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Intrathecal morphine for postoperative analgesia: Current trends

DeSousa K *et al*. Intrathecal morphine for postoperative analgesia

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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.

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**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-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 described the efficacy of IT morphine for postoperative analgesia in a group of eight patients with genitourinary malignancy in 1979[3]. 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 US 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*[6].

**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.

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[8], 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*[9] Hence the site of administration and the dose given have an important role to play in the extent of spread of desired analgesic effects[9]. 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 minutes 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[10].There are a number of issues that have not been considered so far for pharmacokinetics of IT morphine 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 morphinewithout LA is used as a single dose injection together with general anaesthesia to prevent pain after major surgery[11], though only additive-free formulation of morphine is approved for IT use by the FDA[12]. 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[13].

Through a large range of doses, there is a lack of evidence of linear dose-responsiveness, for any of the beneficial or harmful effects. [13] 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 and Table 2). In a meta-analysis based on studies on spinal anesthesia, with morphine as an adjuvant of an LA without general anesthesia[21], the rate of adverse effects of IT morphine was analysed. And it was shown that the use of IT morphine at doses <0.3mg, 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[14, 15, 17]. In the other study, use of 0.1 mg did not show any respiratory depression[14]. However, 24 hour monitoring should be strictly followed in all obstetric patients receiving IT morphine like all other surgical patients who receive IT morphine[15].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[16]. Another study compared 0.1mg and 0.2 mg IT morphine for postoperative analgesia after Caesarian section and reported that there was longer duration of analgesia with 0.2mg though the incidence of pruritus, nausea and vomiting was significantly higher than with 0.1mg[17]. 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[18].

***Spinal surgery***

IT morphine has shown to be effective in patients undergoing spinal surgeries. Ziegeler *et al*[5] demonstrated the efficacy of 0.4 mg of IT morphine in providing postoperative analgesia in patients undergoing posterior inter-body 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[19]. Studies by Urban *et al*[5, 20] 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*[22] 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[22], demonstrated that the use of rescue opioids was significantly lower for 72 h in a group given 0.2mg 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 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[24]. 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[25]. In one study for postoperative pain relief after THA, 0.1mg 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[26].

***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[27]. De Pietri *et al*[27] 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.

Similar study by Koea *et al*[28] 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*[29] 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[30]. 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[30].

***Urology***

Small doses of 0.05mg 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[31]. 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[32].

***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[13].

In a recent study[48] 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 – 4mg in patients having cardiac surgery[33-35]. Fitzpatrick *et al*[33, 35] demonstrated that use of 1mg 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. [32] Meta-analysis by Liu *et al*[34, 37] on the use of IT morphine in patients having cardiac surgery showed a reduction in time to extubation, pain scores and use of postoperative IV morphine[36, 37]. 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[36-38]. 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[13]. 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[41]. In this study, the mean morphine administered via IT catheter in 48 h was 2.56 mg (± SD 0.88 mg). Only one patient required rescue morphine. There were no serious complications or sequel at 6-month follow-up. The authors concluded that IT morphine for post-op analgesia is efficacious and safe in a post-thoracotomy population. [41]

**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[44]. 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[40], the others suggest that use of IT morphine provides effective and safe analgesia in children for over 12 h[42-47].

***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[49, 50].

***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[51, 52]. 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[51-53]. According to Murphy *et al*[52] andAuburn *et al*[54], 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**

***Local anesthetics***

Local anesthetics (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 [56]: 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)[39, 56] (Table 3).

***Fentanyl***

When IT morphine is combined with fentanyl, pain relief is obtained within 10 minutes. The advantage of concomitant use of IT fentanyl with IT morphine has been questioned. Carvalho *et al*[57], 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[58].

***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[59]. 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[60]. Sites *et al*[61] have also indicated that co-administration of IT clonidine and morphine decreases the 24-h IV morphine consumption and improves the 24-h VAS score when compared with IT morphine alone.

***Ketorolac***

One random controlled trial has indicated that use of IT 2 mg ketorolac along with IT 0.2mg morphine provided better and longer analgesia after TKR with no significant side effects and lower consumption of ketoprofen[62].

**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[63], priapism[64], resistant hypothermia[65] and nystagmus[66] 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[13]. 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[67].

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*[68], measurement of transcutaneous carbon dioxide and oxygen saturation revealed respiratory depression in 17.8% when 0.3mg 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[13].

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 Gehling *et al*[21] and Gwirtz *et al*[69] One meta-analysis has shown an increased rate of respiratory depression when the dose of IT morphine was ≥ 0.3 mg and the risk of respiratory depression was low in patients receiving < 0.3 mg of IT morphine[20]. 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[70].

Whilst the concern of respiratory depression still ranks high, the most practical and effective method for detecting respiratory depression remains unclear[13]. The incidence of respiratory depression raises the questions of the necessity of increased monitoring in the immediate postoperative period[13], 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[72] 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[67, 71].

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[73].

The best treatment of respiratory depression is prevention. Table 5 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[74]. In a study of 5969 patients who received between 0.2 and 0.8 mg morphine IT, Gehling *et al*[21] and Gwirtz *et al*[69] found 25% incidence of nausea and vomiting. Various drugs have been used for prevention and treatment of nausea and vomiting after IT morphine. Baciarello *et al*[74] 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[75], combination of IV dexamethasone 4 mg and IV droperidol 0.625 mg[76], transdermal 1.5 mg scopolamine[77], IV 50 mg cyclizine[78] and oral 30mg mirtazapine[79] have been found to be effective in preventing IT morphine induced PONV. For intractable PONV some researchers have recomended low dose naloxone infusion[80]. Nalmefene 0.020 mg IV after vaginal delivery in patients who received IT morphine decreased the incidence of PONV remarkably[81]. Naltrexone (6 mg) is an effective oral prophylaxis against IT morphine induced PONV but it shortens the duration of analgesia[82].

***Pruritus***

Although pruritus is one of the most common side effects of IT morphine administration, severe pruritus occurs only in 1% of patients[83]. Meta-analysis by Meylan *et al*[13] 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%[83, 84]. 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[83, 85, 86]. 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 substanstia gelationsa of the dorsal horn initiating the itch reflex[83]. 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 5mcg/kg per hour IV can be used in the treatment of pruritus and this does not reverse analgesia[87]. Other drugs such as ondansetron, nalbuphine have also use in the treatment of pruritus[88].

IV butorphanol administration after delivery of the baby is also effective in obstetric patients to relieve itching after IT morphine[88]. There is evidence that κ-opioid receptor agonists have antipruritic activity[88]. 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[89]. 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[87].

Some studies have shown low dose (10-20 mg) IV propofol to be effective for IT morphine-induced pruritus in humans[90-92]. In a recent study, rats were studied to understand the mechanism of action of propofol in preventing IT morphine-induced pruritus[93]. 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[93].

***Urinary retention***

The inability to micturate spontaneously is considered as one of the most distressing non-respiratory complication of IT morphine[94]. Meta-analysis of the relevant studies[13] has shown an increased incidence of urine retention amongst the patients who received IT morphine[13]. 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[95]. 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[96]; 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[97]. 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[98]. 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[98, 99].

***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[99-101]. 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[100]. 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[100]. 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[100, 102].

**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. Anti-emetics 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

**REFERENCES**

1 **Kehlet H**, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001; **87**: 62-72 [PMID: 11460814 DOI: 10.1093/bja/87.1.62]

2 **Brill S**, Gurman GM, Fisher A. A history of neuraxial administration of local analgesics and opioids. *Eur J Anaesthesiol* 2003; **20**: 682-689 [PMID: 12974588 DOI: 10.1097/00003643-200309000-00002]

3 **Wang JK**, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *Anesthesiology* 1979; **50**: 149-151 [PMID: 373503 DOI: 10.1097/00000542-197902000-00013]

4 **McQuay HJ**, Sullivan AF, Smallman K, Dickenson AH. Intrathecal opioids, potency and lipophilicity. *Pain* 1989; **36**: 111-115 [PMID: 2537486 DOI: 10.1016/0304-3959(89)90118-8]

5 **Hindle A**. Intrathecal opioids in the management of acute postoperative pain. C*ontin Educ Anaesth Crit Care Pain* 2008; **8**: 81-85 [DOI: 10.1093/bjaceaccp/mkn016]

6 **Raphael JH**, Duarte RV, Southall JL, Nightingale P, Kitas GD. Randomised, double-blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain. *BMJ Open* 2013; **3**: [PMID: 23903811 DOI: 10.1136/bmjopen-2013-003061]

7 **Dickenson AH**. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. *J Psychopharmacol* 1991; **5**: 342-351 [PMID: 22282839 DOI: 10.1177/026988119100500424]

8 **Neustein SM**, Cottone TM. Prolonged respiratory depression after intrathecal morphine. *J Cardiothorac Vasc Anesth* 2003; **17**: 230-231 [PMID: 12698408 DOI: 10.1053/jcan.2003.53]

9 **Kroin JS**, Ali A, York M, Penn RD. The distribution of medication along the spinal canal after chronic intrathecal administration. *Neurosurgery* 1993; **33**: 226-30; discussion 230 [PMID: 7690122 DOI: 10.1097/00006123-199308000-00007]

10 **Nordberg G**, Hedner T, Mellstrand T, Dahlström B. Pharmacokinetic aspects of intrathecal morphine analgesia. *Anesthesiology* 1984; **60**: 448-454 [PMID: 6546839 DOI: 10.1097/00000542-198405000-00010]

11 **Giovannelli M**, Bedforth N, Aitkenhead A. Survey of intrathecal opioid usage in the UK. *Eur J Anaesthesiol* 2008; **25**: 118-122 [PMID: 17672923 DOI: 10.1017/s0265021507001305]

12 **Rathmell JP**, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. *Anesth Analg* 2005; **101**: S30-S43 [PMID: 16334491 DOI: 10.1213/01.ane.0000177101.99398.22]

13 **Meylan N**, Elia N, Lysakowski C, Tramèr MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* 2009; **102**: 156-167 [PMID: 19151046 DOI: 10.1093/bja/aen368]

14 **Lim Y**, Jha S, Sia AT, Rawal N. Morphine for post-caesarean section analgesia: intrathecal, epidural or intravenous? *Singapore Med J* 2005; **46**: 392-396 [PMID: 16049608]

15 **Abouleish E**, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. *Reg Anesth* 1991; **16**: 137-140 [PMID: 1883770 DOI: 10.1097/00132586-199236030-00020]

16 **Sawi W**, Choy YC. A comparative study of post operative analgesia, side effects profile and patient satisfaction using intrathecal fentanyl with and without morphine 0.1 mg in caesarean section. *Middle East J Anesthesiol* 2013; **22**: 21-26 [PMID: 23833846]

17 **Sharma NR**, Timalsena P, S DC. Intrathecal morphine in combination with bupivacaine: a comparative study following caesarean section. *Nepal Med Coll J* 2013; **15**: 37-39 [PMID: 24592792]

18 **Carvalho FA**, Tenório SB. Comparative study between doses of intrathecal morphine for analgesia after caesarean. *Braz J Anesthesiol* 2013; **63**: 492-499 [PMID: 24565347 DOI: 10.1016/j.bjane.2013.01.001]

19 **Law CL**, Visser EJ. Unconsciousness and severe respiratory depression following intrathecal morphine analgesia for lumbar spinal surgery. *Acute Pain* 2007; **9**: 163-167 [doi: 10.1016/j.acpain.2007.05.001]

20 **Urban MK**, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O. Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine. *Spine (Phila Pa 1976)* 2002; **27**: 535-537 [PMID: 11880840 DOI: 10.1097/00007632-200203010-00015]

21 **Gehling M**, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 2009; **64**: 643-651 [PMID: 19462494]

22 **Gehling MH**, Luesebrink T, Kulka PJ, Tryba M. The effective duration of analgesia after intrathecal morphine in patients without additional opioid analgesia: a randomized double-blind multicentre study on orthopaedic patients. *Eur J Anaesthesiol* 2009; **26**: 683-688 [PMID: 19307970 DOI: 10.1097/eja.0b013e328329b045]

23 **Boezaart AP**, Eksteen JA, Spuy GV, Rossouw P, Knipe M. Intrathecal morphine. Double-blind evaluation of optimal dosage for analgesia after major lumbar spinal surgery. *Spine (Phila Pa 1976)* 1999; **24**: 1131-1137 [PMID: 10361663 DOI: 10.1097/00007632-199906010-00013]

24 **Bowrey S**, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. *Anaesthesia* 2005; **60**: 449-452 [PMID: 15819764 DOI: 10.1111/j.1365-2044.2005.04174.x]

25 **Fischer HB**, Simanski CJ. A procedure-specific systematic review and consensus recommendations for analgesia after total hip replacement. *Anaesthesia* 2005; **60**: 1189-1202 [PMID: 16288617 DOI: 10.1111/j.1365-2044.2005.04382.x]

26 **Kuchálik J**, Granath B, Ljunggren A, Magnuson A, Lundin A, Gupta A. Postoperative pain relief after total hip arthroplasty: a randomized, double-blind comparison between intrathecal morphine and local infiltration analgesia. *Br J Anaesth* 2013; **111**: 793-799 [PMID: 23872462 DOI: 10.1093/bja/aet248]

27 **De Pietri L**, Siniscalchi A, Reggiani A, Masetti M, Begliomini B, Gazzi M, Gerunda GE, Pasetto A. The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia. *Anesth Analg* 2006; **102**: 1157-1163 [PMID: 16551916 DOI: 10.1213/01.ane.0000198567.85040.ce]

28 **Koea JB**, Young Y, Gunn K. Fast track liver resection: the effect of a comprehensive care package and analgesia with single dose intrathecal morphine with gabapentin or continuous epidural analgesia. *HPB Surg* 2009; **2009**: 271986 [PMID: 20029637 DOI: 10.1155/2009/271986]

29 **Sakowska M**, Docherty E, Linscott D, Connor S. A change in practice from epidural to intrathecal morphine analgesia for hepato-pancreato-biliary surgery. *World J Surg* 2009; **33**: 1802-1808 [PMID: 19548026 DOI: 10.1007/s00268-009-0131-2]

30 A prospective cohort study of intrathecal versus epidural analgesia for patients undergoing hepatic resection. *HPB (Oxford)* 2014 [PMID: 24467320 DOI: 10.1111/hpb.12222]

31 **Ozbek H**, Deniz MN, Erakgun A, Erhan E. Comparison of 75 and 150 μg doses of intrathecal morphine for postoperative analgesia after transurethral resection of the prostate under spinal anesthesia. *J Opioid Manag* 2013; **9**: 415-420 [PMID: 24481930 DOI: 10.5055/jom.2013.0184]

32 **Nuri Deniz M**, Erhan E, Ugur G. Intrathecal morphine reduces postoperative tramadol consumption in patients undergoing radical retropubic prostatectomy: a randomized trial. *Eur Rev Med Pharmacol Sci* 2013; **17**: 834-838 [PMID: 23609368]

33 **Trevor WR**, Lee, Jacobsohn E. Spinal anesthesia in cardiac surgery. *Tech Reg Anesth Pain Manag* 2008; **12**: 54-56 [DOI: 10.1053/j.trap.2007.10.008]

34 **Aun C**, Thomas D, St John-Jones L, Colvin MP, Savege TM, Lewis CT. Intrathecal morphine in cardiac surgery. *Eur J Anaesthesiol* 1985; **2**: 419-426 [PMID: 3841315]

35 **Fitzpatrick GJ**, Moriarty DC. Intrathecal morphine in the management of pain following cardiac surgery. A comparison with morphine i.v. *Br J Anaesth* 1988; **60**: 639-644 [PMID: 3377948 DOI: 10.1093/bja/60.6.639]

36 **Richardson L**, Dunning J, Hunter S. Is intrathecal morphine of benefit to patients undergoing cardiac surgery. *Interact Cardiovasc Thorac Surg* 2009; **8**: 117-122 [PMID: 18755789 DOI: 10.1510/icvts.2008.190686]

37 **Liu SS**, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology* 2004; **101**: 153-161 [PMID: 15220785 DOI: 10.1097/00000542-200407000-00024]

38 **Parlow JL**, Steele RG, O'Reilly D. Low dose intrathecal morphine facilitates early extubation after cardiac surgery: results of a retrospective continuous quality improvement audit. *Can J Anaesth* 2005; **52**: 94-99 [PMID: 15625264 DOI: 10.1007/bf03018588]

39 **Slappendel R.** Aspects of intrathecal morphine for postoperative pain relief in major orthopedic surgery. Document type: Dissertation. 2001: Page: 17, Available on website: http: //dspace.library.uu.nl/bitstream/handle/1874/365/full.pdf?sequence=1 (Drukkerij: SSN bv Nijmegen ISBN: 90-803816-3-2 Vormgeving: Eric Weber Illustratie voorzijde: Birgitte Tax.)

40 **Mugabure Bujedo B**. A clinical approach to neuraxial morphine for the treatment of postoperative pain. *Pain Res Treat* 2012; **2012**: 612145 [PMID: 23002426 DOI: 10.1155/2012/612145]

41 **Ward VD**, Mc Crory CR. An assessment of intrathecal catheters in the perioperative period: an analysis of 84 cases. *Ir J Med Sci* 2014; **183**: 293-296 [PMID: 24013869 DOI: 10.1007/s11845-013-1008-9]

42 **Lesniak AB**, Tremblay P, Dalens BJ, Aucoin M, Mercier P. Intrathecal morphine reduces blood loss during idiopathic scoliosis surgery: retrospective study of 256 pediatric cases. *Paediatr Anaesth* 2013; **23**: 265-270 [PMID: 23301926 DOI: 10.1111/pan.12096]

43 **Nowicki PD**, Vanderhave KL, Gibbons K, Haydar B, Seeley M, Kozlow K, Bhoopal K, Gauger VT. Perioperative pain control in pediatric patients undergoing orthopaedic surgery. *J Am Acad Orthop Surg* 2012; **20**: 755-765 [PMID: 23203935 DOI: 10.5435/JAAOS-20-12-755]

44 **Schmitz A**, Salgo B, Weiss M, Dillier CM, Frotzler A, Gerber AC. [Intrathecal opioid medication for perioperative analgesia in severely handicapped children undergoing spinal operations]. *Anaesthesist* 2010; **59**: 614-620 [PMID: 20574762 DOI: 10.1007/s00101-010-1733-7]

45 **Suominen PK**, Ragg PG, McKinley DF, Frawley G, But WW, Eyres RL. Intrathecal morphine provides effective and safe analgesia in children after cardiac surgery. *Acta Anaesthesiol Scand* 2004; **48**: 875-882 [PMID: 15242433 DOI: 10.1111/j.0001-5172.2004.00449.x]

46 **Tobias JD**. A review of intrathecal and epidural analgesia after spinal surgery in children. *Anesth Analg* 2004; **98**: 956-65, table of contents [PMID: 15041580 DOI: 10.1213/01.ane.0000107938.80562.75]

47 **Jones SE**, Beasley JM, Macfarlane DW, Davis JM, Hall-Davies G. Intrathecal morphine for postoperative pain relief in children. *Br J Anaesth* 1984; **56**: 137-140 [PMID: 6419756 DOI: 10.1093/bja/56.2.137]

48 **Joshi GP**, Bonnet F, Kehlet H. Evidence-based postoperative pain management after laparoscopic colorectal surgery. *Colorectal Dis* 2013; **15**: 146-155 [PMID: 23350836 DOI: 10.1111/j.1463-1318.2012.03062.x]

49 **Mardirosoff C**, Dumont L, Boulvain M, Tramèr MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *BJOG* 2002; **109**: 274-281 [PMID: 11950182 DOI: 10.1111/j.1471-0528.2002.01380.x]

50 **Somboonviboon W**, Kyokong O, Charuluxananan S, Narasethakamol A. Incidence and risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. *J Med Assoc Thai* 2008; **91**: 181-187 [PMID: 18389982]

51 **Rathmell JP**, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. *Anesth Analg* 2003; **97**: 1452-1457 [PMID: 14570664 DOI: 10.1213/01.ane.0000083374.44039.9e]

52 **Murphy PM**, Stack D, Kinirons B, Laffey JG. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. *Anesth Analg* 2003; **97**: 1709-1715 [PMID: 14633547 DOI: 10.1213/01.ane.0000089965.75585.0d]

53 **Sakai T**, Use T, Shimamoto H, Fukano T, Sumikawa K. Mini-dose (0.05 mg) intrathecal morphine provides effective analgesia after transurethral resection of the prostate. *Can J Anaesth* 2003; **50**: 1027-1030 [PMID: 14656781 DOI: 10.1007/bf03018367]

54 **Aubrun F**. Management of postoperative analgesia in elderly patients. *Reg Anesth Pain Med* 2005; **30**: 363-379 [PMID: 16032589 DOI: 10.1016/j.rapm.2005.02.006]

55 **Saxena AK**, Arava SK. Current concept in neuarxial administration of opioids and non-opioids: An overview and future perspectives. *Indian J Anaesth* 2004; **48**: 13-24

56 Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012; **116**: 248-273 [PMID: 22227789 DOI: 10.1097/aln.0b013e31823c1030]

57 **Carvalho B**, Drover DR, Ginosar Y, Cohen SE, Riley ET. Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance. *Int J Obstet Anesth* 2012; **21**: 29-34 [PMID: 22100823 DOI: 10.1016/j.ijoa.2011.09.002]

58 **Karaman S**, Günüsen I, Uyar M, Biricik E, Fırat V. The effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anesthesia for cesarean section. *Agri* 2011; **23**: 57-63 [PMID: 21644105]

59 **Lena P**, Balarac N, Arnulf JJ, Teboul J, Bonnet F. Intrathecal morphine and clonidine for coronary artery bypass grafting. *Br J Anaesth* 2003; **90**: 300-303 [PMID: 12594140 DOI: 10.1093/bja/aeg070]

60 **Engelman E**, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth* 2013; **110**: 21-27 [PMID: 23002167 DOI: 10.1093/bja/aes344]

61 **Sites BD**, Beach M, Biggs R, Rohan C, Wiley C, Rassias A, Gregory J, Fanciullo G. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty. *Anesth Analg* 2003; **96**: 1083-108, table of contents [PMID: 12651665 DOI: 10.1213/01.ANE.0000055651.24073.59]

62 **Lauretti GR**, Righeti CC, Mattos AL. Intrathecal ketorolac enhances intrathecal morphine analgesia following total knee arthroplasty. *J Anaesthesiol Clin Pharmacol* 2013; **29**: 503-508 [PMID: 24249988 DOI: 10.4103/0970-9185.119155]

63 **Loomba V**, Gupta M, Kim D. Persistent hiccups with continuous intrathecal morphine infusion. *Clin J Pain* 2012; **28**: 172-174 [PMID: 21677564 DOI: 10.1097/AJP.0b013e31822364a8]

64 **Hishmeh S**, DiMaio FR. Priapism as a complication after total hip arthroplasty: a case report and review of the literature. *Orthopedics* 2008; **31**: 397 [PMID: 19292271 DOI: 10.3928/01477447-20080401-13]

65 **Ryan KF**, Price JW, Warriner CB, Choi PT. Persistent hypothermia after intrathecal morphine: case report and literature review. *Can J Anaesth* 2012; **59**: 384-388 [PMID: 22161244 DOI: 10.1007/s12630-011-9650-z]

66 **Ueyama H**, Nishimura M, Tashiro C. Nystagmus following intrathecal morphine administration. *J Anesth* 1993; **7**: 102-104 [PMID: 15278503 DOI: 10.1007/s0054030070102]

67 **Whang BY**, Jeong SW, Leem JG, Kim YK. Aspiration Pneumonitis Caused by Delayed Respiratory Depression Following Intrathecal Morphine Administration. *Korean J Pain* 2012; **25**: 126-129 [DOI: 10.3344/kjp.2012.25.2.126]

68 **Dalchow S**, Lubeigt O, Peters G, Harvey A, Duggan T, Binning A. Transcutaneous carbon dioxide levels and oxygen saturation following caesarean section performed under spinal anaesthesia with intrathecal opioids. *Int J Obstet Anesth* 2013; **22**: 217-222 [PMID: 23707035 DOI: 10.1016/j.ijoa.2013.04.003]

69 **Gwirtz KH**, Young JV, Byers RS, Alley C, Levin K, Walker SG, Stoelting RK. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. *Anesth Analg* 1999; **88**: 599-604 [PMID: 10072014 DOI: 10.1097/00000539-199903000-00026]

70 **Bailey PL**, Rhondeau S, Schafer PG, Lu JK, Timmins BS, Foster W, Pace NL, Stanley TH. Dose-response pharmacology of intrathecal morphine in human volunteers. *Anesthesiology* 1993; **79**: 49-59; discussion 25A [PMID: 8342828 DOI: 10.1097/00000542-199307000-00010]

71 **Taylor S**, Voytovich AE, Kozol RA. Has the pendulum swung too far in postoperative pain control? *Am J Surg* 2003; **186**: 472-475 [PMID: 14599609 DOI: 10.1016/j.amjsurg.2003.07.021]

72 **Law CJ**, Viser EJ. Unconsciousness and severe respiratory depression following intrathecal morphine analgesia for lumbar spinal. *Acute Pain* 2007; **9**: 163-167

73 **Bailey PL**, Lu JK, Pace NL, Orr JA, White JL, Hamber EA, Slawson MH, Crouch DJ, Rollins DE. Effects of intrathecal morphine on the ventilatory response to hypoxia. *N Engl J Med* 2000; **343**: 1228-1234 [PMID: 11071674 DOI: 10.1056/nejm200010263431705]

74 **Baciarello M**, Cornini A, Zasa M, Pedrona P, Scrofani G, Venuti FS, Fanelli G. Intrathecal atropine to prevent postoperative nausea and vomiting after Cesarean section: a randomized, controlled trial. *Minerva Anestesiol* 2011; **77**: 781-788 [PMID: 21730925]

75 **Peixoto AJ**, Celich MF, Zardo L, Peixoto Filho AJ. Ondansetron or droperidol for prophylaxis of nausea and vomiting after intrathecal morphine. *Eur J Anaesthesiol* 2006; **23**: 670-675 [PMID: 16805932 DOI: 10.1017/s0265021506000482]

76 **Wu JI**, Lo Y, Chia YY, Liu K, Fong WP, Yang LC, Tan PH. Prevention of postoperative nausea and vomiting after intrathecal morphine for Cesarean section: a randomized comparison of dexamethasone, droperidol, and a combination. *Int J Obstet Anesth* 2007; **16**: 122-127 [PMID: 17275282 DOI: 10.1016/j.ijoa.2006.11.004]

77 **Harnett MJ**, O'Rourke N, Walsh M, Carabuena JM, Segal S. Transdermal scopolamine for prevention of intrathecal morphine-induced nausea and vomiting after cesarean delivery. *Anesth Analg* 2007; **105**: 764-769 [PMID: 17717237 DOI: 10.1213/01.ane.0000277494.30502.db]

78 **Nortcliffe SA**, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo. *Br J Anaesth* 2003; **90**: 665-670 [PMID: 12697596 DOI: 10.1093/bja/aeg120]

79 **Chang FL**, Ho ST, Sheen MJ. Efficacy of mirtazapine in preventing intrathecal morphine-induced nausea and vomiting after orthopaedic surgery\*. *Anaesthesia* 2010; **65**: 1206-1211 [PMID: 21182602 DOI: 10.1111/j.1365-2044.2010.06561.x]

80 **Sposito JA**, Habib AS. Low-dose naloxone infusion for the treatment of intractable nausea and vomiting after intrathecal morphine in a parturient. *Int J Obstet Anesth* 2010; **19**: 119-121 [PMID: 19945849 DOI: 10.1016/j.ijoa.2009.06.006]

81 **Ward RC**, Lawrence RL, Hawkins RJ, DiChiara SE, Biegner AR, Vacchiano CA. The use of nalmefene for intrathecal opioid-associated nausea in postpartum patients. *AANA J* 2002; **70**: 57-60 [PMID: 11887546]

82 **Abboud TK**, Lee K, Zhu J, Reyes A, Afrasiabi A, Mantilla M, Steffens Z, Chai M. Prophylactic oral naltrexone with intrathecal morphine for cesarean section: effects on adverse reactions and analgesia. *Anesth Analg* 1990; **71**: 367-370 [PMID: 2205128 DOI: 10.1213/00000539-199010000-00008]

83 **Ruan X**. Drug-related side effects of long-term intrathecal morphine therapy. *Pain Physician* 2007; **10**: 357-366 [PMID: 17387357]

84 **Chaney MA**. Side effects of intrathecal and epidural opioids. *Can J Anaesth* 1995; **42**: 891-903 [PMID: 8706199 DOI: 10.1007/bf03011037]

85 **Cousins MJ**, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984; **61**: 276-310 [PMID: 6206753 DOI: 10.1097/00000542-198409000-00008]

86 **Morgan M**. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63**: 165-188 [PMID: 2669907 DOI: 10.1093/bja/63.2.165]

87 **Raj PR**. Practical Management of Pain. In: Common analgesic side effects and treatment. 3rd ed. Mosby Elsevier, 2000: Appendix D. 1025-1026

88 **Wu Z**, Kong M, Wang N, Finlayson RJ, De Tran QH. Intravenous butorphanol administration reduces intrathecal morphine-induced pruritus after cesarean delivery: a randomized, double-blind, placebo-controlled study. *J Anesth* 2012; **26**: 752-757 [PMID: 22674156 DOI: 10.1007/s00540-012-1421-7]

89 **Sheen MJ**, Ho ST, Lee CH, Tsung YC, Chang FL, Huang ST. Prophylactic mirtazapine reduces intrathecal morphine-induced pruritus. *Br J Anaesth* 2008; **101**: 711-715 [PMID: 18713761 DOI: 10.1093/bja/aen241]

90 **Borgeat A**, Wilder-Smith OH, Saiah M, Rifat K. Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76**: 510-512 [PMID: 1550275 DOI: 10.1097/00000542-199204000-00004]

91 **Naganuma R**, Tsuchida H, Okanuma M, Iwasaki H, Namiki A. [The efficacy of low-dose propofol for intrathecal morphine-induced pruritus]. *Masui* 1998; **47**: 562-565 [PMID: 9621665]

92 **Törn K**, Tuominen M, Tarkkila P, Lindgren L. Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. *Br J Anaesth* 1994; **73**: 411-412 [PMID: 7946871 DOI: 10.1093/bja/73.3.411]

93 **Liu X**, Zhang J, Zhao H, Mei H, Lian Q, Shangguan W. The effect of propofol on intrathecal morphine-induced pruritus and its mechanism. *Anesth Analg* 2014; **118**: 303-309 [PMID: 24445631 DOI: 10.1213/ANE.0000000000000086]

94 **Rawal N**. Epidural and intrathecal opioids. *Acta Anaesthesiol Scand* 1993; **37:** 126–131 [DOI: 10.1111/j.1399-6576.1993.tb03656.x]

95 **Raffaeli W**, Marconi G, Fanelli G, Taddei S, Borghi GB, Casati A. Opioid-related side-effects after intrathecal morphine: a prospective, randomized, double-blind dose-response study. *Eur J Anaesthesiol* 2006; **23**: 605-610 [PMID: 16507190 DOI: 10.1017/s026502150600038x]

96 **Yilmaz A**, Sogut A, Kilinc M, Sogut AG. Successful treatment of intrathecal morphine overdose. *Neurol India* 2003; **51**: 410-411 [PMID: 14652457 DOI: 10.1097/00000542-199501000-00035]

97 **Kakinohana M**, Marsala M, Carter C, Davison JK, Yaksh TL. Neuraxial morphine may trigger transient motor dysfunction after a noninjurious interval of spinal cord ischemia: a clinical and experimental study. *Anesthesiology* 2003; **98**: 862-870 [PMID: 12657847 DOI: 10.1097/00000542-200304000-00012]

98 **Erickson DL**, Blacklock JB, Michaelson M, Sperling KB, Lo JN. Control of spasticity by implantable continuous flow morphine pump. *Neurosurgery* 1985; **16**: 215-217 [PMID: 3838369 DOI: 10.1227/00006123-198502000-00015]

99 **Fuller JG**, McMorland GH, Douglas MJ, Palmer L. Epidural morphine for analgesia after caesarean section: a report of 4880 patients. *Can J Anaesth* 1990; **37**: 636-640 [PMID: 2208533 DOI: http: //dx.doi.org/10.1007/bf03006481]

100 **Crone LA**, Conly JM, Clark KM, Crichlow AC, Wardell GC, Zbitnew A, Rea LM, Cronk SL, Anderson CM, Tan LK. Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. *Anesth Analg* 1988; **67**: 318-323 [PMID: 3354864 DOI: http: //dx.doi.org/10.1213/00000539-198804000-00004]

101 **Davies PW**, Vallejo MC, Shannon KT, Amortegui AJ, Ramanathan S. Oral herpes simplex reactivation after intrathecal morphine: a prospective randomized trial in an obstetric population. *Anesth Analg* 2005; **100**: 1472-146, table of contents [PMID: 15845709 DOI: 10.1213/01.ane.0000153013.34129.a7]

102 **Boyle RK**. A review of anatomical and immunological links between epidural morphine and herpes simplex labialis in obstetric patients. *Anaesth Intensive Care* 1995; **23**: 425-432 [PMID: 7485931]

103 **Horlocker TT**, Burton AW, Connis RT, Hughes SC, Nickinovich DG, Palmer CM, Pollock JE, Rathmell JP, Rosenquist RW, Swisher JL, Wu CL. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. *Anesthesiology* 2009; **110**: 218-230 [PMID: 19194148 DOI: 10.1097/aln.0b013e31818ec946]

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

**Table 1** C**omparison of intrathecal morphine with hydrophilic opioids (Fentanyl and Sufentanil)[55]**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| 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.

**Table 2 Recommended intrathecal morphine dosages for various surgical procedure[40]**

|  |  |  |
| --- | --- | --- |
| 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.

**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.

**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 |

**Table 5 Guidelines by American Society of Anaesthesiologists task force for the prevention, detection, and management of respiratory depression associated with intrathecal morphine administration[56, 103]**

|  |  |  |  |
| --- | --- | --- | --- |
| 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 (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 | 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  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.