

Intrathecal morphine for postoperative analgesia: Current trends

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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.

Key words: Intrathecal morphine; Morphine; Post-operative analgesia; Intrathecal opioids

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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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/ <i>iv</i> 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*: Intravenous.

Pitess, 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-

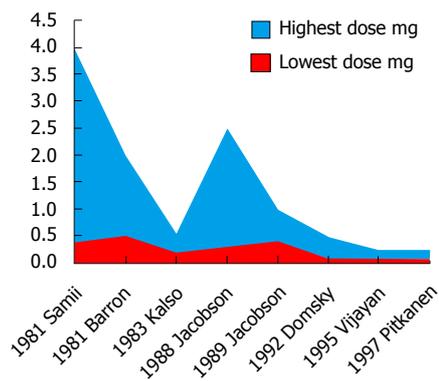


Figure 1 History of intrathecal morphine dose for hip surgery. Modified from ref. [39].

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 of 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 lumbar 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 (Domskey 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 retro-pubic 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 (\pm 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 *in vivo* 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 con-

cern 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 Gwartz *et al*^[71]. One meta-analysis has shown an increased rate of respiratory depression when the dose of IT morphine was \geq 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 (SpO₂), pCO₂, 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, Gwartz *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
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Monitor, respiration (rate and depth), oxygenation (SaO₂%) 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 	<ul style="list-style-type: none"> • O₂ therapy when altered level of consciousness, respiratory depression, or hypoxemia • Routine O₂ 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 • <i>Iv</i> 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* ondansetron 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 recommended 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 accidentally 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 lumbar 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 caesar-

ian 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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