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REVIEW

Intrathecal morphine for postoperative analgesia: Current trends

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Core tip: Intrathecal (IT) morphine for postoperative pain relief is being used for over 100 years but till today there are no clear guidelines or fixed dose regimes for its use. After an extensive review of the literature, we conclude that: (1) IT morphine is very useful yet cost-effective and reliable albeit with some risk of serious effects; (2) After IT morphine administration, mandatory monitoring for respiration, oxygenation and sedation should be done for the first 24 h; and (3) Further studies are required to determine the exact dose on the basis of body weight for IT administration of morphine.

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Abstract

The practice of anesthesiology has always been governed by evidence-based medicine. The quick turnover rate of patients in the operating room and patient safety and satisfaction, have also further changed the way we practice anesthesia. The use of intrathecal (IT) opiates as an effective form of postoperative pain relief has been established for many years. Morphine was the first opioid used by IT route. In clinical practice, morphine is regarded as the gold standard, or benchmark, of analgesics used to relieve intense pain. Perhaps for this reason, IT morphine has been used for over 100 years for pain relief. IT morphine is one of the easiest, cost-effective and reliable techniques for postoperative analgesia and technical failures are rare. And yet there is no consensus amongst anesthesiologists regarding the dose of IT morphine. Like all other methods of pain relief, IT morphine also has some side effects and some of them are serious though not very common. This review article looks into some of the key aspects of the use of IT morphine for post-operative analgesia and various doses for different procedures are discussed. This article also describes the side effects of IT morphine and how to treat and prevent them.

INTRODUCTION

Ineffective management of post-operative pain can cause many harmful acute and chronic effects. Optimal pain control, which encompasses effective pain control with minimum side effects, may decrease complications and facilitate recovery during immediate postoperative period[1]. Optimal pain control can be achieved by a multimodal technique, or balanced analgesia, which is not a new concept. The multimodal analgesia may include regional techniques, systemic or neuraxial opioids, non-steroid anti-inflammatory drugs and centrally acting drugs like paracetamol. Thus spinal or intrathecal (IT) administration of morphine is seldom used alone for the management of post-operative pain, though it is known to provide excellent analgesia.

The first published report on IT administration of morphine was by a Romanian surgeon, Racoviceanu-

Table 1 Comparison of intrathecal morphine with hydrophilic opioids (Fentanyl and Sufentanil)[9]

Opioid	IT/*iv* potency ratio	Onset of IT analgesia (min)	Duration of analgesia (h)	Time of peak respiratory depression	Clinical dose range
Morphine	200-300:1	60-120	18-24	8-10 h	0.1-0.5 mg
Fentanyl	10-20:1	< 10	1-4	5-20 min	6-30 mcg
Sufentanil	10-20:1	< 10	2-6	5-20 min	2.5-10 mcg

IT: Intrathecal; *iv*: Inravenous.

Pitest, who presented his experience using a mixture of cocaine and morphine in 1901, in Paris[2]. After the discovery of opioid receptors by Pert and Snyder in 1973 and the subsequent identification of dorsal horn opioid receptors by radioligand techniques in 1977, Wang *et al*[3] described the efficacy of IT morphine for postoperative analgesia in a group of eight patients with genitourinary malignancy in 1979. Since then, the use of IT morphine has become widely acceptable technique. It is one of the easiest, cost-effective and reliable methods of analgesia albeit with some risk of serious side effects. Morphine was the first opioid approved by the United States Food and Drug Administration (FDA) for its neuraxial use and perhaps it is the most widely neuraxially used opioid.

This review article looks into some of the key aspects of the use of IT morphine for postoperative analgesia and various doses for different procedures are discussed.

MECHANISM OF ACTION

Unlike IT administration of local anesthetics, administration of IT morphine or other opioids is not associated with skeletal muscle weakness, loss of proprioception or sympathetic denervation. IT opioids bind with a family of G-protein linked pre- and postsynaptic opioid receptors in laminae I and II of the dorsal horn. This binding to the receptors leads to opening of potassium channels and closure of calcium channels with subsequent reduction in intracellular calcium levels. These changes reduce the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibers, but not A fiber terminals with consequent reduction in nociceptive transmission[4,5]. Other suggested mechanisms of action include: Adenosine mediated hyperpolarization of nerve fiber and reduced release of GABA from the dorsal horn[5].

Effective action of morphine or other opiates can be achieved by their specific action at the dorsal horn[6]. IT opioids act both pre and post synaptically by reducing the neurotransmitter release and hyperpolarize the membranes of neurons in the dorsal horn[6,7]. The concentration of the drug needed for such effects cannot be achieved by the standard parenteral and non-parenteral doses used in clinical practice[6]. A direct delivery to the IT space leads to required high concentrations with ease[6]. The effect of opioids on the dorsal horn to provide specific analgesic effect with minimal sensory, motor and autonomic effects has been named as "selective spinal analgesia" by Cousins *et al*[8].

PHARMACODYNAMICS AND PHARMACOKINETICS

The distribution of IT administered opioids between water (cerebrospinal fluid) and fat (nervous structures, membranes) phase is determined by the hydrophilicity or lipophilicity and the magnitude of the ionized fraction. Highly water-soluble drugs with large ionized fraction will linger in the water phase (CSF) and ascend rostral. The lipid solubility is an important property that contributes to the likelihood of respiratory depression. Moreover, lipophilic drugs with large unionized fraction will cross the lipid barriers fast and easily. High lipid-solubility facilitates an easy access to the receptor sites and fast elimination, with little tendency to linger in the water phase. Comparisons of morphine and some lipophilic opioids are summarized in Table 1[9].

Secondary to its hydrophilic property, morphine binds to high affinity receptors in the dorsal horn but has a lower propensity for binding to the non-receptor sites in the myelin and white matter[5]. This hydrophilic property of morphine minimizes the spinal cord capillary loss[10], which results in a higher concentration of available morphine in the CSF, leading to a wider band of analgesia but not extending to much higher levels as shown by Kroin *et al*[11]. Hence the site of administration and the dose given have an important role to play in the extent of spread of desired analgesic effects[11]. Also, due to high hydrophilicity, morphine stays in the CSF for a long time leading to a long duration of action, up to 24 h.

After IT morphine administration, CSF concentrations gradually decline after 12 h[5]; there is slow diffusion into the epidural space with a consequent slow increase in plasma concentrations. Cephalad spread may occur as early as 30 min when drug is detectable in cisternal CSF[5]. There is poor circumferential CSF spread around the cord from the injection point; and minimal metabolism to water-soluble metabolites in the CSF and spinal cord. Radiolabelled (14C) morphine persists for 2 h with only 4.5% of the injected dose remaining at 3 h post injection. The removal of drug from CSF is facilitated *via* a glycoprotein carrier transport system located in the choroid plexus[5]. In one study, where fifteen patients undergoing thoracotomy were injected with IT morphine either 0.25 or 0.5 mg at L2-3 or L3-4 levels, the terminal elimination half-life of morphine in CSF was close to three hours in all patients[12]. There are a number of issues that have not been considered so far for pharmacokinetics of IT mor-

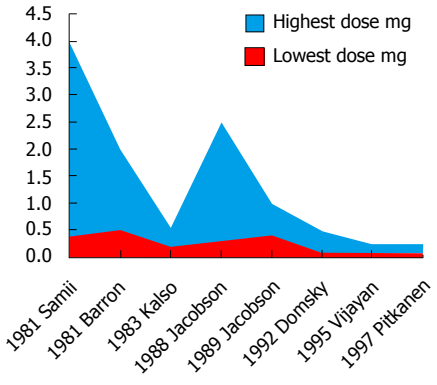

Figure 1 History of intrathecal morphine dose for hip surgery. Modified from ref. [39].

phine and these include: the effects of positive pressure ventilation or alterations in the baricity of opioid solutions[5].

CLINICAL USES AND DOSAGE

IT morphine with or without a local anaesthetic (LA) is still a popular analgesic technique in many institutions around the world; and every year several studies are published. IT morphine without LA is used as a single dose injection together with general anaesthesia to prevent pain after major surgery[13], though only additive-free formulation of morphine is approved for IT use by the FDA[14]. IT morphine provides excellent post-operative analgesia and with low dosage it gives segmental analgesia, resulting in localized nociception without motor, sensory or autonomic side effects.

It is important to emphasize that IT morphine cannot be used for day surgery due to its prolonged action. It has an established role for obstetrics, spinal and orthopedic surgery while it is also used for general surgery, urology and thoracotomies. IT morphine decreases pain intensity at rest and on movement up to 24 h after major surgery. Decreased requirement of supplemental analgesics is more pronounced after abdominal than after cardiac-thoracic surgery[15].

Through a large range of doses, there is a lack of evidence of linear dose-responsiveness, for any of the beneficial or harmful effects[15]. Late last century very large doses up to 4 mg were used while today the doses range from 0.1-0.5 mg, depending on the type of surgery (Figure 1[16] and Table 2[17]). In a meta-analysis based on studies on spinal anesthesia, with morphine as an adjuvant of an LA without general anesthesia[18], the rate of adverse effects of IT morphine was analysed. And it was shown that the use of IT morphine at doses < 0.3 mg, the rate of episodes of respiratory depression was not higher compared to the placebo group who received systemic opioids[13].

Obstetrics

IT morphine in the dose range of 0.05-0.2 mg has been used for effective post-caesarean section analgesia in many studies. Use of 0.2 mg, in some studies, was associated with an increased risk or respiratory depression[19-21]. In the other study, use of 0.1 mg did not show any respiratory depression[19]. However, 24 h monitoring should be strictly followed in all obstetric patients receiving IT morphine like all other surgical patients who receive IT morphine[20]. In a recent study involving 60 parturients, addition of 0.1 mg morphine to the routine bupivacaine plus fentanyl spinal anesthesia, led to significantly lower verbal pain score for 20 h postoperatively and respiratory depression was not reported[22]. Another study compared 0.1 mg and 0.2 mg IT morphine for postoperative analgesia after Caesarian section and reported that there was longer duration of analgesia with 0.2 mg though the incidence of pruritus, nausea and vomiting was significantly higher than with 0.1 mg[21]. Recently, a Brazilian group has demonstrated same quality of analgesia with 0.05 mg and 0.1 mg IT morphine after Caesarian section in 123 women[23].

Spinal surgery

IT morphine has shown to be effective in patients undergoing spinal surgeries. Ziegeler *et al*[24] demonstrated the efficacy of 0.4 mg of IT morphine in providing postoperative analgesia in patients undergoing posterior interbody fusion surgeries. Severe hypercarbia of 181 mm of Hg has been reported in a 58 kg patient who received 0.4 mg IT morphine after lumber spinal surgery[25]. Studies by Hindle *et al*[5] and Urban *et al*[26] showed that a dose of 0.02 mg/kg of IT morphine reduced the requirements of supplemental analgesia in the first 12 h of the postoperative period. However, Boezaart *et al*[27] recommended much lower dose of 0.002-0.004 mg/kg IT morphine for lumbar IT surgery and this was injected under direct vision at the end of surgery. This study concluded that such patients had effective analgesia with minimal side effects and could be managed on the surgical ward.

Orthopaedic surgery and joint replacements

Many studies (Domsky 1992, Kalso 1983, Grace 1996, Reat 1989) have shown that IT administration of morphine provides excellent postoperative pain relief in major orthopedic surgery. Early studies reported late respiratory depression in some cases, when IT dose of morphine as high as 2.5 mg was used (Reay 1989, Jacobson 1988, Gustafsson 1982). In recent studies, 0.1-0.2 mg IT morphine has been recommended for the use in patients undergoing total hip arthroplasty (THA), without the need for supplemental analgesia or monitoring in High Dependency Unit (HDU)[5]. One multicentre study involving 188 patients undergoing orthopaedic surgery[28], demonstrated that the use of rescue opioids was significantly lower for 72 h in a group given 0.2 mg of IT morphine than among those who received 0.1 mg ($P < 0.05$) and in both groups with respect to the placebo group ($P < 0.0001$). Further, IT morphine administration was not associated with increased rate of respiratory depression and almost 70% of the patients who received 0.2 mg IT

Table 2 Recommended intrathecal morphine dosages for various surgical procedure[17]

Low dose (with LA or RA)	Moderate dose (with GA)	High dose (with GA)
TURP: 0.05 mg	Abdominal hysterectomy: 0.2 mg (plus LA)	Thoracotomy surgery: 0.5 mg
Caesarian section: 0.1 mg	Abdominal colon surgery: 0.3 mg	Abdominal aortic surgery and cardiac surgery: 7-10 mcg/kg
Hip replacement: 0.1 mg	Spinal surgery: 0.4 mg	
Knee replacement: 0.2 mg		

LA: Local anesthesia; RA: Regional anesthesia; GA: General anesthesia.

morphine did not require rescue medication for 48 h.

Several authors recommend 0.3 mg dose for Total knee replacement (TKR)[5]. Other studies have shown a greater efficacy of 0.5 mg IT morphine as compared to 0.2 mg in patients undergoing TKR without any increased side effects[29]. Recently, a cross-surgical specialities European collaborative (PROSPECT) has recommended IT morphine 0.1-0.2 mg after THA without the need for supplementation by patient controlled analgesia (PCA) or monitoring in an HDU[30]. In one study for postoperative pain relief after THA, 0.1 mg IT morphine and periarticular local infiltration with ropivacine, ketorolac and epinephrine were compared. Much lower pain scores up to 24 h were demonstrated in IT morphine group[31].

Liver resection

The use of epidural catheters in patients undergoing liver resection is often placed under the peril of postoperative coagulation disturbances. This has largely limited the use of epidurals in patients undergoing liver resections. De Pietri *et al*[32] showed that analgesic effect of IT morphine was similar to continuous epidural infusion of local anesthetics in patients undergoing liver resections and concluded that a single dose of 0.2 mg IT morphine followed by PCA morphine analgesia provided satisfactory postoperative analgesia[33].

Similar study by Koea *et al*[33] showed IT morphine to be safe and effective in providing postoperative analgesia for liver surgery and these patients also benefitted from reduced perioperative physiological disturbances and a shorter hospital stay. Sakowska *et al*[34] also demonstrated similar results for the use of IT morphine for hepato-pancreato-biliary surgeries. In another high-volume hepato-pancreato-biliary unit 68 patients were studied for the efficacy of IT morphine, and was compared with thoracic epidural analgesia for hepatic resection[35]. There was no difference in the outcome or pain scores between two groups but there was an increase in the incidence of intraoperative blood loss in IT morphine group compared to thoracic epidural analgesia group[35].

Urology

Small doses of 0.05 mg have been used to treat detrusor muscle spasms in patients undergoing transurethral resection of prostate (TURP)[5]. One study compared 0.075 and 0.150 mg IT morphine for postoperative analgesia after TURP under spinal anesthesia[36]. The group with 0.150 mg IT morphine had reduced demand for rescue analgesia with low incidence of mild pruritus which did not require any treatment, while both groups had similar low incidence of nausea and vomiting. For radical retropubic prostatectomy patients who received 0.2 mg IT morphine showed a significant reduction in tramadol consumption, postoperative pain scores, rescue analgesia, and postoperative nausea[37].

General surgery

IT morphine in the dose of 0.075-0.1 mg has been used for laparoscopic cholecystectomies without any fear of respiratory depression. For colon surgery, a dose of 0.3 mg was found to be effective without any respiratory depression in one study[15].

In a recent study[38] with PROSPECT collaboration, for laparoscopic colorectal surgery, neither the use of IT morphine nor epidural analgesia is recommended due to high risk: benefit ratio. Instead, multimodal analgesia with infiltration of surgical incisions with local anesthetic at the end of surgery, with systemic steroids, conventional nonsteroidal anti-inflammatory drugs or cyclooxygenase-2-selective inhibitors in combination with paracetamol with opioid used as rescue are recommended.

Cardiac and thoracic surgery

Various researchers have used IT morphine in doses of 1-4 mg in patients having cardiac surgery[39-41]. Trevor *et al*[39] and Fitzpatrick *et al*[41] demonstrated that use of 1 mg of IT morphine was associated with fewer side effects. Peak expiratory flow rates were also found to be better in these groups receiving IT morphine[39]. Meta-analysis by Aun *et al*[40] and Liu *et al*[42] on the use of IT morphine in patients having cardiac surgery showed a reduction in time to extubation, pain scores and use of postoperative intravenous (*iv*) morphine[42,43]. The concern of bleeding was also alleviated by no reported incidence of spinal hematomas. It was also shown that the intensive care and the hospital stays were shorter amongst patients receiving IT morphine[41,42,44]. However, in a recent review article, meta-analysis of 27 studies did not point out benefit of IT morphine more than that of parenteral non-steroidal anti-inflammatory drugs; and morphine sparing was more pronounced for abdominal surgery than for cardiothoracic surgery[15]. In one study, IT catheter was inserted at L2-L3 interspace prior to induction of anesthesia, in 84 patients undergoing thoracotomy, for repeated morphine boluses for postoperative analgesia[45]. In this study, the mean morphine administered *via* IT catheter in 48 h was

Table 3 Concomitant use of other intrathecal drugs with intrathecal morphine

Additional IT drug to IT morphine	Effect
Local anesthetic-bupivacaine	Improved pain score and lower requirement of additional analgesia
Fentanyl	May induce acute tolerance to IT morphine and no real advantage
Clonidine	Increased duration of analgesia with better pain scores but higher incidence of hypotension
Ketorolac	Increased duration of analgesia without significant side effects

IT: Intrathecal.

2.56 mg (± SD 0.88 mg). Only one patient required rescue morphine. There were no serious complications or sequel at 6-mo follow-up. The authors concluded that IT morphine for post-op analgesia is efficacious and safe in a post-thoracotomy population[45].

DIFFERENT PATIENT GROUPS

Many research papers have been published regarding use of IT morphine in all patient groups since 1979.

Pediatric age group

Administration of IT morphine has been reported in children as small as 3 kg[46]. Majority of publications in this age group relate to spinal surgery and cardio-thoracic surgery. While one study concluded that the use of IT morphine reduced blood loss significantly during scoliosis surgery in pediatric age group[47], the others suggest that use of IT morphine provides effective and safe analgesia in children for over 12 h[46-51].

Obstetric patients

Bradycardia can occur with systemic opioid administration and also with IT morphine. There is a significant high risk of fetal bradycardia when IT morphine is used for labor analgesia or for caesarian section[52,53].

Elderly patients

Most studies in this age group include patients undergoing orthopedic, spinal or colorectal surgery. Elderly patients are more sensitive to opioids when administered *via* PCA or any other systemic route due to decreased clearance and decreased volume of distribution. Similarly, they will be more sensitive to IT route. Compared with systemic dosing of morphine, IT administration is effective in providing analgesia at a fraction of the systemic dose and thus has a much lower side-effect profile[54,55]. A smaller dose of IT morphine may provide effective analgesia and reduce postoperative analgesic requirement while minimizing the incidence of adverse effects. Hence no added risks have been reported with the use of IT morphine and in fact, sedation scores are much lower with IT morphine when compared with PCA morphine. IT morphine provides effective analgesia after hip or knee arthroplasty, gynecological procedures or transurethral resection of prostate[54-56]. According to Murphy *et al*[55] and Auburn *et al*[57], 0.1 mg IT morphine provides the best balance between analgesic efficacy and adverse effect profile in older patients after hip surgery.

CONCOMITANT USE OF OTHER IT DRUGS WITH IT MORPHINE

LA

LA are the most commonly used drugs with IT morphine. IT morphine for joint replacements and urological procedures has generally been used with concomitant spinal anesthesia. The LAs and morphine have different sites of action and thus the combination of the two leads to additive effect and better analgesia. Practice guidelines for acute pain management in the perioperative setting from American Society of Anaesthesiologists (ASA) Task Force on Acute Pain Management suggest that[58]: There is an improvement in pain scores when neuraxial morphine is combined with LA compared with neuraxial morphine alone (Category A1 evidence). Findings for the frequency of nausea and vomiting and pruritus are equivocal when neuraxial morphine is added to LAs (Category C1 evidence)[58] (Table 3).

Fentanyl

When IT morphine is combined with fentanyl, pain relief is obtained within 10 min. The advantage of concomitant use of IT fentanyl with IT morphine has been questioned. Carvalho *et al*[59], suggest that IT fentanyl may induce acute tolerance to IT morphine. However, in this study though the pain scores with different doses of IT fentanyl with IT morphine were higher than with only IT morphine, the requirement of postoperative analgesia was similar. Addition of IT fentanyl to IT morphine and bupivacaine for caesarian sections in another study did not show any advantage and analgesia with only IT morphine and bupivacaine was much superior[60].

Clonidine

In one double blind randomized study from France, IT morphine and clonidine provided effective analgesia after coronary artery bypass graft surgery and allowed earlier extubation when compared with only IT morphine or only PCA morphine[61]. Meta-analysis of seven studies by Engelman and Marsala, indicates that there was an increase in the duration of analgesia and reduced morphine requirement when IT clonidine was added to IT morphine for postoperative analgesia, however, there was a greater incidence of hypotension when clonidine was added[62]. Sites *et al*[63] have also indicated that co-administration of IT clonidine and morphine decreases the 24-h *iv* morphine consumption and improves the 24-h VAS

Table 4 Summary of side effects of intrathecal morphine

	Serious	Not serious
Common	Respiratory depression Sedation	Pruritus Nausea and vomiting Urinary retention
Uncommon	Bradycardia	Sweating Delayed gastric emptying Constipation Headache Persistent hiccups Resistant hypothermia Priapism Nystagmus

score when compared with IT morphine alone.

Ketorolac

One random controlled trial has indicated that use of IT 2 mg ketorolac along with IT 0.2 mg morphine provided better and longer analgesia after TKR with no significant side effects and lower consumption of ketoprofen[64].

SIDE EFFECTS OF IT MORPHINE

The side effects are summarized in Table 4. Pruritus, nausea, vomiting and urinary retention are the commonest side effects while sedation and respiratory depression are serious side effects. Bradycardia can occur with systemic administration of morphine and is also seen with IT administration. Some rare complications like persistent hiccup[65], priapism[66], resistant hypothermia[67] and nystagmus[68] have also been reported.

Sedation, respiratory depression and ventilatory response to hypoxia

Sedation and respiratory depression are the most serious side effects of the IT morphine[67]. The sedation from IT opioids can range from full consciousness to complete loss of consciousness and respiratory arrest[67].

Definition of respiratory depression is not well defined or universal throughout the literature. It may include a respiratory frequency of less than 8 or even 10 breaths/min (bpm), oxygen saturation of less than 85% or even 96%, or the need for naloxone to maintain an adequate tidal volume[15]. IT opioid administration can cause early and delayed respiratory depression. Early respiratory depression is typically seen within 2 h and delayed respiratory depression is seen from 6-12 h[69].

It is important to note that the respiratory rate and pulse oximetry can be poor measures of respiratory depression in the postoperative period. Levels of sedation, and ultimately blood gas analysis, are more reliable[5]. In a recent study by Dalchow *et al*[70], measurement of transcutaneous carbon dioxide and oxygen saturation revealed respiratory depression in 17.8% when 0.3 mg IT morphine was used for caesarian section. The respiratory depression caused by IT morphine continues to be a concern despite the reduction in the dosages of morphine used, though the meta-analysis of 21 RCTs by Meylan, reported the NNH at 84[15].

The dose of IT morphine necessary to cause respiratory depression has been unclear. In a study of 5969 patients receiving IT morphine, respiratory depression was observed in 3% by Slappendel *et al*[16] and Gwirtz *et al*[71]. One meta-analysis has shown an increased rate of respiratory depression when the dose of IT morphine was $\geqslant$ 0.3 mg and the risk of respiratory depression was low in patients receiving < 0.3 mg of IT morphine[22]. In 22 healthy, young male volunteers, significant respiratory depression was observed when 0.2-0.4 mg IT morphine was administered while profound and prolonged respiratory depression was observed with 0.6 mg IT morphine[72].

Whilst the concern of respiratory depression still ranks high, the most practical and effective method for detecting respiratory depression remains unclear[15]. The incidence of respiratory depression raises the questions of the necessity of increased monitoring in the immediate postoperative period[15], and poses challenges in hospitals where the options of postoperative monitoring are limited.

With the choices of multiple parameters to monitor namely, respiratory rate, oxygen saturation (SpO_2), pCO_2, pupil size and sedation scores, researchers have looked into the most sensitive parameter in detecting opioid induced respiratory depression. Some researchers[25] opine that sedation scores are more sensitive than respiratory rate in detecting opioid induced respiratory depression[72]. Deep sedation is a sign indicating the requirement of more intense monitoring as these patients are at risk of respiratory depression[69,73].

Studies have also shown that the depression in ventilatory response to hypoxia although similar in magnitude is longer lasting than that seen after the administration of an equi-analgesic dose of intravenous morphine[74].

The best treatment of respiratory depression is prevention. Table 5[58,75] summarizes the guidelines set up by ASA Task Force for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. If respiratory depression does occur then naloxone should be given as an intravenous infusion and if required, non-invasive positive pressure ventilation should be carried out. There are many instances where significant carbon dioxide retention may occur much before any drop in the oxygen saturation. Many institutes have a protocol to monitor sedation scores like Ramsay sedation score after IT morphine administration.

Nausea and vomiting

Postoperative nausea and vomiting (PONV) is a common adverse effect of IT morphine, especially after Cesarean section[76]. In a study of 5969 patients who received between 0.2 and 0.8 mg morphine IT, Gwirtz *et al*[71] found 25% incidence of nausea and vomiting[71]. Various drugs have been used for prevention and treatment of nausea

Table 5 Guidelines by American Society of Anaesthesiologists task force for the prevention, detection, and management of respiratory depression associated with intrathecal morphine administration[58,75]

Identification of patients who may have increased risk respiratory depression	Prevention of respiratory depression	Detection of respiratory depression	Treatment of respiratory depression
• History of sleep apnea or OSA • Diabetes • Obesity • Concurrent systemic opioids • History of opioid intolerance • Physical examination of airway, heart, lung, cognitive function and vital signs	• NIPPV should be used for known OSA patients • Single shot neuraxial opioid preferred over systemic continuous opioids • IT morphine is not to be given in outpatient settings • Minimal effective dose to be used • Cautious use of parenteral opioids and hypnotics in the presence of neuraxial opioid • Concomitant use of parenteral hypnotics, opioids, magnesium, or sedatives will require increased monitoring in terms of duration, intensity or additional methods	• Monitor, respiration (rate and depth), oxygenation (SaO_2%) and sedation (Sedation score) • Monitor for at least 24 h every hour for the first 12 h then every 2 h for the next 12 h • After 24 h check the patient's condition and concurrent medication and decide on frequency of monitoring	• O_2 therapy when altered level of consciousness, respiratory depression, or hypoxemia • Routine O_2 therapy not advised as it may prolong the duration of apneic episodes and prevent detection of atelectasis, transient apnea and hypoventilation • Use of reversal agents like naloxone • *Iv* access should be maintained at all times • NIPPV should be considered and initiated when there is frequent and severe airway obstruction or hypoxemia

OSA: Obstructive sleep apnea; NIPPV: Noninvasive positive pressure ventilation; *iv*: Intravenous.

and vomiting after IT morphine. Baciarello *et al*[76] found the incidence of PONV to be close to 50% after IT morphine, which decreased to 15% after administration of 0.1 mg IT atropine. *iv* ondensetron 4 mg[77], combination of *iv* dexamethasone 4 mg and *iv* droperidol 0.625 mg[78], transdermal 1.5 mg scopolamine[79], *iv* 50 mg cyclizine[80] and oral 30 mg mirtazapine[81] have been found to be effective in preventing IT morphine induced PONV. For intractable PONV some researchers have recomended low dose naloxone infusion[82]. Nalmefene 0.020 mg *iv* after vaginal delivery in patients who received IT morphine decreased the incidence of PONV remarkably[83]. Naltrexone (6 mg) is an effective oral prophylaxis against IT morphine induced PONV but it shortens the duration of analgesia[84].

Pruritus

Although pruritus is one of the most common side effects of IT morphine administration, severe pruritus occurs only in 1% of patients[85]. Meta-analysis by Meylan *et al*[15] showed the NNH for pruritus to be 6. This study however did not indicate dose responsiveness. Other studies have shown the incidence of pruritus to vary from 0%-100%[85,86]. Pruritus occurs most frequently in pregnant females where gestational hormones may cause alterations in the opioid receptor population[5]. The distribution of pruritus is mainly in the upper half of the body, although in some cases it may be generalized[85,87,88]. The proposed mechanism causing pruritus is the cephalad spread of the drug in the CSF interacting with the trigeminal nucleus, where mu opioid and 5-HT3 receptors are collocated[5]. The interaction of morphine with trigeminal nucleus stimulates the substantia gelatinosa of the dorsal horn initiating the itch reflex[85]. There is no associated histamine release with opioid induced itching[5].

Multiple drugs have been used in the treatment of IT morphine induced pruritus. Naloxone at a rate of 5 mcg/kg per hour *iv* can be used in the treatment of pruritus and this does not reverse analgesia[89]. Other drugs such as ondansetron, nalbuphine have also use in the treatment of pruritus[90].

Iv butorphanol administration after delivery of the baby is also effective in obstetric patients to relieve itching after IT morphine[90]. There is evidence that κ-opioid receptor agonists have antipruritic activity[90]. Butorphanol has agonist actions at both κ-opioid and μ-opioid receptors and hence it may be effective but the sedation scores remain high in these patients.

Also, activation of the serotonergic system may be an important factor in the pathogenesis of IT morphine-induced pruritus[91]. Mirtazapine is a new antidepressant that selectively blocks 5-HT2 and 5-HT3 receptors. Mirtazapine premedication reduces the incidence of pruritus induced by IT morphine in patients undergoing lower limb surgery with spinal anesthesia[92].

Some studies have shown low dose (10-20 mg) *iv* propofol to be effective for IT morphine-induced pruritus in humans[92-94]. In a recent study, rats were studied to understand the mechanism of action of propofol in preventing IT morphine-induced pruritus[95]. This study hypothesized

that propofol relieved IT morphine-induced pruritus in rats by up-regulating the expression of cannabinoid-1 [CB (1)] receptors in anterior cingulate cortex (ACC). This study revealed that increased protein expression of CB (1) receptors in ACC might contribute to the reversal of IT morphine-induced scratching by propofol[95].

Urinary retention

The inability to micturate spontaneously is considered as one of the most distressing non-respiratory complication of IT morphine[96]. Meta-analysis of the relevant studies[15] has shown an increased incidence of urine retention amongst the patients who received IT morphine[15]. In one study, the incidence of urinary retention was as high as 20%-40% after 2 h of IT morphine injection and decreased to 10% after 24 h[97]. Urinary retention may persist for 10 to 20 h and is less common in women. Patients who develop urinary retention usually respond to cholinomimetic treatment and/or judicious use of catheters. Also, if the urinary retention is left unattended, neurogenic bladder may develop later. So it is imperative to either monitor patient's bladder clinically or with ultrasound or to place a urinary catheter aseptically in the operation theatre at the end of the surgery.

Neurotoxicity

There is no evidence that administration of IT morphine in single, repeated or as continuous infusion causes neurotoxicity[5]. In one case report where accidently 510 mg of morphine was injected IT[98]; naloxone infusion, blood pressure and seizure control led to complete neurological recovery indicating that morphine does not have any neurotoxicity.

Neuraxial morphine may trigger transient motor dysfunction after a non-injurious interval of spinal cord ischemia[99]. During the immediate reflow following a non-injurious interval of spinal ischemia, IT morphine potentiates motor dysfunction. This effect is transient and can be reversed by IT naloxone, which suggests that this effect results from an opioid receptor-mediated potentiation of a transient block of inhibitory neurons initiated by spinal ischemia[96]. This may be particularly applicable for patients undergoing abdominal aortic aneurysm repair who may suffer from non-injurious spinal cord ischemia during aortic cross clamping. It is interesting to note that in patients with chronic spinal injury leading to spasticity, IT morphine can diminish the elevated motor tone[99,100].

Infection

There are no reports of increased rate of surgical infection or meningitis after single shot IT morphine. Aseptic precautions have to be taken like any other lumber puncture technique. For chronic pain, where IT catheters are used for morphine delivery, infection can be one of the complications.

There are reports of association between the use of epidural or IT morphine and reactivation of herpes simplex labialis (HSL) in patients recovering from caesarian section[101-103]. Regardless of the route of morphine administration (parenteral or neuraxial), HSL reactivation occurs in parturients. However, patients who received IT morphine plus PCA experienced a more frequent reactivation compared with those who received PCA only[102]. Pregnancy is an immunosuppressed state, which enables the mother to tolerate the fetal allograft. This, together with increased physical and emotional stress of surgery, may predispose to the increased reactivation rate of HSV[104]. The fact that both facial pruritus and HSL reactivation affect the trigeminal nerve distribution has led many investigators to suggest that scratching causes skin damage predisposing to HSL reactivation[103,104].

CONCLUSION

IT morphine for postoperative pain relief is cost-effective, moderately safe and reliable technique with low risk of technical failure. IT morphine should be used as a part of multimodal analgesia. There is no consensus on the dose of IT morphine nor is it defined per body weight in most studies. IT morphine dose higher than 0.3 mg has a risk of respiratory depression. IT morphine should not be used for day surgery patients. Use of IT morphine has been reported in all age groups. IT morphine has definitive benefits in obstetrics, joint replacement and spinal surgeries, the latter especially in pediatric age group. Antiemetics should be prescribed routinely with IT morphine. After IT administration of morphine, mandatory hourly respiratory monitoring should be done for the first 12 h and then two hourly for another 12 h. IT morphine should not be administered when adequate monitoring and resuscitation facilities are not available.

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REVIEW

Human factors in anaesthetic crisis

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Abstract

This paper discusses some of the key aspects of human factors in anaesthesia for the improvement of patient safety. Medical errors have emerged as a serious issue in healthcare delivery. There has been new interest in human factors as a means of reducing these errors. Human factors are important contributors to critical incidents and crises in anaesthesia. It has been shown that the prevalence of human factors in anaesthesia can be as high as 83%. Cognitive thinking process and biases involved are important in understanding human factors. Errors of cognition linked with human factors lead to anaesthetic errors and crisis. Multiple errors in the cognitive thinking process, known as "Cognitive dispositions to respond" have been identified leading to errors. These errors classified into latent or active can be easily identified in the clinical vignettes of serious medical errors. Application of the knowledge on human factors and use of cognitive de-biasing strategies can avoid human errors. These strategies could involve use of checklists, strategies to cope with stress and fatigue and the use of standard operating procedures. A safety culture and health care model designed to promote patient safety can compliment this further. Incorporation of these strategies strengthens the defence layers against the "Swiss Cheese" models, which exist in the health care industry.

Key words: Safety; Errors; Human errors; Human factors; Crisis; Anaesthesia crisis

Core tip: Human factors contribute to human errors and anaesthetic crisis situation. These human factors can be identified and studied in detail. Progression of the non-routine events coupled with human factors when left unchecked lead to serious errors in health care. When the knowledge of human factors is incorporated into the practice of anaesthesia, patient safety is promoted.

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INTRODUCTION

Patient safety has taken centre stage in all aspects of anaesthesia. In the last few years, human factors have appeared time and again as an important contributor in many aspects of patient safety. Lessons from aviation safety have also made way into training in anaesthesia. Many of these lessons involve human factors, which are less spoken about, generally not included in the routine training of anaesthesia or at least certainly not studied in great depth.

In the past decade, many critical incidents in anaesthesia have been compared to the aviation disasters, leading to human factors affecting the performance of anaesthetist to be looked into at a greater depth. Understanding the nature of interaction between these various factors can be complex. However it is pertinent that every anaesthetist should possess a basic idea of human factors, which can affect his or her performance in a crisis situation. Knowledge on this subject can be used in orga-

nizing training programs, creating simulation sessions, debriefing critical incidents and most importantly looking into one's own practice to refine the non technical skills to make the anaesthetic practice much safer.

Retrospective analysis of critical incidents and disasters in anaesthesia often brings human factors to be flagged up as important contributors. Therefore, gaining an insight into human factors in itself can mitigate the risks associated with them in times of anaesthetic crisis. Research in this field has shown that important contributions can be made to patient safety[1].

Importance

Mishaps, errors, critical incidents, near misses all speak the same language geared towards promoting patient safety. It is now well recognized that human factors play an important role in preventable anaesthetic mishaps. A review of critical incidents by Cooper *et al*[2] revealed that human factors were contributory in 82% of the 359 incidents reported. These incidents ranged from simple equipment malfunction in some cases, to death in others, indicating seriousness and importance of the problems. These errors due to human factors are not isolated events picked up by researchers and studies. In fact it has been reported that 44000 to 98000 deaths occur annually in the United States secondary to medical errors[3].

Human errors have been blamed in over 60% of nuclear power plant accidents and 70% of all commercial aviation accidents. It has been shown that human error was an important contributory factor in 83% of anaesthetic incidents in analysis of 2000 incident reports from Australia[4].

Lessons from aviation

The necessity of safety system in any organization is of paramount importance. This safety system is most needed as a provider to a medium, wherein systematic approach to safety is sought. The analysis and use of human factors can be embedded into this system[5]. Anaesthetists often have a unique way of practice, rather a safety system unique to their practice. This safety system is refined, acquired or adopted through the lessons learnt in their working lives. In aviation a similar system exists, this is known as the Safety Management System[5].

It is under the tenets of this safety system, often referred to as clinical governance in the health care setting, the understanding of human factors gains a strong hold in enhancing patient safety. In the 1970's, rising concerns over the safety of anaesthesia gas machines triggered interest in the application of human factors. In the late 1990's medical error emerged as a serious issue in the delivery of healthcare, spawning new interest in human factors as a means of reducing error.

HUMAN FACTORS AND HUMAN ERRORS

In simple terms, "human factors include all the factors that can influence people and their behaviour"[6]. The Institute of ergonomics and human factors (United Kingdom) defines human factors as a "scientific discipline dealing with the interactions among humans and other factors in the system and deals with the theory, principles, data and methods to design and optimise human well being and overall system performance"[6]. It can also be defined in terms of performance of a person working within a complex mechanical system. Performance is dependent on the individual's capabilities, limitations and attitudes. Performance is also directly related to the quality of instructions and training provided.

Human error is defined as performance that deviates from the ideal[7]. This may take the form of cognitive or procedural error. Cognitive errors are usually thought-process errors in decision-making, and may be attributed to the individual or to the anaesthetic team. They usually cause morbidity or mortality. Procedural errors occur when the wrong drugs are administered[8] or if mistakes are made with nerve blocks or other similar procedures.

COGNITIVE ERRORS

The most important human error is the error of cognition. Studies have shown cognitive errors as important contributors in medical errors. Groopman[9] reported that most medical errors are mistakes in thinking and that technical error only constituted a small proportion. This aspect of psychology involved with decision-making has been looked into with interest as an important contributor of human factor in errors. Despite the ample evidence of cognitive bias in decision-making leading to errors, the need to focus on this area in greater depth has been long over due[10]. The impact of cognitive errors in medicine needs to be acknowledged and it is time, that anaesthetists and every other healthcare personnel pay heed to lessons on cognitive errors and enter a new era of patient safety.

Whilst a detailed discussion on cognition is beyond the scope of this article, it is important to understand some basic fundamental principles of cognition. Cognition is generally defined as a process involving conscious intellectual activity[11]. This intellectual activity consists of many different aspects such as attention, memory, logic and reasoning.

Croskerry[10] defined multiple aspects of the cognitive thinking process leading to diagnostic errors and called them cognitive dispositions to respond (CDR's). These errors occur due to failures in perception, failed heuristics and biases. Some of the CDR's mentioned by Croskerry[10,12] and Stiegler *et al*[13] have been listed below.

Anchoring

Also known as fixation, is focusing on some of the features of patient's initial presentation and not responding to other aspects of patient care in the light of other new information being presented.

Much discussed in literature is the case of Elaine Bromiley, where in the focus was to intubate rather than rec-

ognizing a "cannot intubate, cannot ventilate situation" (CICV) and proceeding for emergency cricothyroidotomy. More common examples include focus on alarms of the infusion pump and ignoring the surgical bleed and hypotension[13].

These errors of fixation can be classified into three main categories[14]: (1) This and only this: *e.g.*, in a case of airway obstruction, having a persistent belief of bronchospasm and not thinking of kinked EndoTracheal tube; (2) Everything but this: *e.g.,* not looking for wrong drug administration when the drug does not solve the problem. In a hypertensive patient not responding to antihypertensive infusion should arouse the suspicion of wrong drug administration; and (3) Everything is OK: *e.g.*, A clinician assumes that a low pulse oximeter value is due to equipment malfunction or peripheral vasoconstriction when, in fact, there is severe hypoxemia.

Ascertainment

The thought process is governed by prior expectation in this bias, *e.g.*, expectations of intubation to be easy when the assessment of airway point towards a difficult intubation, *e.g.*, apnoea after administration of opioids is a prior expectation, but when this occurs due to wrong drug administration of muscle relaxant, it becomes an error due to ascertainment bias.

Aggregate

Aggregate fallacy is the belief that clinical guidelines do not apply to the individual's patients. This often leads to errors of commission, *e.g.*, choosing to perform a central neuraxial blockade in a patient with coagulation disorder, clearly against the guidelines and standards, *e.g.*, administering non steroidal anti inflammatory drug in a severe asthmatic patient.

Availability

This bias can be defined as a tendency to judge things based on what comes to mind readily. This is also influenced by previous bad experience, *e.g.*, diagnosing a simple case of bronchospasm as anaphylaxis because of a previous bad experience[13], *e.g.,* treating ST depression, purely as an effect of bleeding and hypotension and not worrying about myocardial infarction.

Commission bias

In simple words, the tendency to act rather than be inactive in response to information. It is more likely seen in physicians who believe that harm to the patient can only be prevented by active intervention. Unnecessary interventions and investigations fall under this category, *e.g.*, trying to fix a central vein catheter in a simple case of bronchospasm and producing pneumothorax.

Confirmation bias

This is the tendency to look for confirming evidence to support a diagnosis rather than disconfirming evidence. It's also known as "Cherry-picking" or trying to force data to fit a desired or suspected diagnosis, *e.g.*, repeated check at the blood pressures, changing the blood pressure cuff in order to get a better blood pressure reading and failing to acknowledge the low reading[13] or changing the pulse oximeter probe when there is low reading due to actual hypoxemia.

Diagnosis momentum

Typical example is that of a differential diagnosis when carried over on multiple records by multiple health care workers tends to become a more definitive diagnosis. This bias often ends in excluding all other possibilities.

Omission bias

Contrary to the commission bias, this is exactly the opposite. Here the physician has a tendency towards inaction, *e.g.*, delays seen in use of cardioversion in fast arrhythmias when the clinical situation demands it.

Overconfidence bias

The tendency to believe that one knows much more than what he or she actually does. Both anchoring and availability augment this bias. Fuelled by commission bias, this may lead to catastrophic results, *e.g.*, often linked to unconscious incompetence, examples of this bias include a junior anaesthetist with little or no skill of fibre-optic intubation attempting an "awake fibre-optic" technique on a patient with difficult airway.

Premature closure

The tendency to stop the decision making process prematurely and accept a diagnosis before it has fully been verified is known as premature closure, *e.g.*, assessing and diagnosing the cause of low oxygen saturations (as displayed on the monitor) to be secondary to the low perfusion of the cold fingers on which the pulse oximetry probe has been placed, rather than looking for other reasons.

Unpacking principle

This is the failure to elicit all information in making a diagnosis, *e.g.*, failure to elicit information regarding ischaemic heart disease or angina in the pre-anaesthetic assessment.

Linked to these errors of cognition are human failures causing errors in health care. Human failures can be broadly classified into latent and active errors. Latent errors include the equipment, management, administration and the processes involved. Active errors include the errors occurring at the site of action[15]. Active errors can further be classified as shown in the Figure 1.

Skill based errors commonly occur when analytical thinking is not employed. These occur with normal routine tasks. Knowledge based errors occur when an expert judgement is used contrary to the prevailing standards[15]. Knowledge based errors occur when there is deficiency of knowledge. This needs to be differentiated from violations, which are deliberate deviations from the prevailing

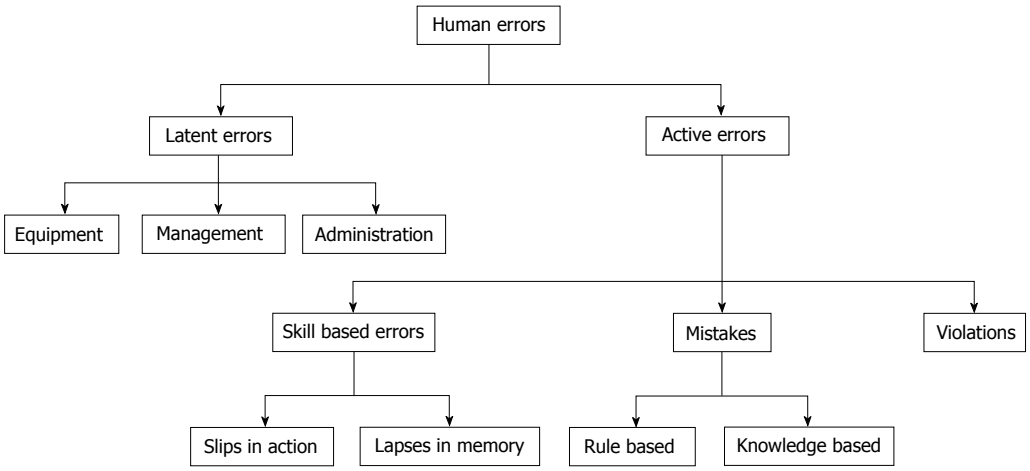

Figure 1 Human errors based on cognitive mechanisms[15].

Table 1 Human factors in pediatric anaesthesia incidents by Marcus[15] (modified)

Human factors	Cognitive mechanism
Error of judgement	Rule or knowledge
Failure to check	Violation
Technical failures ok skill	Skill
Inexperience	Knowledge
Inattention/distraction	Skill
Communication	Latent
Poor preoperative assessment	Rule or knowledge
Lack of care	Skill
Drug dosage slip	Skill
Teaching	Skill
Pressure to do the case	Latent

standards.

Rule based errors occur when the standard rules in practice are not used or inappropriately used[16].

The list of human factors influencing anaesthetic practice is endless. Some of the important human factors influencing anaesthetic practice have been well elucidated by Marcus[15]. In his study of human factors, in which 668 incidents were reported, a total of 284 anaesthetic human factors were identified. These human factors accounted for 42.5% of the total incidents. Needless to say, the involvement of human factors in critical incidents ranked high. These factors are presented in the Table 1.

A combination of non-routine events (NRE's) and human factors provides a medium prone for medical errors to thrive. These when unchecked by the safety measures incorporated by the hospital safety net or even worse when unchecked by the anaesthetists individual safety system often lead on to anaesthetic crisis with catastrophic results.

ANAESTHESIA CRISIS

Merriam Webster defines crisis as "a situation that has reached a critical phase", "an unstable or crucial time or state of affairs in which a decisive change is impending; especially with the distinct possibility of a highly undesirable outcome"[11].

In simple words it is a disaster waiting to happen. The difference between an anaesthetic emergency and a crisis is often difficult to elucidate. Not all emergencies are crisis bound by human factors. The following sections look into the human factors, which contribute in some way to anaesthetic crisis and its management.

The clinical vignettes below illustrate some of the many anaesthesia crises in which human factors have had an important role to play.

Clinical vignettes

Epidural/spinal blunders: (1) Theatre nurse Myra had received an epidural for labour analgesia. Post delivery, the epidural anaesthetic was mistakenly connected into her arm intravenous cannula. Myra died[17]; (2) Grace Wang's spinal canal was mistakenly injected with chlorhexidine instead of the local anaesthetic solution. Grace Wang is now virtually quadriplegic[18,19]; and (3) Wayne Jowett aged 18 was recovering from leukaemia. Vincristine, which was to be given intravenously, was administered intrathecally. Wayne Jowett died a month later[20].

Air embolism: Baby Aaron was being operated for pyloric stenosis. Towards the end of the operation, the anaesthetist was asked to inject air into the nasogastric tube to distend the stomach. The air was injected mistakenly into the veins. Baby Aaron died[21].

Airway disasters: (1) A 9-year-old boy was posted for a minor operation. The cap of the intravenous fluid administration set blocked the angle piece of the anaesthetic tubing. Treatment for presumed bronchospasm was unsuccessful. The 9-year-old died from hypoxemia[22]; and (2) Elaine Bromiley was due to have surgery on her nose. After induction of anaesthesia, a CICV situation was encountered. In the prolonged period of hypoxia, which ensued, repeated attempts at intubation were unsuccessful. Elaine died of severe hypoxic brain injury a few days

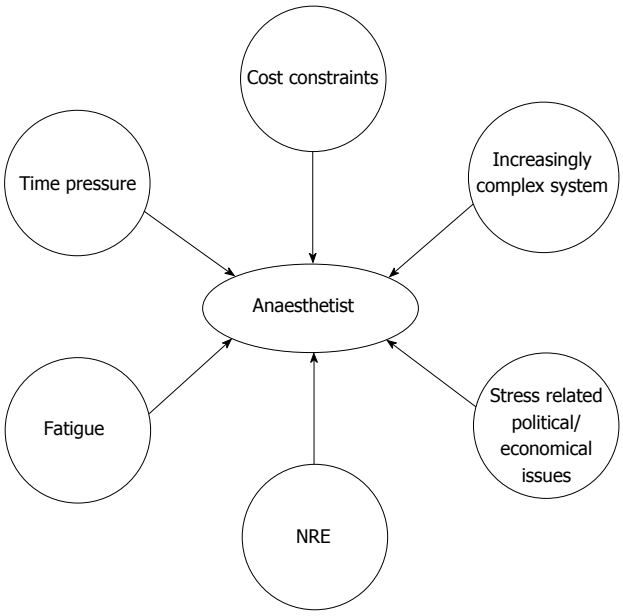

Figure 2 Factors affecting the performance of anaesthetist. NRE: Non routine events.

later[23].

Wrong side errors: A medical student warned the surgeon of the concerns of wrong kidney being removed. The surgeon dismissed the concerns of the medical student and proceeded with the operation. Patient was left with no kidney function and died a few weeks later[24].

The above clinical vignettes are just a few of the many medical errors, which have occurred with catastrophic consequences. An impossible error as it may seem, these impossibilities become distinct realities when the levels of defence are weak, latent conditions supportive of errors are rampant and human factors contributory.

Reflection of one's own practice of anaesthesia would identify multiple instances of similar "Swiss cheese models" often ending up in near misses or critical incidents. The multiple layers of defence as described by Reason[25,26] in his Swiss cheese models consisted of engineered defence systems, procedures and administrative controls and finally the individuals and their skills. For errors to occur, they need to originate from a chain of failures percolating through all the defence layers. The last layer of defence is the human. And humans sometimes fail. Human factors play a major role in these failures. The following section looks into the various human factors, which contribute to human error and lead to anaesthetic crisis.

THE HUMAN FACTORS ASSOCIATED WITH ANAESTHETIC CRISIS

Time pressure, cost constraints, complex environment, fatigue, stress related to political and economic issues, non-routine events and many other factors can affect anaesthetist's performance (Figure 2).

Frequently, NRE are precursors of anaesthetic disasters. Weinger *et al*[1] defined NRE as an unusual, out of ordinary or atypical event contributing to a dangerous dysfunctional clinical system[1]. Not all NRE's lead to disasters or patient harm. It is however important to note that retrospective analysis of NRE's often represent a disruption to the other wise smooth processes involved in health care[1]. Most often it is the progression of the non-routine events coupled with human factors that lead to serious errors in health care.

Among the important human factors are: (1) Lack of vigilance. Clearly, recognizing NRE's will require the anaesthetist to be vigilant. Vigilance is nothing but situational awareness and depends on a number of factors. These factors include alertness, attention span and diagnostic skills[1]. It has been shown that increased workload is associated with an increased incidence of critical incidents[27]. Cognitive resources are diminished when the anaesthetist is exposed to a heavy workload leading to a decreased attention span and vigilance. This predisposes the anaesthetists to errors[1]. Cooper *et al*[2] presented evidence of this important role of vigilance in preventing anaesthetic mishaps as early as 1978. They reported that the causes of common anaesthetic errors could all have been avoided if appropriate attention was directed to the patient. Some researchers have reported the inattention and distraction as a cause in 5.6% of incidents studied[15]. It is easy to say that the wrong administration of drugs, wrong site surgery, injection of air into the venous system could all have been avoided if the concerned anaesthetist was more vigilant. "Asking staff to be more vigilant is a weak improvement approach to providing safer care"[28]. Performing a task analysis and workload assessment provides valuable clues on the performance of individuals with increased workload[1]. Organizations promoting patient safety and keen to deal with human factors should look into this aspect as well; (2) Stress. Stress is defined as "divergence between the demands and capabilities of a person in a situation, giving rise to impaired memory, reduced concentration and difficulties in "decision making"[29]. Researchers[30-32] have shown that the indecision and delays with decision-making are frequently seen in resuscitation practice courses. These are secondary to stress reaction from the stressful situations faced. It can only be extrapolated that anaesthetic crisis and emergencies can be extremely stressful and can lead to situations wherein delays with decision-making are witnessed. The stress during anaesthetic crises or emergencies should be differentiated from the stress occurring from life's stress events.

Increased awareness is needed in understanding the effects of stress. It is illusory to believe that anyone can be immune to stress. In fact stress is normal and seen in many. This however is transitory and most people cope well. Having an already stressed person (from life's many stressors) in a stressful situation such as an anaesthetic crisis will generally be accepted as a bad idea. A similar situation when occurs in aviation is known as "aviator

at risk"[16]. Stressed anaesthetists are aviators at risk and need help. In many countries, systems are in place to help these "anaesthetists at risk". This can be in the form of local arrangements with colleagues to ease the workload, allocation of mentors, arranging time off or avail stress related sick leave. It is important that a request for help should not be looked upon as a failure to function. All these are geared at one thing, and that is to make the entire system safe and improve the overall quality of care in terms of patient safety. Not all anaesthetists will admit that they are stressed and need help. Some experts[16] opine that vigilance should also be employed by colleagues to identify "anaesthetists at risk"; (3) Error of judgement. Marcus[15] showed that error of judgement was as high as 43% in 668 paediatric anaesthetic incidents reported in his study. The flawed clinical decisions made can be categorized into rule-based and knowledge-based mistakes. It is often difficult to inherit knowledge-based mistakes into the spectrum of human factors. However an argument can still be made for the case. As discussed above error of judgement and decision-making can be flawed under stressful conditions or when the anaesthetist is stressed; (4) Fixation errors. Lessons from Elaine Bromiley case speak in great depth about fixation errors. Fixation errors are errors which occur when the anaesthetist's attention and focus is fixated on one aspect of care. The other aspects of care are often overlooked or ignored; and (5) Physical demands. Physical tiredness in itself contributes to the decision making process and can make the anaesthetist prone for errors. It will be wrong to say that vigilance can and should be maintained at all times, when we fail to address other parts of the equation. Analytical thinking involved in decision-making and vigilance are linked to physical tiredness. Anaesthetists like other humans are prone to physical and mental fatigue especially after a long busy night shift. Effective and safe patient care involves thorough patient assessment, planning and executing strategies complimented with intense monitoring. The ability to perform at various levels of physical and mental fatigue is variable, differing amongst individuals. This process requires high amounts of energy. It is not surprising that the level of vigilance falls when physical stress of fatigue sets in[33]. Continuing to work under fatigue, invariably leads to exhaustion. Decisions can be erroneous, attention to detail can be lacking and vigilance generally poor. Sinha *et al*[33] reported some of the frequently observed problems due to fatigue. These include lapses in attention, inability to stay focussed, reduced motivation, compromised problem solving, confusion, irritability, impaired communication, faulty information processing and diminished reaction. Needless to stay, anaesthetists showing symptoms of fatigue as mentioned above are prone to make errors. These errors can translate to patient harm and in some cases even death.

STRATEGIES TO AVOID HUMAN ERRORS

Mere understanding of the list of human factors discussed in the above paragraphs is not enough to reserve a definite momentum towards patient safety, and may lead only to illusory benefits. To obtain true and real benefit, this needs to be coupled with practice of multiple cognitive de-biasing strategies and in-depth reflection on the important lessons learnt from human errors.

As opined by Croskerry[10] and Yates *et al*[34], "one of the first steps is to overcome the bias of overcoming bias".

Table 2 illustrates the Cognitive de-biasing strategies, which can be used to reduce diagnostic errors[10].

Other strategies (Table 3) include application of knowledge of human factors in practice to prevent errors. These include: (1) Checklists. Some of the common examples in healthcare, which can be drawn as a parallel to that in the aviation industry, include checklists. It is common knowledge that wrong side surgeries have been prevented by the use of these checklists. So is the case with anaesthetic machine checks, checking the emergency intubation trolley, emergency drugs trolley and so on. The list of checklists is non-ending. But is important to realise that the checklists in itself act as a deterrent in preventing some very basic errors, which might be caused, but with catastrophic results. The importance of these checklists should never be underestimated. Evidence to the seriousness it commands can be derived from the 9000 critical incidents reported between 1990 and 2010 from the United States[35]. These incidents resulted in a mortality of 6.6%, permanent injury in 32% and resulted in total malpractice payments of $1.3 billion in payouts. The World Health Organization checklist, which addresses some of the issues leading to these 9000 critical incidents, has largely reduced the mortality and morbidity in major surgeries. These were mainly in the way of avoiding wrong site, wrong patient, and wrong procedure surgery. It is however interesting to note that the implementation and usage of checklists designed to counter some of the human factors leading to critical incidents in itself can largely be influenced by human factors. O'Connor *et al*[35] showed that the sociocultural issues, workload and support from senior personnel often affected the desired performance of these checklist. Munigangaiah *et al*[36] opined that human factors in the form of decision making, lack of communication, leadership and team work were largely responsible for the 152017 incidents reported by the National Reporting and Learning System database in England in 2008. The aim of the checklists is to have a structured communication to avoid these basic errors[36]. Enough evidence has been drawn to support the routine use of checklists prior to surgeries. Learning from aviation, checklists can be used under normal and emergency situations. It is in the emergency situations like an anaesthetic crisis, when things are missed easily, a checklist is most mandated. The AAGBI checklist for the anaesthetic equipment 2012, checklists for sedation, handover checklist, all look into the same basic human factors, which make our practice of anaesthesia prone to effect of human factors. It is extremely important for the junior doctors and the anaesthetists in training

Table 2 Cognitive de-biasing strategies[10]

Plan	Action	Example
Develop insight or awareness	Illustration of the errors caused by biases in the cognitive thinking process with the help of clinical examples leads to a better understanding and awareness	The case of intraoperative low oxygen saturations presumed to be due to cold fingers, when the actual cause was endo-bronchial intubation
Consider alternatives	Forming a habit wherein alternative possibilities are always looked into	Continuing with the above example, establishing a habit of looking for other (true) causes of low oxygen saturation, rather than simply blaming the cold fingers could direct the anaesthetist to look for other causes including a possible endotracheal intubation
Metacognition (strategic knowledge)	Emphasis on a reflective approach to problem solving	Knowing when and how to verify data is a good example of Strategic Knowledge
Decreased reliance on memory	Use of cognitive aids, pneumonics, guidelines and protocols protects against errors of memory and recall	Use of guidelines and protocols in the use of intralipids to treat Local Anaesthetic toxicity
Specific training	Identify specific flaws and biases and providing appropriate training to overcome these flaws	Early recognition of a "cannot intubate, cannot ventilate" scenario to guard against fixation errors
Simulation exercises	This is focussed at the common clinical scenarios prone for errors and emphasis on prevention of these errors secondary to human factors	Use of simulation training for difficult airway management
Cognitive forcing strategies	A coping strategy to avoid biases in particular clinical situations is often reflected in the practice of experienced clinicians	Checking for the availability of blood products as a routine ritual prior to the start of major surgery every single time can be considered as strategy to avoid
Minimize time pressures	Allowing adequate time for decision making rather than rushing through	Allowing time to check on patients airway prior to induction can help avoid surprises in airway management
Accountability	Establish clear accountability and follow up for decisions made	A decision to use frusemide intra operatively is followed up by checking the serum potassium levels
Feedback	Giving a reliable feedback to the decision maker, so that the errors are immediately appreciated and corrected	Junior anaesthetist reminding the senior of the allergy to a certain antibiotic, when the antibiotic is about to be administered

Table 3 Practical strategies to prevent human errors

Practical strategies to prevent human errors
Checklists
Resuscitation training or simulations
Managing Stress
Dealing with Fatigue
Standard operating procedures or protocols or guidelines
Team work with good communication

to understand that irrespective of the growing number of checklists available for use, the most important one is the checklist one can prepare for himself/herself to guard the patient from their own inadequacies and that of others; (2) Resuscitation training. The increasing focus on human factors and anaesthesia has found its way into training as well. Norris *et al*[30] reported the emphasis of human factors in resuscitation training. Multiple problems have been identified in resuscitation practice. These problems identified can be used as a possible guide to the difficulties faced in a real resuscitation scenario. These included team dynamics, influence of stress, debriefing and conflict within teams. Team dynamics and team leadership play an important role in resuscitation. Emphasis has also been given to the importance of debriefing in resuscitation training; (3) Coping with Stress. A number of methods for dealing with stress have been proposed. Meichenbaum[37] proposed the stress inoculation training in which use of conceptualization, coping strategies and application phase have all been proposed as a way of dealing with stress. Multiple other techniques, which have been proposed, include the STOP technique described by Norris *et al*[30] and Flin *et al*[38]. This technique helps with cognitive thinking by allowing the person to assess the situation and not acting immediately as a "knee jerk reaction". "S-stop, do not act immediately, and assess the situation. T-take a breath in and out a couple of times. O-observe. What am I thinking about? What am I focusing on? P-prepare oneself. P-practice what works? What is the best thing to do? Do what works." Other techniques include "Mindfulness" as described by Norris *et al*[30] and Hayes *et al*[39]. Mindfulness involves removal of panicky thoughts and replaces them with ordered thinking; (4) Dealing with fatigue. Organizations should ensure that the anaesthetists are properly rested between shifts. This can be carried out at a departmental level or at an organizational level. The Joint Commission[33] recommends a number of steps to be carried out by organizations to ensure that anaesthetists are adequately rested. These include awareness amongst senior authorities of the organization, evaluation of risks, analysis of inputs from staff and generating a fatigue management plan. This fatigue management plan can incorporate sleep breaks, maximum hours of continuous work, mandatory rest period, *etc*.; (5) Standard operating procedures. These are standard formal procedures in aviation and include a number of steps and procedures, which are carried out as a ritual every time. The use of standard operating

Table 4 The systems engineering initiative for patient safety model components and elements[41] (modified)

Components		Elements
Work system	Person	Skills, knowledge, motivation, physical and psychological characteristics
	Organization	Organizational culture and patient safety culture, work schedules, social relationships
	Technology and tools	Human factors characteristics of technologies and tools
	Tasks	Job demands, job control and participation
	Environment	Layout, noise and lighting
Process	care process	Information flow, purchasing, maintenance and cleaning
Outcomes	Employee and organizational outcomes	Job satisfaction, stress and burnout, employee safety and health, turnover
	Patient outcomes	Patient safety, quality of care

procedures with intent of reducing errors has now also been employed in the operating theatre environment and anaesthesia[5]. Anaesthetic machine checks, resuscitation trolley checks can be compared to some of the standard operating procedures in aviation. The list of comparables between anaesthesia and aviation is exhaustive. It is important to note that these standard operating procedures are not limited to protocols, guidelines, and checklists. Unique practicing styles of anaesthetists, in itself is a standard operating procedure. Individuals through years of training and experience build in these safety mechanisms to guard themselves against the pitfalls posed by human factors, *e.g.*, a particular way of ensuring that a throat pack is removed at the end of surgical procedure: sticky label on the forehead, tying one end of the throat pack to the endotracheal tube, reminder on the swab count board, reminder on the anaesthetic chart, using laryngoscopy for suctioning prior to extubation. These are nothing but standard operating procedures in the simplest sense, designed to be a safety net guarding the patient against the various human factors and errors. Every anaesthetist should look into his own standard operating procedure and adapt it to the environment making it a safer system, wherein percolation of errors through the various defence layers is not easily possible. This importance of a safety system should be realized both at an individual level and at an organizational level; and (6) Teamwork**.** The introduction of the concept of teamwork in human factors and patient safety is not new. Teams represent a form of synergy, in which teams work more effectively, efficiently, reliably and safely. The safety aspects of teamwork are much more than an individual or group of individuals working separately[40].

Hunt *et al*[40] identified the characteristics of high performing teams. These include situational awareness. Team performance is improved when the team members are constantly aware of the environment and update each other in a process known as shared cognition. This shared cognition helps in having a shared mental model wherein decisions are made based on current state of affairs. The other aspects of high performing teams include leadership skills. An effective leader allows flow of information in both directions, thereby improving safety to the patient. Closed loop communication is also important in understanding that the information has been received and will be acted upon. Various other aspects of teamwork have also been looked into namely, assertive communication, adaptive behaviours, workload management, *etc*.

HEALTH CARE MODELS TO PROMOTE PATIENT SAFETY

Lessons on human factors in healthcare can never be complete without acknowledging the added patient safety certain health care models can offer.

It is known that systems addressing human factors emphasize on interactions between people and their environment, and this in turn contributes to patient safety. Carayon *et al*[41,42] described the Systems Engineering Initiative for Patient Safety (SEIPS) model as a human factors systems approach. The key characteristics of the SEIPS model include the relationship between the work system and the interacting elements, identification of important contributing factors, integration of patient outcomes with organization/employee outcomes and feedback loops between all the above-mentioned characteristics. In many ways the SEIPS model is employed in different organizations to promote safety. Root cause analysis of critical incidents in anaesthesia is an application of the SEIPS model in itself.

Analysis of the anaesthetist job description and the interaction between various components using the SEIPS model (Table 4) should be performed both at an individual, departmental and organizational level. This would identify some of the factors influencing human errors, and remedial actions can be taken.

The use of the above SEIPS model can be many. It can be used for system design, proactive hazard analysis, and accident investigation and certainly for patient safety research. Utilization of the SEIPS model brings about balance to the work system and steadies the various interactions, making the system less prone for errors secondary to human factors. It is also important to note that individuals can also use the SEIPS model, in looking at their own adaptability to different components of the SEIPS model. This will enhance the performance in a direction towards better patient safety.

STUDY OF PERFORMANCE SHAPING FACTORS

Irrespective of the health care model used, all models aim

at identifying factors contributing to errors. Performance shaping factors are attributes that affect human performance[43]. Examples of performance shaping factors include factors affecting an individual, teams, technology, work environment and the work process involved. Identification of these factors can be used for risk mitigation, simulation training and future research.

THE CULTURE OF SAFETY

Central to the ways of avoiding human errors and utilising models for safety is to promote a positive safety culture[28]. This safety culture can only be established when there is strong commitment from the senior management. Multiple aspects of safety culture need to be adopted by organizations wanting to promote patient safety. These include: (1) Open culture: Patient safety incidents are openly discussed with colleagues and senior managers; (2) Just culture: Staff and carers are treated fairly after a patient safety incident; (3) Reporting culture: A robust incident reporting system, wherein staff are encouraged and not blamed for reporting; (4) Learning culture: The organization is committed to learn safety lessons; and (5) Informed culture: These safety lessons are used to identify and mitigate future incidents.

CONCLUSION

Human errors continue to be an important cause of industrial accidents, aviation disasters and anaesthesia related deaths. Study of human factors should be encouraged to identify various interactions taking place in the health care systems, which make the practice of anaesthesia prone to the effects of human factors, causing human errors translating to anaesthesia mishaps and incidents. This ultimately affects the overall standard of care given to the patients. The care in terms of technical and non-technical skills, which are influenced by human factors, should be delivered in a manner to promote and maintain patient safety.

When we accept and acknowledge that human factors do play an important role in anaesthesia crisis, it is only imperative that strategies to avoid, cope and deal with these human factors are practiced.

Much more work both in terms of research, training and familiarity is needed to understand human factors at a greater depth to further strengthen the already existing strategies to avoid human errors in the practice of anaesthesia.

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REVIEW

Mechanisms of hepatic ischemia/reperfusion injury and clinical anesthesia-related protections

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Abstract

This review focuses on the mechanisms involved in hepatic ischemia-reperfusion (I/R) injury and effective therapeutic treatments associated with clinical anesthesia. Although hepatocytes are the main target cells in the whole process of I/R injury, Kupffer cells, as an initiator of harmful cascades, may play a vital role by releasing some proinflammatory mediators and reactive oxygen species in the early phase of I/R injury. The subsequent activation and recruitment of neutrophils are also involved in inflammatory response and immune activation. According to the above mechanisms, a number of strategies have been put forward in some experimental and clinical studies. Most of these therapeutic treatments originated from the generation of oxygen radicals and cytokines, the infiltration of neutrophils, the impairment of microcirculation and so on. Furthermore, increasing evidence has suggested that short periods of ischemic preconditioning have protective effects against liver I/R injury. Depending on these investigations, pharmacological preconditioning and clinical anesthesia-related effective methods have been proposed. A better understanding of the present progress on experimental statistics will bring about novel therapeutic treatments for the improvement of liver surgeries and transplantation.

Key words: Hepatic ischemia reperfusion injury; Clinical anesthesia; Protections

Core tip: Hepatic ischemia/reperfusion injury has directly affected the clinical outcomes after hepatic surgery. This review shows the essential concepts on the mechanisms of hepatic ischemia/reperfusion injury and conventional applications of protective strategies. In addition, effective therapeutic treatments associated with clinical anesthesia will be discussed. The latest research and the ongoing clinical experiments in this field are delivered to the reader.

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INTRODUCTION

Liver ischemia/reperfusion (I/R) injury[1] is a major cause of morbidity and mortality in the clinical perioperative settings, including liver resection and transplantation, vascular disease and hemorrhagic shock. Regardless of the underlying health problems, blocking hepatic blood supply is sometimes indispensable during surgeries or is essential to the liver transplantation, and causes further multi-organ dysfunction. During these procedures, ischemia is partly restored by the reperfusion[2] of blood flow to the organ, which initiates cascades of harmful responses: ion accumulation, generation of reactive oxygen species (ROS), microcirculation dysfunction and so on.

Ischemia is caused by temporary hepatic vascular inflow occlusion or inflow and outflow occlusion during liver surgeries or the shortage of the blood supply. Ischemic liver injury is caused by a deficiency of oxygen, which occurs due to hepatic vascular occlusion during liver resection or cold preservation before liver transplantation. The liver tolerates prolonged ischemia poorly, and hepatic I/R injury can lead to multiple system organ failure and systemic inflammatory response syndrome. Although reperfusion relieves ischemia, it concurrently initiates a cascade of harmful events and aggravates the hypoxic or ischemic insult.

The outcomes of hepatic I/R injury are positively correlated with the degree of underlying hepatic diseases, including liver dysfunction, non-alcoholic fatty liver disease and hepatic cirrhosis. These factors will lead to an increase in high-risk procedures. The pathological process can roughly be divided into surgical and pharmacological interventions. Surgical treatments have mainly concentrated on ischemic preconditioning (local and remote preconditioning). Pharmaceutical approaches[3] have primarily addressed the use of antioxidants, vasodilators and various anesthetics. In this review, the mechanisms and conventional applications of protective strategies will be discussed and we will clarify the potential hazards and benefits of anesthetic-related therapeutic treatments and the vital role of their fundamental utilization in the setting of hepatic I/R injury.

CLINICALLY RELEVANT RISKS

Hepatic I/R injury widely occurs in many clinical settings, particularly in patients undergoing liver transplantation (cold ischemia), diverse surgeries (warm ischemia) and hypovolemic shock[4]. The tolerance of the liver to ischemia has directly affected the treatment outcome of liver resection and transplantation, especially the chronic end-stage liver disease cases. It is clear that the chronically cirrhotic liver is easily susceptible to a shortage of oxygen supply[5].

Meanwhile, because of the obvious deficiency of livers for transplantation, more and more steatotic donor livers are considered for use in liver transplantation, thus the function of graft organ is further impaired and the patient's vulnerability to infections and multiple organ dysfunction syndrome is intensified as an outcome of hepatic I/R injury[6]. As an important clinical risk factor for the long-term recovery of transplanted livers, liver lesion caused by I/R can also lead to acute liver failure or initial liver dysfunction or decreased success index of liver transplantation.

INVOLVED MECHANISMS

The cellular metabolic disturbances by ischemia, oxidative stress, inflammatory response and homeostasis failure of the immune system are the most significant pathogenic mechanisms of hepatic I/R injury. They not only induce hepatic lesion in the early ischemia phase, but also cause the release of many kinds of cytokines and chemokines exacerbating hepatic injury in the reperfusion phase.

Pathophysiology of I/R injury

The liver lesion succeeding the initiation of I/R is an outcome of varying intricate mechanisms[7]. In the period of ischemia, the metabolic disturbances (containing glycogen consumption, shortage of oxygen supply and deficiency of ATP) are a key factor of cellular homeostasis failure, which gives rise to the intracellular edema of Kupffer cells and endothelial cells. In the early stage of reperfusion, Kupffer cell and endothelial cell swelling, decreased generation of endogenous nitric oxide (NO)[8] and increased production of endothelin lead to narrowing and malfunctioning of sinusoidal lumen and then result in vasoconstriction and microcirculation disturbance. The microcirculation failure lengthens the ischemic state and worsens the hepatic blood flow obstacle, further aggravating liver I/R injury.

Oxidative stress

Oxidative stress arises from a redox imbalance: increased generation of oxidants or decreased production of antioxidants[9]. The generation of oxidants rise superior to that of antioxidants in hepatic I/R injury. A growing body of evidence indicates that the overproduction of ROS[10] is one of the most important initial factors of I/R injury. The production of ROS is mainly derived from the mitochondrion.

When ROS concentration sharply increases, cellular homeostasis failure or cell death[11] happens. Excessive ROS can result in oxidative injury of biosomes, molecules containing proteins and DNA. The inhibitors of ROS, including superoxide dismutase, tempol and diphenylene iodonium, can suppress mitochondrial oxidative stress during the period of hepatic ischemia/reperfusion and also attenuate hepatic injury.

As a form of successful *in vitro* experimental model, hypoxia-reoxygenation effectively mimics the oxidative stress state of ischemia and succeeding reperfusion[12], and it can eventually provoke the processes of cellular necrosis and apoptosis. Cellular hypoxia stimulates transcriptional regulators, including hypoxia-inducible factor (HIF)-1 and nuclear factor-kappa B (NF-κB). After hypoxia, the internal environment of cells changes, including mitochondrial function, enzyme activities and redox systems[13].

Inflammatory response

Free radicals produced during the phase I of I/R injury can potentially activate the inflammatory response that leads to the phase Ⅱ cascades. Hepatic I/R injury causes harmful effects on liver functions and histology as well as increases inflammatory states in the liver. Hepatic inflammation immediately happens after the initiation of reperfusion. As the main reasons of inflammatory response, activated Kupffer cells and recruited neutrophils have

been clarified in hepatic I/R injury. Although Kupffer cells and neutrophils have long been clarified as the chief culprits in I/R injury, the oxidants produced directly lead to further liver tissue destruction.

Kupffer cells, a type of macrophage, reside in liver sinusoidal space and are activated in the phase of reperfusion. After being activated, they generate many cytokines and chemokines, which directly induce cell necrosis and membrane structure changes. Niwano *et al*[14] and Moriga *et al*[15] reported that the blocking of Kupffer cells leads to the survival of sinusoidal endothelial cells and alleviation of liver damage.

The recruitment of neutrophils involves many chemoattractants and adhesion molecules. Activated neutrophils have been associated with the microvascular disorder and hepatocyte lesion in liver I/R injury[16-18]. Lentsch *et al*[1] and Martinez-Mier *et al*[19] reported that hepatic damage can be attenuated by exhausting the circulating neutrophils and blocking their adhesion.

Some studies demonstrated significant increases in concentrations of proinflammatory cytokines tumor necrosis factor-α and interleukin-6 (IL-6) after liver I/R injury. Diverse inflammatory related stimuli induce different types of cells to generate tumor necrosis factors (TNF)-α, which directly causes toxicity to mitochondria and induce cell apoptosis and necrosis. Muraoka *et al*[20] reported that the release of IL-6 can be induced by hypoxia, but not reoxygenation.

Immune activation

Tissue inflammation, which is mediated by pattern recognition receptor system, is a type of innate immune response. As endogenous self-antigens, danger-associated molecular patterns (DAMPs) play a vital role in hepatic I/R injury. DAMPs, as functional cellular components, are released from damaged cells to extracellular microenvironment. These circulating ligands, recognized by antigen presenting cells, are the provoker of excessive immune activation. T lymphocytes, especially $CD4^+$ T-cells, play a role in regulation of liver tissue immune response in hepatic I/R injury. It has been proved[21] that the suppression of the immune system, *e.g.*, the use of ciclosporin or tacrolimus, can alleviate liver lesion in the period of I/R. Further research[22] has demonstrated the vital role of $CD4^+$ T-cells in T-cells$^{-/-}$ and $CD4^{-/-}$ mice subjected to I/R injury. Caldwell *et al*[23] has detected that $CD4^+$ T-cells invaded into damaged livers after local accumulation of neutrophils. This invasion happens by releasing IL-17, which might promote hepatocytes and macrophages to generate the neutrophil chemotactic factor (CXCL2).

By releasing chemokines, these T-cells result in the recruitment of neutrophils in the liver during sterile inflammation. In order to recruit more chemotactic mediators on neutrophils, the immune cells activated by endogenous ligands produce a large number of pro-inflammatory mediators. In general, T cells of different stages provide stimulatory signaling *via* interactions with Kupffer cells or dendritic cells to activate the innate immune system in hepatic I/R injury[24].

Potential therapeutics

A better understanding of the above mechanisms will help us to propose therapeutic strategies by inhibiting the initiation of oxidative stress, production of inflammatory mediators and activation of the immune system. The potential treatments eligible for the protective effects are divided into four categories, including the additive to University of Wisconsin solution, gene therapy, pharmacological treatment, and ischemic preconditioning.

Additive agents in preservation solutions

A number of studies[25-27] reported that many components, including FR167653 (p38 inhibitor), Ruthenium red (mitochondrial Ca^{2+} uniporter inhibitor) and Trifluoperazine (calmodulin inhibitor) have already been added into preservation solutions in animal models of liver transplantation. Pretreatment with a NO donor can prevent liver I/R injury by decreasing expression of P-selectin and intercellular adhesion molecule-1 (ICAM-1), thus alleviating neutrophil-related sinusoidal endothelial cell death and tissue lesion[28]. Nevertheless, these compounds have little effect on liver damage and cannot provide relevant protections in clinical settings.

Pharmacological treatment

A great number of experimental studies[29-31] have concentrated on the novel pharmacological treatments, which are aimed at attenuating the negative effects of I/R. Anti-TNF-α antibodies reduce liver damage in a rat hepatic I/R model. Antioxidants α-tocopherol[32], allopurinol[33] and glutathione[34] can improve the long-term survival after hepatic resection and liver transplantation. The protective effect of NO depends on inhibiting the interaction between the endothelium and adhesion molecules. Peralta *et al*[35] reported that adenosine has a protective role by activating the adenosine A2 receptor in liver I/R injury. L-arginine, as a precursor of NO, significantly reduces hepatic damage by increasing NO availability. Neutralizing monoclonal antibodies to ICAM-1 also attenuate the release of cytokines and infiltration of neutrophils in a rat hepatic I/R model.

Gene therapy

With the development of molecular biology, numerous types of gene therapy are used to attenuate hepatic liver I/R injury[3,36,37]. Redox regulation, as we know, is one of the crucial patterns in hepatic I/R injury. The application of a vector carrying related genes (such as recombinant MnSOD)[38] to target cells may prevent tissues from the harmful damage by blocking the production of oxidants.

It is well understood that heme oxygenase-1 (HO-1) is a sensitive indicator of cellular oxidative stress. The induction of HO-1 has a great effect on hepatic cellular protection following I/R injury, not only *via* the antioxidative pathway, but also *via* the immunomodulatory system. The effective over-expression of the *HO-1* gene

provides a protective effect against the cascade of liver lesions. The bcl-2 family[39,40] is another kind of apoptosis-related protein. de Moissac[41] reported that up-regulation of bcl-2 with an adenoviral vector attenuates TNF-α induced myocyte apoptosis by anti-degradation of IκBα and activation of NF-κB. In summary, with the further investigation of gene therapy, more genetic treatments, by activating protective pathways or inhibiting harmful pathways, will extend the effective choices for treating hepatic I/R injury.

Ischemic preconditioning

Ischemic preconditioning, an endogenous protective mechanism, lessens necrosis and apoptosis of cells and improves outcome of hepatic ischemia and liver transplantation[42]. Murry *et al*[43] first reported that short-term ischemic preconditioning could have a protective effect against the myocardial injury following an ischemic insult with reperfusion. Since then, ischemic preconditioning has been clarified in other organs, including the liver[44], brain[45], kidney[46], intestine[47] and so on.

Ischemic preconditioning protect lethal I/R injury through numerous mechanisms, including anti-apoptosis and activation of adenosine A2 receptor[48], protein kinase C[49] and monophosphate-activated protein kinase[50], which increase the tolerance of cells and trigger regenerative processes from progenitor cells to mature cells[51]. Teoh *et al*[51] and Peralta *et al*[52] reported that the ischemic period for protective preconditioning is very short, and this period is dependent on the relative NO concentration by elimination of xanthine and generation of adenosine[53].

A prospective randomized study[54] in humans confirmed that ischemic preconditioning effectively protects the liver against I/R damage by the preservation of ATP content. Serafín *et al*[55] reported that ischemic preconditioning increases the tolerance of steatotic livers to I/R injury in a rat model. In this study of fatty rats, compared to the non-preconditioned group, the ischemic preconditioned group demonstrated improved long-term survival. Because of its practicality and simplicity, ischemic preconditioning is an attractive method in clinical situations by increasing the tolerance of ischemic livers.

Remote ischemic conditioning

Remote ischemic conditioning (RIC), an endogenous nonlethal therapeutic strategy, was first proposed by Przyklenk *et al*[56] in 1993. It can be induced by one or more cycles of noninvasive ischemia and reperfusion. Birnbaum *et al*[57] reported that RIC could be initiated by performing RIC to the skeletal muscle of upper or lower limbs in a rabbit model. Günaydin *et al*[58] first applied RIC to clinical research in 2000. The protection of RIC against acute I/R injury occurs in a wide range of organs and tissues, including the liver, brain, kidney, lung, and intestine.

Lai *et al*[59] primarily clarified that four 10-min cycles of RIC attenuated liver I/R injury by inducing increased ALT and over-expressed HO-1. Since this study, an increasing number of RIC strategies[60-63] concentrated on liver protection have confirmed the effects of RIC, which involves many potential mechanisms including elevated nitrite/nitrate levels, decreased neutrophil adhesion and necrosis, increased mitochondrial oxygenation and so on. Wang *et al*[64] proved that RIC may promote hepatic proliferation in liver transplantation.

While IPC offers many advantages, its shortcoming as a promising therapeutic treatment is that it needs direct blocking of the blood supply to the organ or tissue, which is suitable for some surgeries, but not for other clinical settings. In order to further compare the practicability of IPC and RIPC, our own study is presently investigating their protections in clinical settings. Yu *et al* are evaluating the clinical outcomes of IPC and RIPC in patients with liver surgeries. The results from these studies will guide clinicians to apply for a better option in different clinical settings.

HEPATIC PROTECTION OF ANESTHETICS

Volatile anesthetics in vivo

Many studies have confirmed the protection of volatile anesthetics on the liver, myocardium, and kidney in animal models. Volatile anesthetics (sevoflurane, isoflurane, desflurane) attenuate the inflammatory response and improve the therapeutic outcomes not only in patients subjected to I/R but also in those with ischemic disease undergoing other surgeries.

Buzaleh *et al*[65] reported that various volatile anesthetics have different effects on perfusion of the liver and expression of genes. Hoetzel *et al*[66] and Schmidt *et al*[67] showed that volatile anesthetic isoflurane, a type of daily clinical anesthetic for induction and maintenance of general anesthesia, induces up-regulation of HO-1 expression and increases blood supply in the early reperfusion period in a rat liver I/R model. The augment of hepatic flux is possibly mediated by vasodilator CO. Wang *et al*[68] reported that emulsified isoflurane protected primary Kupffer cells against hypoxia reoxygenation induced injury by diminishing the generation of ROS and TNF-α and inhibiting apoptosis in Kupffer cells. We also found that isoflurane preconditioning with clinical relevant doses strikingly attenuated hepatic I/R injury by inducing the expression and activity of HO-1 in rats[69].

Although many studies have demonstrated that pharmacological agents are quite effective in animal models, most of them are not greatly suitable for patients because of severe side effects and uncertain practicality. The inflammatory regulatory effect of volatile anesthetics and their effect on patients in clinical settings are still to be determined in the future. Further studies are necessary for investigating the long-term prognosis of patients with volatile anesthetics in surgeries.

Better inhalational anesthetics

Anesthetics are usually well used in patients with normal

liver function but must be carefully applied in patients with hepatic dysfunction, because they may cause further hepatic failure and extended depression of cognitive function. Volatile anesthetics can decrease hepatic blood flow and cause hepatic function damage in patients with severe liver disease.

Because of their minimal effect on liver flow and metabolism, many studies[70,71] reported that sevoflurane and isoflurane are deemed to be less toxic to the liver than other volatile anesthetics. Moreover, our group[72] concluded that emulsified isoflurane preconditioning can attenuate lung injury caused by hepatic I/R in rats, thus sevoflurane and isoflurane have become better options in patients with hepatic dysfunction. However, Hitt *et al*[73] reported that metabolism of isoflurane and trifluoroacetyl acid can lead to hepatic lesion and even fulminant hepatic failure[74]. Sevoflurane, which is similar to isoflurane, causes liver dysfunction after anesthesia[75], but its role is uncertain.

Many reasons are responsible for the induction of liver injury during general anesthesia, such as reduced liver blood supply, excessive generation of intracellular Ca^{2+} or noxious metabolites[76]. The different interventional effects on intracellular Ca^{2+} may be one of the vital factors between the different outcomes of isoflurane and sevoflurane in patients with cirrhosis. The hepatotoxicity of isoflurane is possibly mediated by a mechanism which is similar to that of halothane, enflurane, but not sevoflurane. Nishiyama *et al*[77] reported that isoflurane caused an increase of serum liver enzyme levels compared with sevoflurane after anesthesia, though there was no obvious liver lesion. Above all, existing data do not provide additional and convincing evidence to prove the choice of sevoflurane over isoflurane in patients with hepatic dysfunction.

Inhalational or intravenous anesthetics

When carrying out the anesthetic program for patients with severe liver disease, the optimal choice of anesthetics is more important for their long-term survival outcomes. Intravenous anesthetics (such as remifentanil, propofol, ketamine) have been reported to have a protective effect by promoting the expression of inducible nitric oxide synthase and an antioxidant effect by inhibiting the generation of lipid peroxides in the liver microsomes and mitochondria of the rat[78-80]. Propofol, a kind of intravenous anesthetic and sedative agent, is widely used in the operating theatre and intensive care unit[81]. And propofol is a remarkable intravenous anesthetic agent, especially in patients with liver dysfunction, because it maintains a short half-life period even in patients with liver cirrhosis.

However, Yang *et al*[80] reported the effect on postoperative liver function between propofol and isoflurane. They demonstrated that isoflurane provided better postoperative liver protection after large liver resections than propofol. Beck-Schimmer *et al*[82] inferred that sevoflurane preconditioning showed better protection in the liver I/R injury than propofol. Subsequently, our group[83] concluded that sevoflurane and propofol led to similar results of liver function after hepatectomy with inflow occlusion and they had no significant difference in this clinical setting.

Remifentanil, an ultra-short-acting intravenous opioid analgesic agent, can inhibit the inflammatory response and the expression of inducible nitric oxide synthase. Because of its extrahepatic metabolism, it has been widely used in hepatic surgeries and postoperative recovery. Yang *et al*[80] clarified that remifentanil preconditioning can alleviate hepatic I/R injury both *in vivo* and *in vitro*. Beaussier commented that anesthesiologists' expanding role, through their choice of anesthetics, may occur in protection of the liver.

Various inhalational or intravenous anesthetics have different adverse effects. According to the medication history of patients and specific clinical situations, it is important for patients to choose the most appropriate anesthetic agent. Although many of the persuasive experiments have been carried out *in vivo* or *in vitro*, the clinical evidence is far from enough to evaluate the differences between inhalational and intravenous anesthetics, thus most of the conclusions could not be immediately conducted in the clinical situation. Considering these above reasons, further research is needed to clarify the interactions of different anesthetics and particular mechanisms involved in liver damage.

CONCLUSION

The liver I/R injury is a multi-factorial process involving different cell types and various cellular and molecular mechanisms rather than merely a fixed state. In order to attenuate I/R injury and improve the prognosis of patients, it is required to better understand the pathophysiology of liver I/R injury and apply anesthetics or anesthesia-related methods to clinical settings. Many studies focusing on the I/R injury have reported that I/R injury can be reduced by the anesthetics or anesthesia related methods *in vivo* and *in vitro*. Ischemic preconditioning may become a practical protection strategy in clinical hepatic surgeries and liver transplantation. Despite its complexity, we have learned a lot about the importance of clinical anesthesia-related strategies on the protection of liver I/R injury in the past few years. Many kinds of inhalational and intravenous anesthetics have been proved to have a useful effect on I/R injury. Thus, the extensive application of these regimens will successfully raise the hope of improving the outcomes of liver surgeries.

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CASE REPORT

Unusual complications of spinal surgery: A report of life-threatening vascular injury

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Abstract

Kyphoplasty and lumbar spine fusion are rarely associated with significant vascular damage and internal bleeding. However, anaesthesiologists must maintain vigilance in order to detect rare, but potentially life-threatening haemorrhagic complications of these procedures which may present intra-operatively or in the immediate post-operative period. We present two cases of life-threatening haemorrhagic complications of spine surgery, one from T12 kyphoplasty and the other from a redo lumbar laminectomy and fusion. In both cases, prompt recognition of vascular injuries with internal or covert bleeding which presented shortly after surgery allowed timely and life-saving treatment.

Key words: Post-operative complication; Spinal surgery; Kyphoplasty

Core tip: Kyphoplasty and lumbar spine fusion are rarely associated with significant vascular damage and internal bleeding. However, life-threatening complications can occur at any time during the perioperative period. Rapid diagnosis and quick action can save life and this can be achieved by the awareness of the possibility of such complications. The clinical presentation can be deceiving, especially during the perioperative period when multiple factors can mask the real problem (use of narcotic or sedative agents) and the best way to ensure rapid diagnosis is high index of suspicion and the application of imaging technology as in our cases.

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INTRODUCTION

The lumbar and thoracic spine lies in close proximity to many important vascular structures which are vulnerable to surgical injury. Aggressive surgical exploration or even misplacement of a kyphoplasty needle may result in serious vascular injuries with life-threatening bleeding. In this article we describe two cases where such injuries occurred and were discovered in the early post-operative period.

CASE REPORT

Case 1

This patient presented with impending respiratory failure and hypoxia in the post-anaesthesia care unit within less than 60 min after uneventful kyphoplasty. This was a 66-year-old female with a history of severe back pain from osteoporotic compression fracture presented for T12 kyphoplasty. Her past medical history was significant for obesity, asthma, type II diabetes mellitus, and

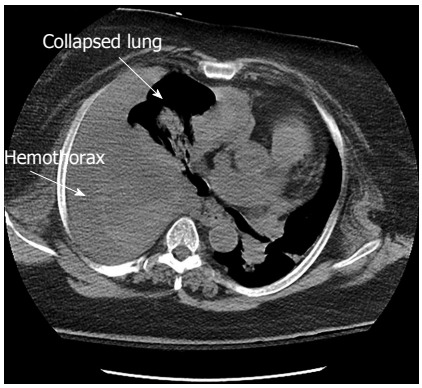

Figure 1 Computed tomography scan of the thorax for the kyphoplasty case, showing right-sided hemothorax.

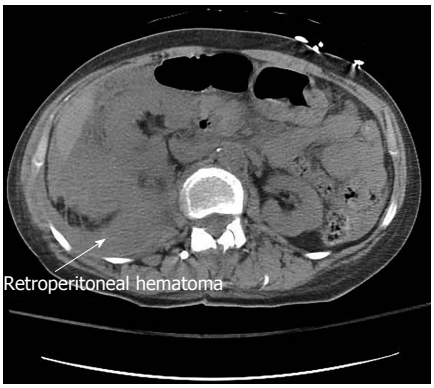

Figure 2 Computed tomography of the abdomen for the lumber spine decompression case, showing retroperitoneal hematoma.

hypertension. She denied any history of easy bruising or bleeding or use of any blood thinning medications. Her physical exam was unremarkable and she had no preoperative neurologic deficits. Kyphoplasty was performed under general anaesthesia as is the typical practice at our institution. During kyphoplasty she was haemodynamically stable and maintained adequate oxygenation throughout the case, after which she was extubated and taken to the post-anaesthesia care unit (PACU). Shortly after arrival to the PACU the patient began to experience respiratory distress with hypoxia for which she was emergently intubated. The differential diagnosis included; pulmonary edema due to fluid overload or left-sided heart failure, pneumothorax due to barotrauma and/or residual muscle paralysis. Chest X-ray showed a new right-sided pleural effusion with collapsed lung. Immediate follow-up computed tomography (CT) scan (Figure 1) revealed a tension haemothorax and due to development of haemodynamic instability, she was taken to the OR for drainage and thoracotomy. After drainage of the haemothorax the thoracotomy failed to reveal any source of active bleeding. The procedure was complicated by three brief episodes of asystolic cardiac arrest which were successfully treated with epinephrine and cardiac massage. Exploratory laparotomy was also performed to evaluate for an abdominal source of bleeding, but none was found. During the surgical procedure she received 4 units of packed red blood cells (PRBCs). The incisions were closed and the patient was taken to the intensive care unit (ICU) for further management. She had no further bleeding in the ICU and was extubated on postoperative day-3. The rest of her postoperative course was uneventful aside from a persistent oxygen requirement and she was discharged home on postoperative day-10 with supplemental home O_2.

Case 2

This patient presented with severe cardiovascular instabilities within less than 24 h after uneventful lumber spine procedure. The patient was a 51-year-old female with a worsening facet arthropathy above the site of her prior L3-L5 spinal fusion presented for re-do L2-3 laminectomy, exploration of fusion, removal of instrumentation, and extension of fusion from L2-L5 for persistent refractory back pain. Her past medical history was significant for rheumatoid arthritis, hypertension, mitral valve prolapse, bipolar disorder, gastroesophageal reflux disease, alcohol abuse and smoking. She previously had several orthopaedic surgeries including cervical fusion, L3-L5 laminectomy and fusion, and right shoulder surgery. Physical exam was unremarkable and neurologic exam revealed no objective deficits at the time of surgery. During the surgery as the surgeon was exposing the transverse process, bleeding was noted which was presumed to be coming from a small branch of the lumbar segmental artery. After cauterization, adequate haemostasis was apparently obtained. Vital signs were stable throughout. She was also noted intraoperatively to have a dural tear which was repaired prior to surgical wound closure. Initial intraoperative labs showed haemoglobin of 13.1 g/dL and repeat laboratory tests 4 h later, near the end of the surgery, showed haemoglobin of 11.0 g/dL. The estimated blood loss was 850 mL and she received 1 L of albumin and 2 L of crystalloids without blood products. After completion of the procedure, surgical haemostasis was obtained and the surgical incision was closed. The patient recovered uneventfully from anaesthesia in the post-anaesthesia care unit and was transferred to the surgical floor. Overnight she became hypotensive and tachycardic without signs of external bleeding through the surgical wound or in the drains. She was transferred to the ICU for further management. Her haemoglobin reached a nadir of 4.8 g/dL despite transfusion of 4 units of PRBCs. She also began to complain of abdominal pain and new onset of right leg weakness and numbness consistent with femoral nerve compression. Non-contrast CT scan revealed a large retroperitoneal hematoma extending from the right perinephric region into the pelvic sidewall (Figure 2). She was taken emergently to the operating room for evacuation of the retroperitoneal hematoma and ligation of a lumbar artery which was found to be the source of the bleeding. Her abdomen was packed and she was returned to the ICU for continued management. The next day she was taken back to the operating room for removal of

packing and definitive closure. Postoperatively she developed a mild consumptive coagulopathy which eventually resolved and she was transferred to the surgical floor on postoperative day-10 and discharged home on postoperative day-13. During her hospital course she received a total of 8 units of PRBCs, 3 pools of platelets, 1 unit of fresh frozen plasma, and 1 pool of cryoprecipitate.

DISCUSSION

The lumbar and thoracic spine lies in close proximity to many important vascular structures which are vulnerable to surgical injury. The descending aorta is situated to the left of the spine in the thoracic region and descends anteromedially to the spine before bifurcating into the common iliac arteries around the 4th lumber vertebra. The segmental arteries which supply the spinal column, paraspinal muscles, dura, nerve roots, and spinal cord arise from the posterior aspect of the descending aorta and travel along the surface of the vertebral bodies. Aggressive surgical exploration or even misplacement of a kyphoplasty needle may result in penetration through the anterior longitudinal ligament into the retroperitoneal space or abdominal cavity where vascular laceration may occur[1].

Despite the close proximity to various arterial and venous structures, vascular injury during spine surgery is rare and constant vigilance on the part of both intra-operative and postoperative care providers is required to prevent a possibly fatal outcome associated with such injuries. Analysis of the Food and Drug Agency and Manufacturer and User Facility Device Experience safety database revealed only a single documented episode of haemothorax after kyphoplasty. In this case, the episode was mild and resolved with chest tube drainage. In that particular case the patient had been on blood thinners previously, but the prothrombin time was within normal limits at the time of surgery[2]. A meta-analysis of complications after kyphoplasty and vertebroplasty revealed that the most common complications were cement leakage (8.1%), pulmonary embolism (0.17%), spinal cord compression (0.16%), and radiculopathy (0.17%)[3]. The 30-d perioperative mortality was found to be 0.13%, which may be overestimated due to the inclusion of patients with metastatic or primary bone malignancy. Thus, haemorrhagic complications of kyphoplasty appear to be exceedingly rare as reported in the literature, particularly in patients without bleeding predisposition or anticoagulant use. We suspect that in this case, the kyphoplasty needle transgressed anterior to the vertebral body at some point during the initial needle placement causing a small injury to an anterior arterial structure resulting in a slow haemorrhage that was not apparent intra-operatively. Review of the intra-operative fluoroscopy images demonstrated proper needle placement at the time of cement injection. Though not evident in our case, intraoperative fluoroscopy may reveal a developing haemothorax, allowing more prompt surgical intervention to repair a lacerated vessel.

Serious complications after lumbar laminectomy and fusion are also rare, though more common than during kyphoplasty and with perioperative mortality rate of around 0.3%. Reported complications include dural tear (5.9%), deep wound infection (1.1%), superficial infection (2.3%), and deep venous thrombosis (2.8%)[4]. The incidence of vascular injury during lumbar disc surgery is estimated to be between 0.039% and 0.14%. The right common iliac artery the vessel most frequently injured overall. Specific vessels are vulnerable to injury at different spinal levels including the aorta and inferior vena cava at L2-L4, and the iliac vessels at L4-L5 and L5-S1. The L4 lumbar artery, internal iliac vessels, median sacral, inferior mesenteric, superior rectal artery, and superior mesenteric artery are also at risk during lumbar spine surgery[5]. In our case the culprit lumbar segmental artery was identified during the initial procedure but bleeding was thought to have been adequately controlled prior to closure. A review of vascular complications during a 12-year period at a single hospital reported that arterio-venous fistula and pseudoaneurysm formation occurred, when a transperitoneal approach rather than posterior approach was used[6]. Vascular injuries often present as hypotension and tachycardia during surgery and have a fairly high mortality rate at 10% (or as high as 38% for injuries involving the aorta). Once suspected, these injuries are generally treated by emergent laparotomy with surgical repair of the lacerated vessel, though endovascular repair may be possible in some cases[5]. Prior spine surgery is likely a risk factor for such injuries as in our second case.

Anaesthesiologists and surgeons should maintain a high index of suspicion for vascular injury when hypotension and/or tachycardia are encountered during or shortly after spine surgery. It is important to note that neither case presented here demonstrated any evidence of haemodynamic instability intra-operatively even on careful retrospective anaesthesia record review. Thus, it is important for post anaesthesia care unit providers as well as the medical professionals who care for patients after spine surgery to be aware of the small but not insignificant risk of hidden vascular damage so that prompt resuscitation and vascular repair are possible. The awareness of the possibility of this kind of complication will allow rapid diagnosis and proper management which can save patient's life and/or prevent serious outcome.

COMMENTS

Case characteristic

The two patients that the authors presented in this case report underwent uneventful surgical spinal procedures but showed serious signs of hemodynamic instabilities in the early postoperative period.

Clinical diagnosis

The presentation in the thoracic kyphoplasty case (1st case) was an impending respiratory failure and hypoxia within the 1st hour of after the surgery. While the lumber spine decompression case (2nd case), the presentation was hours later with severe hypotension, tachycardia, abdominal pain and right leg weakness signs of femoral nerve compression.

Differential diagnosis

In the 1st case the differential diagnosis included; pulmonary edema due to fluid overload or left-sided heart failure, pneumothorax due to barotrauma and/or

residual muscle paralysis and for the 2nd case was acute abdomen for surgical or non-surgical causes.

Laboratory diagnosis

In the two cases there is no laboratory testing that can confirm the diagnosis except for the falling haemoglobin value and in particular the 2nd case from massive retroperitoneal bleed (4.8 g/dL).

Imaging diagnosis

In the thoracic kyphoplasty case an urgent chest X-ray was helpful in revealing the hemothorax which was confirmed by the computed tomography (CT) chest. While in the lumber spine case, the CT abdomen established the accurate diagnosis of retroperitoneal bleeding.

Treatment

Both patients underwent an urgent surgery (thoracotomy in the 1st case and laparotomy in the 2nd case) to control the bleeding, and to establish an exact aetiology of the source of the bleeding.

Related reports

The reported cases of vascular injuries in lumber laminectomy and decompression procedure especially the ones that presented in the postoperative period are extremely uncommon and only appeared in the neurosurgical literatures and not in the anesthesia literatures. While, bleeding complication in post-kyphoplasty is extremely rare and only one published case report was found.

Experiences and lessons

It is important for post anaesthesia care unit providers as well as the medical professionals who care for patients after spine surgery to be aware of the small but not insignificant risk of hidden vascular damage so that prompt resuscitation and vascular repair are possible. The awareness of the possibility of this kind of complication will allow rapid diagnosis and proper management which can save patient's life and/or prevent serious outcome.

Peer review

The article reports two cases of hemorragic complications during spinal surgery, correctly managed with good results.

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CASE REPORT

Anesthetic challenges in ventilating patients with tracheal diverticulum: Case reports and review of literature

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Abstract

The spectrum of disorders involving the tracheobronchial tree is diverse and tracheal diverticulum is an extremely rare entity accounting for 1%-2% of cases. Tracheal diverticulum is mainly asymptomatic and discovered incidentally either on radiological examination or at autopsy. We hereby report two cases of tracheal diverticulum with hoarseness in one case and dysphagia in the second case, where intubation was difficult in both cases. However, laryngeal mask airway was inserted successfully in case one and endotracheal intubation using a smaller size intubation tube in case two.

Key words: Tracheal diverticulum; Dysphagia; Hoarseness; Difficult intubation

Core tip: Tracheal diverticula are extremely rare. They are usually asymptomatic. We report two cases of tracheal diverticulum with dysphagia and hoarseness. Difficult intubation is exceedingly rare, however, we encountered difficulty in intubation in both cases. With recent imaging techniques, the future anesthetic management of a patient with tracheal diverticulum involves performing intubation under bronchoscopic guidance and ventilation strategies to prevent fatal complications.

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INTRODUCTION

Tracheal diverticulum is extremely rare. This uncommon entity is seen incidentally at post-mortem examination and has an incidence of 1%-2%[1]. Common symptoms include chronic cough, recurrent respiratory tract infections, chronic bronchitis, recurrent pneumonia in the elderly and occasionally dysphagia. The differential diagnosis of diverticula includes laryngocele, bronchogenic cysts, esophageal diverticula and apical lung hernia[2]. From an anesthetic point of view, these tracheal diverticula can sometimes cause difficulty in ventilation and intubation with profound or fatal consequences if not detected and corrected expediently. A paratracheal air shadow on chest X-ray indicates the possibility of a paratracheal cyst or tracheocele. We hereby report two cases of tracheal diverticulum who underwent successful surgery under general anesthesia without any complications.

CASE REPORT

Case report 1

A 54-year-old lady was scheduled for excision of a trache-

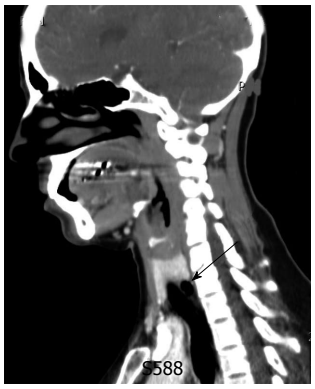

Figure 1 Neck computed tomography scan showing an air-containing cyst adjacent to the tracheal wall.

al diverticulum. She had a mild cough and hoarseness for 2 mo with no history of dyspnea on exertion, hemoptysis, or dysphagia. Physical examination of the neck and chest was unremarkable. Computed tomography (CT) scan of the neck and chest with 3D reconstruction of the scan revealed a 3 cm × 4 cm tracheal diverticulum in the right postero-lateral retrotracheal position (Figure 1). Routine blood investigation, barium swallow, chest X-ray, electrocardiogram and lung function tests were all normal.

After general anesthesia, an endotracheal tube 7.5 mm in size was passed under direct vision, however, it was unable to proceed below the vocal cords, after which endotracheal tubes 7, 6.5 and 6 mm in size were inserted, however, resistance was felt as each tube passed the vocal cords.

A gum elastic bougie was also tried without excessive force. As manual ventilation was easy, a size 4 supreme laryngeal mask airway was applied. The procedure was uneventful. A chest X-ray was performed to rule out mediastinal or subcutaneous emphysema and pneumothorax. Histopathology revealed a cystic mass lined with respiratory epithelium with no cartilage consistent with acquired tracheal diverticulum. At the three week follow-up, the patient's voice had returned to normal. A follow-up flexible bronchoscopic examination revealed normal movement of the right vocal cord. A follow-up CT scan of neck was normal.

Case report 2

A 40-year-old female presented for resection of a tracheal diverticulum. She had a mild cough and cervical dysphagia for one month without associated respiratory or digestive symptoms. Oropharyngeal, neck and chest examinations were normal. Neck and chest CT scans and 3D reconstruction revealed a 3 cm × 3.5 cm tracheal diverticulum in the right postero-lateral position (Figure 2A and B). Routine blood investigation, spirometric values and barium swallow were unremarkable (Figure 2C). Flexible bronchoscopy showed a diverticulum, opening in the proximal trachea. Resection of the diverticulum was planned. After induction of anesthesia, intubation was attempted with size 7.5 mm endotracheal tube, but the tube could not be advanced approximately 1 cm beyond the vocal cords, even, with progressively smaller sized tubes. Resistance was felt on gentle manual ventilation.

Flexible bronchoscopy revealed that the endotracheal tube was impinging on the tracheal diverticulum. An endotracheal tube of size 6 mm was placed successfully in the trachea beyond the diverticulum. The intra-operative course was uneventful. Chest X-ray was performed to rule out perforation or pneumothorax. At two weeks follow-up, her dysphagia had resolved. A follow-up neck CT scan was normal (Figure 2D).

DISCUSSION

Tracheal diverticulum or paratracheal cyst is an uncommonly encountered and reported clinical entity and only a handful of cases have been described in the literature. It was first described by Rokinsky in 1838[3]. Tracheal diverticulum is a rare entity with a prevalence of 1% at autopsy[4]. It is usually diagnosed as an incidental finding on computed tomography or bronchoscopy in otherwise asymptomatic patients. Only three cases of difficult intubation in the presence of tracheal diverticula have been reported worldwide[5]. Tracheal diverticula should be ruled out to avoid airway complications[6]. As in both of our cases, the authors reported that the endotracheal tube was unable to be passed beyond the vocal cords, although diagnosis of tracheal diverticulum was made.

The exact prevalence of tracheal diverticulum is unknown, but in an autopsy series of more than 800 patients, the prevalence was 1%[7]. Usually, patients with tracheal diverticulum present with symptoms of recurrent laryngeal nerve palsy[8] or tracheocele[9].

Tracheal diverticula can cause difficult ventilation[10] or pneumomediastinum secondary to tracheal perforation during intubation[11]. The two recognized types of tracheal diverticula are congenital and acquired. Congenital diverticula present as tracheal out pouching connected to the trachea *via* the isthmus. An acquired tracheal cyst is the result of herniation of tracheal mucosa through the weak tracheal wall due to increased luminal pressure[12]. The right posterolateral wall of the trachea is the most common site of both congenital and acquired tracheal diverticula. The most probable cause is the absence of support offered by the presence of the aortic arch and esophagus as found on the left side[13].

Direct visualization through a bronchoscope is diagnostic[14]. In our cases, the patients had already been diagnosed with tracheal diverticulum, thus excessive force during manual ventilation or after intubation was not performed. A tracheal cyst should be considered in the differential diagnosis of difficult intubation, as it is a rare, but recognized cause of difficult intubation[15,16]. In surgically corrected tracheoesophageal fistula, unexpected ventilatory difficulties may be encountered secondary to a large tracheal diverticulum[10]. A tracheal bronchus, better known as displaced or supernumerary bonchus, can be mistaken for a tracheal diverticulum especially when the

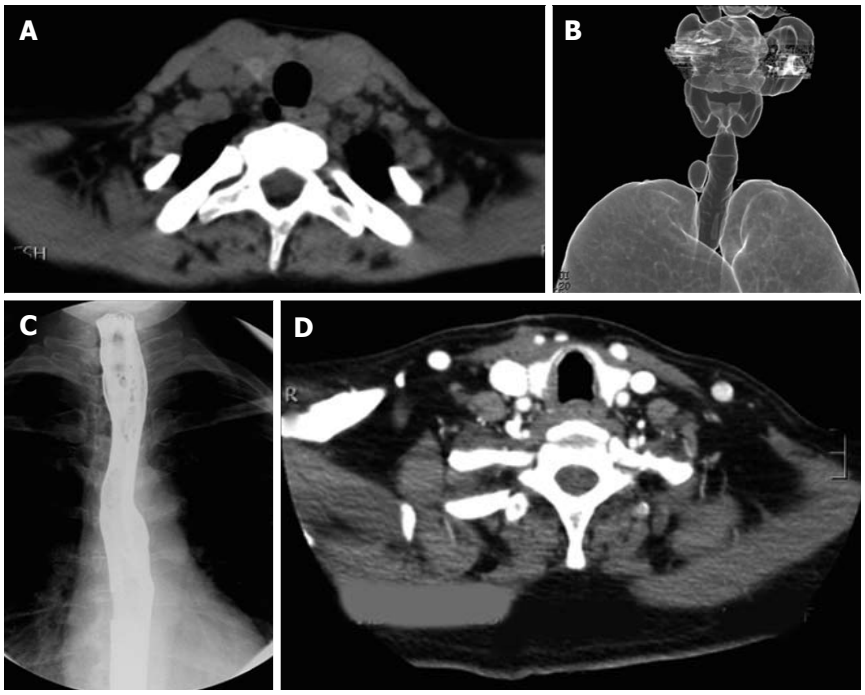

Figure 2 Neck computed tomography scan. A: Neck computed tomography (CT) scan showing an air-containing cyst adjacent to the right tracheal wall; B: Reconstructed image of the airway showing the tracheal diverticulum at the thoracic inlet; C: Normal esophagogram; D: CT scan of the neck after surgery.

supernumerary bronchus ends blindly. The treatment of asymptomatic cases is generally conservative. Treatment with surgical resection is reserved for young patients and includes extirpation and reinforcement of the tracheal wall; and conservative, symptomatic treatment in the elderly[8]. In our two cases, the patients were symptomatic with dysphagia and hoarseness, therefore surgical intervention was carried out.

In conclusion, to prevent lethal complications, even in diagnosed tracheal diverticulum, advanced imaging methods such as multidetector CT and 3-dimensional reconstruction will help in future anesthetic management. Intubation under bronchoscopic guidance and ventilation strategies are indicated to prevent fatal complications.

COMMENTS

Case characteristics

A 54-year-old lady was scheduled for excision of a tracheal diverticulum. She had a mild cough and hoarseness for 2 mo with no history of dyspnea on exertion, hemoptysis, or dysphagia. A 40-year-old female presented for resection of a tracheal diverticulum. She had a mild cough and cervical dysphagia for one month without associated respiratory or digestive symptoms.

Clinical diagnosis

Physical examination of the neck and the chest was unremarkable in case 1. Oropharyngeal, neck and chest examinations were normal in case 2.

Laboratory diagnosis

Routine blood investigation, barium swallow, chest X-ray, electrocardiogram and lung function tests were all normal in case 1. Routine blood investigation, spirometric values and barium swallow were unremarkable in case 2.

Imaging diagnosis

Computed tomography (CT) scan of the neck and chest with 3D reconstruction of the scan revealed a 3 cm × 4 cm tracheal diverticulum in the right posterolateral retrotracheal position in case 1. Neck and chest CT scans and 3D reconstruction revealed a 3 cm × 3.5 cm tracheal diverticulum in the right posterolateral position in case 2.

Pathological diagnosis

Histopathology revealed a cystic mass lined with respiratory epithelium with no cartilage consistent with acquired tracheal diverticulum in case 1.

Peer review

This is an interesting topic. The images are of excellent quality and help to illustrate the authors' cases.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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