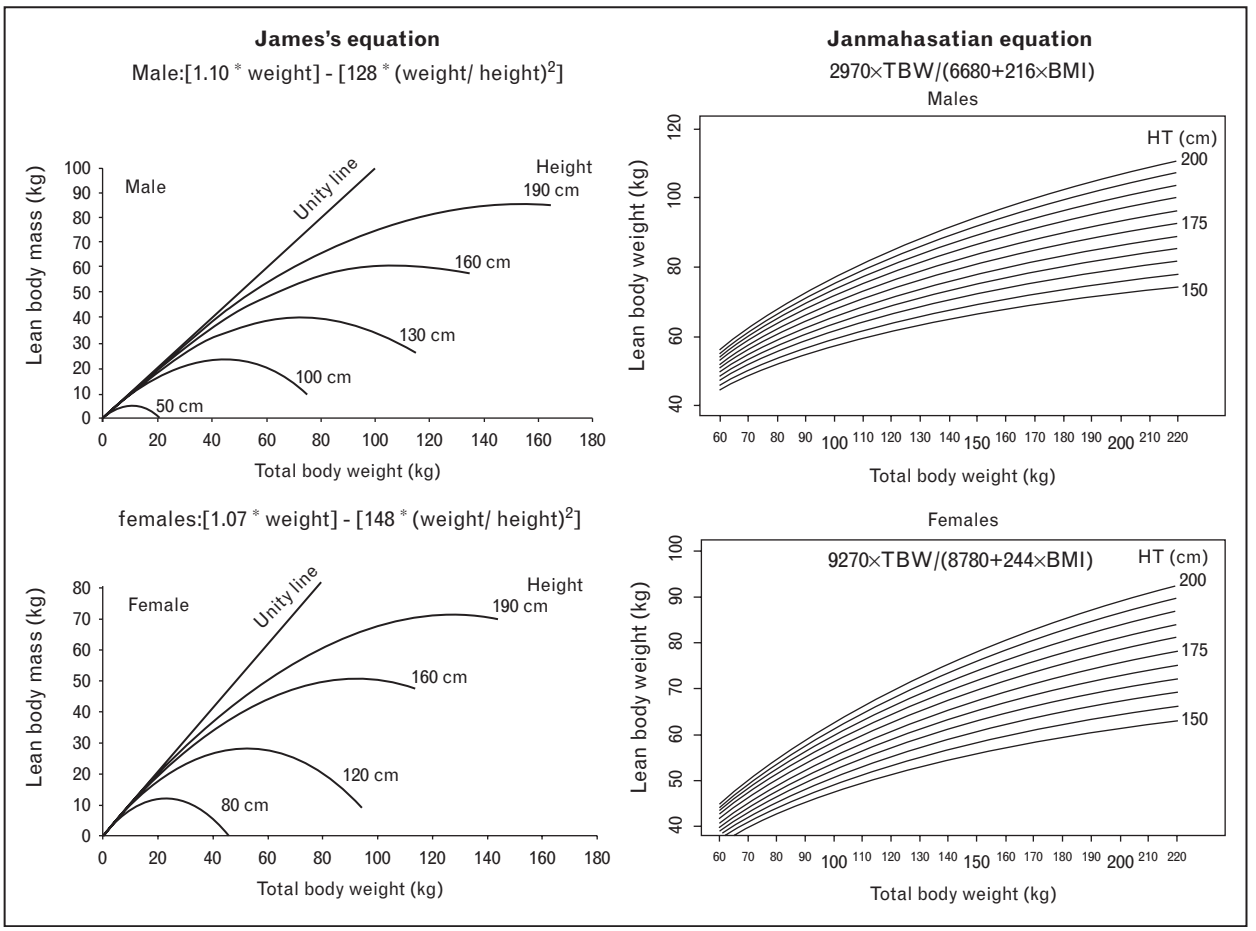

FIGURE 2. Lean body mass with the James's equation and with Janmahasatian formulae. Notice that in the James' equation lean body mass decreases with increasing total body weight. Adapted with permission from [34] and [55].

composition. Different body size descriptors in the allometric formulae have to be included to correct for body composition.

Volatile agents

Modern anaesthetics (e.g. sevoflurane and desflurane) with low blood–gas partition coefficients and low oil–gas solubilities offer the advantage of a rapid onset and offset combined with a high degree of control over the anaesthetic level obtained, as measured by the end-tidal concentrations [36]. Obesity only moderately affects the pharmacokinetics of agents like sevoflurane [37] and desflurane [38]. A recent meta-analysis exploring the differences in emergence between sevoflurane and desflurane report reduced mean time to extubation in favour of desflurane [39]. Studies where the end-tidal concentration was reduced to higher Bispectral index values or 0.5 minimal alveolar concentration did not show a significant difference in emergence [40,41]. The standardized use of antiemetics minimises the increased incidence of PONV induced by using volatile agents [9]. Desflurane increased intestinal motility more than sevoflurane during gastric bypass surgery [42].

N_2O is our oldest agent, with the lowest blood–gas solubility and a lipid solubility in an order of magnitude less than Desflurane, and is being increasingly used in morbidly obese patients as a volatile-sparing adjunct [43]. The second gas effect of N_2O at induction and emergence has been underestimated and can accelerate wash in and wash out of volatiles [44]. N_2O might have the potential of reducing chronic postoperative pain, which does occur even after laparoscopic surgery [45].

With the use of volatiles alone, respiratory depression leading to profound hypoventilation can reanaesthetize the patient after the end of anaesthesia. Computer modelling, following a single case report, has shown how this could occur because of volatile agent redistribution from the muscle compartment [46▪▪].

Propofol

The induction dose of propofol can be calculated on LBM [47], however, the continuous infusion rate requires an adjusted scalar more closely related to TBW [48]. Classic TCI models have poor predictive ability when used in the obese. The performance of TCI models incorporating allometric scaling [49,50,51▪▪] were compared to commercially available TCI models of Marsh and Schnider. The Eleveld PK model proved superior [51▪▪]. Interestingly, the predictive error of the Schnider and Marsh model became the lowest of the tested models when adjusted body weight was used [52▪▪].

Propofol-based anaesthesia did not increase the incidence of rhabdomyolysis compared with volatile-based anaesthesia [53]. In nonobese patients, propofol anaesthesia impaired early postoperative lung function more than desflurane in surgical procedures lasting 120 min or less [54].

Neuromuscular blocking agents

Nondepolarising muscle relaxants – cisatracurium, rocuronium, and vecuronium – should be scaled to LBW; (although in the morbidly obese the need for rapid control of the airway makes 'rapid sequence' doses desirable to achieve early intubating conditions, for 1.2 mg/kg of rocuronium). It is recommended that succinylcholine and neostigmine be dosed to TBW [55]. The safest reversal dose of sugammadex for rocuronium and vecuronium is calculated on TBW [56], although adjusted body weight has been studied for reversal of moderate rocuronium-induced curarization [57]. There is a trend toward monitored continuous deep neuromuscular blockade (PTC 0–2) during laparoscopy, since this might improve surgical access and postoperative pain [58]. In this setting, the use of the combination steroidal neuromuscular blocking agent (NMBA) with sugammadex reversal almost becomes mandatory, since full reversal with neostigmine of a deep neuromuscular block is practically impossible. The new agent Calabadion reverses both benzylisoquinolones and steroidal NMBAs and has the potential to reverse deep NMB induced by both classes, but is not yet in commercial distribution [59].

Opioids

Countering the positive effects of analgesia and euphoria, opioids do carry significant risk and danger in the morbidly obese: risk of hyperalgesia, negative effects on the immune system, increased incidence of PONV, respiratory depression, and even 'dead in bed' events in OSA patients can occur, because of opioid/sedative administration (type 2 events) or sleep apnoea arousal failure (type 3 event) (Fig. 3) [60]. The combination of our anaesthesia, opioids and surgery is likely to be responsible for the majority of early (24–72 h) complications in patients with OSA [61].

In adherence with ERAS protocols, use short acting opioids or at least minimize the use of long acting opioids in morbidly obese patients [7]. Dosage of remifentanil and fentanyl can be calculated on LBM. Pharmacokinetic models for sufentanil and alfentanil incorporate TBW, but for high-BMI patients, dose reductions toward LBM are probably justified [62].

Analgesia

In providing postoperative pain relief in morbidly obese patients, several aspects should be targeted by the anaesthesiologist:

(1) Using core analgesics in line with the steps in the WHO pain ladder.
(2) Incorporation of adjuvant agents.
(3) Early detection and prevention of neuropathic pain.
(4) Use of regional anaesthesia whenever feasible.
(5) Avoidance of potent opioids where possible.

Multimodal analgesia makes use of opioid-sparing adjuvant drugs and strategies to provide safe postoperative pain relief, with as little use of strong opioids as possible.

Step 1

Paracetamol (Acetaminophen)

Use of a 2 g paracetamol i.v. as a loading dose 30–60 min before the end of surgery, followed by 1 g/6 hrs appears to be a well tolerated clinical practice in the obese patient [63]. A smaller loading dose of 1 g can be used in patients with hepatic disease or haemostatic dysfunction [64▪]. Paracetamol has supra-additive effect when combined with NSAID and tramadol [65▪].

Granisetron and tropisetron may block the analgesic effect of paracetamol [66]. Safety concerns over paracetamol have been recently raised and involved more cardiovascular and gastrointestinal adverse events in a general population [67].

NSAIDs

NSAIDs are some of the most effective foundational analgesics and Ketorolac (40 mg loading, 3×10 mg/day) or Diclofenac (150 mg loading or

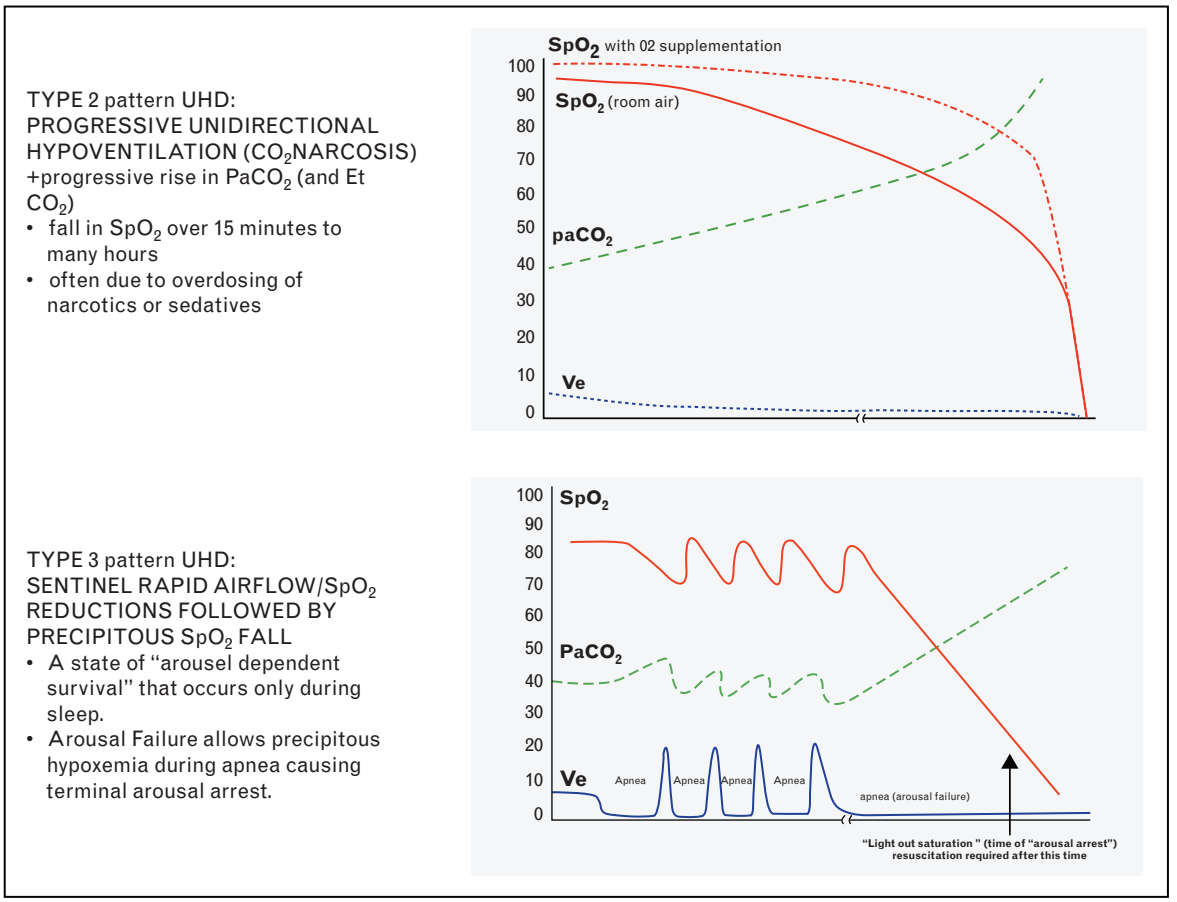

FIGURE 3. Respiratory patterns in unexpected hospital death. Adapted from www.asahq.org American Patient Safety Foundation (APSF) fall 2011 [58].

2×75 mg/day) should probably be used in all patients unless contraindicated. Only one study reported that ketorolac may increase the risk of postoperative haemorrhage after laparoscopic Roux-en-Y gastric by-pass [68]. NSAIDS only increase the risk for anastomotic leak in nonelective colorectal surgery [69▪▪]. The risk of ulcer development at the gastrojejunostomy site in gastric bypass depends more on the type of procedure and the patient's compliance to avoid nicotine, alcohol, and chronic use of NSAIDS. In the acute perioperative setting NSAIDs are not contraindicated on this basis.

Step 2

Tramadol/tapentadol

Although used in many multimodal strategies, few studies can be found on the use of these drugs in morbidly obese patients. Tramadol (50–100 mg/6 hrs with a max of 400 mg) has the disadvantage of increasing nausea and vomiting and can cause serotoninergic syndrome in patients on antidepressant drugs. It is also a prodrug and needs to be converted to the active form, with variable consistency. It is a μ receptor agonist and can cause respiratory arrest. Tapentadol is a newer active agent not requiring metabolism and is twice as potent but with minimal serotoninergic activity.

Step 3

Longer-acting opioids like morphine should only be used with caution in the obese and following appropriate loading with foundational (step one) analgesics, large doses should not be required. Dosing regimens vary in both dose and timing of administration, with a prudent intraoperative loading dose of 50 μg/kg IBW morphine at the moment of stopping the pneumoperitoneum. Patient controlled analgesia is generally set with no basal infusion of morphine, use bolus doses of 0.5–1.0 mg with a 10-min interval and titrate to a desirable effect within the first few hours after surgery [70].

Adjuvants to core analgesics

Dexamethasone

Intraoperative glucocorticoids have analgesic (at rest and during mobilization) and antihyperalgesic effects. They prevent postoperative nausea and vomiting (PONV) and reduce postoperative fatigue. Dexamethasone had no demonstrable effect on infection and wound-healing, glycemia was higher but without any apparent detriment, and it is suggested there is no reason to withhold this therapy [71].

Most studies on the use of dexamethasone in the obese patient use 8 mg i.v. at induction of anaesthesia.

Magnesium

Magnesium acts as an N-methyl-D-aspartate antagonist, and as such has effects on postoperative pain. Dosage is 40 mg/kg IBW and can be followed by a 10 mg/kg IBW/h continuous infusion. Magnesium potentiates the nondepolarizing NMBA and ideally should be administered early, and there must be awareness of this interaction and the potential for residual muscle weakness.

Ketamine

As an NMDA antagonist, low-dose ketamine has analgesic, antihyperalgesic, and opioid-sparing effects but in addition has local anaesthetic and anti-inflammatory effects.

Side-effects (hallucination, cognitive impairment) are minimized when doses of 0.25–0.5 mg/kg loading dose are used followed by a continuous infusion of 2–2.5 μg/kg/min [65▪].

Lidocaine

Analgesic effects of systemic lidocaine are well demonstrated (in general and bariatric surgery) [72▪]. A bolus of 1.5 mg/kg is followed by a 2 mg/kg/h infusion until the end of the surgical procedure. Afterwards, the continuous infusion is set at 1.33 mg/kg/h for another 23 h and stopped (calculated on IBW).

Clonidine/dexmedetomidine

The α-2 agonists have anxiolytic, analgesic, and sedative effects. Dexmedetomidine is more analgesic than clonidine because it has increased selectivity for the alpha-2A receptor located at the spinal cord and central nervous system. It maintains airway tone and respiratory drive together with an easily arousable sedation state.

Clonidine has been administered at doses of 150–300 μg at induction, but can be markedly sedating and most would limit doses to around 50 μg. Dexmedetomidine is usually started with a loading dose of 0.5 mg/kg LBM over 10 min, followed by continuous infusion of 0.2–0.8 μg/kg/h.

If necessary postoperative dexmedetomidine can be continued at an infusion rate of 0.1–0.2 μg/kg/h.

Antiemetics

Nausea following bariatric surgery is very common and probably in large part mechanical in origin, related to staple lines and pressure on the stomach tissues. The incidence of nausea is highest after gastric sleeve surgery, and least after gastric banding. It tends to be self-limiting but is clearly unpleasant. Good studies directly comparing the efficacy of antiemetics following bariatric surgery are lacking. The mainstays of antiemetic practice are the same as those used in the nonobese population, namely the 5-HT3 antagonists and dexamethasone.

The use of an opioid-free technique for bariatric surgery, utilizing Propofol Total Intravenous Anaesthesia, ketamine, and dexmetetomidine has been reported to reduce the incidence of PONV, compared to a standard morphine and volatile technique [67]. In this study both groups received dual antiemetic therapy with dexamethasone and ondansetron.

Aprepitant is a Neurokinin-1 receptor antagonist and given orally preoperatively appears to have benefit in bariatric surgery [68]. It is, however, very expensive and is not yet available as a rescue i.v. preparation.

CONCLUSION

ERAS protocols are being successfully used in obese patients undergoing bariatric surgery, and the principles of multimodal analgesia using adequate foundational analgesia and adjuvant coanalgesic therapy are minimizing the requirement for opioids. The high incidence of OSA and sleep disordered breathing amongst the obese makes the avoidance of long acting agents and in particular minimizing opioids highly desirable. Nausea in the early postoperative period after bariatric surgery, especially gastric sleeve resection, remains problematic.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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