CURRENT CONCEPTS IN NEURAXIAL ADMINISTRATION OF OPIOIDS AND NON-OPIOIDS: AN OVERVIEW AND FUTURE PERSPECTIVES

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Introduction

In the context of “Augmentation strategies” for epidural and intrathecal analgesia, the discovery of opioid receptors and the subsequent development of the technique of epidural and intrathecal opioid administration is undoubtedly one of the most significant advances in pain management in the last three decades. Plethora of studies has shown that spinal opioids can provide profound postoperative analgesia with fewer central and systemic adverse effects than with opioids administered systemically. A wide variety of non-opioids have also been used in epidural or subarachnoid space to achieve pain relief without the risk of respiratory depression. Segmental analgesia induced by spinal administration of opioids and non-opioids has been used successfully to treat intraoperative pain, postoperative pain, traumatic pain, obstetric pain, chronic pain and cancer pain (table-1).

Historical aspects

The identification of opioid receptors has opened new horizons in pain management. Yaksh and Rudy, in 1976, were the first investigators to demonstrate direct opioid analgesia at the spinal cord level.¹ Their study involved subarachnoid fentanyl and morphine in rats. However, the first application of neuraxial opioids can be traced to that in 1901, when a Japanese surgeon used 10 mg intrathecal (IT) morphine with the local anaesthetic eucaine in two cancer patients.² In 1979, Wang et al³ observed significant analgesia with 0.5-1 mg spinal morphine. The use of IT hydrophilic opioids (usually morphine) quickly spread to perioperative care with excellent postoperative analgesia in a wide array of surgical procedures.

Pharmacology

Though intrathecal or epidural opioids were among the first drugs (morphine was the first opioid administered intrathecally) used to augment neuraxial blocks, various other non-opioid drugs have recently been proved to demonstrate analgesic effects.

The following table-2 lists the drugs that have been used to augment regional anaesthesia.

Table - 1: Therapeutic applications of neuraxial administration of opioids and non-opioids

| I. Acute Pain: |
| - Intraoperative pain |
| - Postoperative pain |
| - Trauma pain |
| - Labour pain |
| - Non-surgical pain (MI, angina pectoris, herpes zoster, renal colic, thrombophlebitis, etc.) |

| II. Chronic non-malignant pain: |
| - Post herpetic neuralgia |
| - Complex regional pain syndromes (CRPS) |
| - Back pain |
| - Intractable angina pectoris |
| - Ischaemic pain |

| III. Cancer Pain: |
| - Long term therapy with subcutaneous ports |
| - Long term therapy with implantable, programmable pumps |

Table - 2: Neuraxial drugs used to augment regional anaesthesia

| I. Opioids: |
| a) Non-lipophilic: Morphone (commonest) |
| b) Lipophilic: Fentanyl (commonest), Sufentanil, Alfentanil, Pethidine, Hydromorphone, Diacetylmorphine, Buprenorphine, Butorphanol |

| II. Non-opioids: |
| a) α₂-adrenergic agonists: Clonidine, ST91 Tizanidine³ (experimental in rats) |
| b) Anticholinesterases: Neostigmine |
| c) Benzodiazepines: Midazolam |
| d) Steroids : Methylprednisolone |
| e) Ketamine |
| f) Endogenous nucleosides: Adenosine³ (experimental in rats) |
| g) Miscellaneous : Tenoxicam, Somatostatin, Octreotide, Droperidol, Calcitonin.
Pharmacodynamics of neuraxial opioids

Despite detailed characterization of opioid receptor systems at the cellular and even molecular level,7,8 the mechanisms of local anaesthetic - opioid interaction are still largely unknown.9,10 Alone, IT opioids appear to selectively modulate C- and A-fibres, with minimal impact on dorsal root axons.10,11 Somatosensory-evoked potentials remain intact after IT morphine administration.12 Finally with respect to nerve conduction block, none of the opioids applied neuraxially have consistently displayed local anaesthetic effects except possibly pethidine.10

Local anaesthetics potentiate the antinociceptive effects of morphine.13 This synergism does not result in enhanced motor block. With the use of IT pethidine, fentanyl and sufentanil for human labour analgesia, it has been observed that there is transient sensory change to temperature with all three opioids.14

Cohen et al9 observed segmental sensory block and hypotension in parturients after IT sufentanil injection. It is speculated that the active site for conduction block for neuraxial opioids is the dorsal root entry zone. Studies in gravid animal models suggest that hormonal milieu may contribute to drug effectiveness. Jayaram et al observed spinal progesterone potentiates the analgesic effect of spinal progesterone in rats.15 Hydrophilic opioid such as morphine is several hundred times more potent spinally than intravenously. In contrast, lipophilic opioids (fentanyl, sufentanil, etc.) are only 10-20 times more potent with IT administration versus the intravenous route.

Table 3 summarizes the important characteristic differences between IT morphine and lipophilic IT opioids.

Table - 3 : Comparisons between morphine and lipophilic opioids for intrathecal analgesia

<table>
<thead>
<tr>
<th>Opioid</th>
<th>IT/IV Potency Ratio</th>
<th>Onset of IT Analgesia (min)</th>
<th>Duration of Analgesia (hrs)</th>
<th>Time of peak Respiratory Depression</th>
<th>Clinical dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>200-300:1</td>
<td>60-120</td>
<td>18-24</td>
<td>8-10 hrs</td>
<td>0.1–0.5 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>10-20:1</td>
<td>&lt;10</td>
<td>1-4</td>
<td>5-20 min</td>
<td>6-30 g</td>
</tr>
</tbody>
</table>
| Sufentanil | 10-20:1  | <10 | 2-6 | 5-20 min | 2.5-10 g |*

*higher doses of IT sufentanil have been used combined with general anaesthesia (e.g. 50 g). IT (Intrathecal) and IV (Intravenous)

Pharmacokinetics of neuraxial opioids

It is believed that lipophilic opioids (e.g. fentanyl) do not tend to spread rostrally in CSF and move more rapidly than the hydrophilic opioids (e.g. morphine) from the CSF into the spinal cord. This is thought to explain the more rapid onset of analgesic action with fentanyl than morphine.16 Recently, the concept of lipophilic IT opioids remaining localized near their site of injection has been subjected to significant scrutiny. Gourlay et al17 noted high concentrations of fentanyl in cervical CSF within 30 minutes of lumbar administration. There are now several reports18-20 of sudden onset, life-threatening respiratory depression following IT sufentanil administration for labour analgesia. Nearly all episodes occurred 5-15 min after lumbar spinal injection of sufentanil (10-15 g) and required large doses of naloxone for reversal of opioid effects. These findings imply a rapid transit of lipophilic opioids from the lumbar cistern to brainstem respiratory centres. Using a sheep model, it has been observed that peak cerebral sufentanil concentrations occur at 20-30 minutes after lumbar spinal injection. These studies indicate that lipophilic opioids may rapidly move from lumbar IT injection sites to cervical and brainstem levels via CSF.

IT Fentanyl vs IT morphine

With IT morphine, its long duration of action and potential for providing late respiratory depression, effectively limit its use in inpatients. Moreover IT morphine has a slow onset time, which reduces its utility as an effective intraoperative adjunct. In contrast, IT use of lipophilic opioids (fentanyl and sufentanil) result in these -receptor agonists having significant utility as adjuncts to local anaesthetic - based spinal anaesthesia.

Dose response studies for neuraxial opioids:

i) Cesarean delivery studies and neuraxial opioids

Chu et al21 studied IT fentanyl (0-15 g) as a supplement to bupivacaine spinal anaesthesia. Ten micrograms of fentanyl improved intraoperative analgesia; 12.5 g lengthened postoperative analgesia. Dahlgren et al22 compared IT sufentanil (2.5 or 5 g) to fentanyl (10 g) as an adjunct to spinal bupivacaine. Both sufentanil doses were more effective than the fentanyl dose.

D’Angelo et al23 observed in labouring parturients that IT sufentanil is approximately 4.5 times more potent than IT fentanyl. There may be an analgesic ceiling effect with increasing doses of IT lipophilic opioids in the obstetric population.

It is currently recommended that 20-30 g fentanyl or 5-7.5 g of sufentanil be given intrathecally to supplement bupivacaine spinal anaesthesia for cesarean delivery.

In a recent prospective randomized controlled trial,24 on 53 patients undergoing LSCS using either 2 mg of epidural morphine or 0.075 mg of intrathecal morphine, it was observed that VAS pain scores were greater during the first 24 hours in intrathecal group (p=0.032) as was additional morphine consumption (4 vs. 1.5 mg, p=0.030). Time to first demand of morphine was similar in
epidural morphine (307.5 minutes) and intrathecal group (310.0 minutes) as was incidence of side effects such as sedation, pruritus, nausea and vomiting.

Epidural Butorphanol and Postoperative analgesia

Epidural butorphanol 1, 2 and 4 mg were compared with epidural morphine 5 mg, for postoperative analgesia in 92 parturients who had LSCS. At 15, 30, 45, 60 and 90 min and 2 hrs, the pain scores following butorphanol were similar and lower than those following morphine. Only one of 69 patients (1.4%) who received butorphanol developed pruritus compared with 10 (43%) of 23 patients who received morphine.

Labour Pains and Spinal Opioids

The results of combination of spinal opioids and local anaesthetic, are more impressive in labour pain because it is well recognised that labour pain is different from postoperative pain as it is not relieved by epidural opioids alone. Patients receiving epidural injections of local anaesthetic combined with opioids report more rapid onset of analgesia, more profound and long-lasting labour pain relief and less motor blockade than do patients receiving either drug alone. As part of combined spinal epidural (CSE) technique, intrathecal opioids (sufentanil 5-7.5 g or fentanyl 25 g) combined with very small doses of local anaesthetic (bupivacaine 1 mg) provide almost instantaneous pain relief to the labouring parturient and local anaesthetic combined with opioids report more rapid onset of analgesia. We usually use 20-30 g of IT fentanyl with low-dose local anaesthetic (6-7.5 mg hyperbaric bupivacaine) for short duration outpatient procedures under subarachnoid block. Singh et al. reported enhanced sensory analgesia with the addition of IT fentanyl (25 g) to spinal hyperbaric bupivacaine (13.5 mg) in males undergoing lower extremity and genital surgical procedures. In knee arthroscopy patients, Ben-David et al. observed enhanced sensory blockade without increased intensity of motor block or prolonged recovery for ambulatory discharge with 10 g fentanyl added to dilute low-dose (5 mg) hyperbaric bupivacaine. Lu et al. and Chilvers et al. also observed enhanced sensory blockade with varying doses of fentanyl and sufentanil.

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Lu et al. investigated spinal sufentanil (12.5, 25 and 50 g) dose response pharmacology and reported that doses greater than 12.5 g provided no improvement in speed of onset, duration or magnitude / intensity of analgesia. Chilvers et al. observed improved intraoperative analgesia with respect to shoulder pain and prolonged sensory block in the 25 g fentanyl group but no difference in motor recovery or time to discharge compared with the 0 or 10 g fentanyl group all groups comprising of patients undergoing gynaecologic laparoscopy.

Earlier studies used IT morphine in doses up to 100 times larger than those currently being used. Recent experience suggests that doses as low as 0.1 to 0.5 mg IT morphine provide adequate analgesia after abdominal, orthopaedic and thoracic surgery. There is convincing evidence that IT doses lower than 0.5 mg provide excellent postoperative analgesia. There is also a great scope for neuraxial opioids for postoperative pain relief in elective colorectal surgery. In our experience 0.2 mg morphine with bupivacaine given intrathecally provides good to excellent intraoperative and postoperative analgesia. Caldwell et al. observed that IT injection of a combination of 0.25 mg morphine and 25 g fentanyl was ineffective for labour analgesia.

Compared with IT route, epidural route is complicated by pharmacokinetics of dural penetration, epidural fat deposition and systemic absorption of opioids. IT morphine is more predictable, more intense and longer lasting. Epidural dose of morphine is 10-20 times greater than that required for intrathecal injection.

IT morphine (via subcutaneous pump) for intractable pain in pancreatic cancer and other abdominal malignancies

Most of the studies have reported excellent pain relief, improved quality of life with an increased level of activity of daily living following IT morphine ("Duramorph") at 1.62 to 2.40 mg/day (maximum dose range at 3.00 mg/day to 73.10 mg/day) for a mean duration of 137.3 days with a range of 52-354 days therapy. This

<table>
<thead>
<tr>
<th>Table - 4 : Intrathecal lipophilic opioids as adjuncts to spinal anaesthesia – Clinical effects and recommended doses</th>
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<tbody>
<tr>
<td><strong>Clinical feature</strong></td>
</tr>
<tr>
<td>Faster block onset time</td>
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<td></td>
</tr>
<tr>
<td>Improved intraoperative analgesia</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Decreased nausea/vomiting during cesarean delivery</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Postoperative analgesia time</td>
</tr>
<tr>
<td>1-4 hrs*</td>
</tr>
<tr>
<td>*Synergistic interactions with local anaesthetics affect duration of analgesia.</td>
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</table>
continuous infusion of morphine is obviously with the aid of “Implanted Infusion Pumps” (Medtronic Implantable, Programmable SYNCHROMED-EL Pump) placed into a subcutaneous pocket formed in a selected region of the abdomen and sutured to the fascia. This pump also has a “refill port” that allows 25G needle to pass through the septum for reloading of the reservoir with morphine after every 3 months. The pump has extended battery life of 4 to 7 years.

**Merits and demerits of spinal opioids**

In an interesting meta-analysis of randomized controlled trials, Ballantyne et al conclude that in terms of analgesia and restoration of postoperative pulmonary function following abdominal or thoracic surgery, spinal opioids have been superior to alternative methods such as intermittent I.M. opioids, PCA with I.V. opioids, intercostal block or interpleural analgesia.

Table-5 summarizes the merits and demerits of neuraxial opioids.

<table>
<thead>
<tr>
<th>Table - 5 : Merits and Demerits of spinal opioids</th>
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<tbody>
<tr>
<td><strong>Merits :</strong></td>
</tr>
<tr>
<td>• Greater spinal anaesthesia success rate</td>
</tr>
<tr>
<td>• Faster onset of surgical block than LA alone</td>
</tr>
<tr>
<td>• Improved intraoperative analgesia (enhances sensory block without increased motor block)</td>
</tr>
<tr>
<td>• Permits lower LA dose with faster recovery from spinal anaesthesia</td>
</tr>
<tr>
<td>• Postoperative analgesia beyond the duration of LA motor block</td>
</tr>
<tr>
<td>• Less nausea and/or vomiting during cesarean delivery</td>
</tr>
<tr>
<td>• Shorter time to extubation, significantly reduces MAC</td>
</tr>
<tr>
<td><strong>Demerits :</strong></td>
</tr>
<tr>
<td>• Frequent pruritus</td>
</tr>
<tr>
<td>• Sedation (never with lipophilic opioids; Rarely with high doses)</td>
</tr>
<tr>
<td>• Rare respiratory depression (more likely in parturients; especially late onset respiratory depression)</td>
</tr>
<tr>
<td>• Rare urinary retention (more likely with Morphine)</td>
</tr>
<tr>
<td>• IT Fentanyl I ?? cross tolerance to I.V Morphine</td>
</tr>
</tbody>
</table>

LA : Local Anaesthesia IT : Intrathecal

(a) **Merits :** The ability of lipophilic opioids to enhance sensory block without increased motor block or recovery time has already been mentioned. Vaghadia et al observed that laparoscopic surgery patients when randomized to either low dose hypobaric lidocaine (25 mg) with 25 g IT fentanyl or plain hyperbaric lidocaine (75 mg), there was less need for I.V. propofol-alfentanil supplementation for the IT fentanyl group as well as less hypotension and faster recovery. Likewise, very low dose IT bupivacaine/fentanyl have been found to be an acceptable alternative to spinal lidocaine for cerclage placement.

Also it has been observed that IT lipophilic opioids may offer excellent anaesthesia and analgesia for certain non-invasive or minimally invasive procedures. This has been documented for extracorporeal shock wave lithotripsy. Indeed, Eaton observed successful anaesthesia for lithotripsy in three patients with moderate to severe aortic stenosis using 12.5-15 g of IT sufentanil. Also small doses of lipophilic IT opioids can produce adequate surgical anaesthesia for procedures such as tubal ligation.

As already mentioned, IT lipophilic opioids added to local anaesthetic spinal anaesthesia for cesarean delivery improve intraoperative analgesia and may also prevent intraoperative nausea and vomiting. Swenson et al reported shorter time to extubation in coronary artery bypass patients when general anaesthesia was supplemented with IT sufentanil (50 g). Also, markedly lower isoflurane requirements during lower abdominal surgery when IT sufentanil is administered suggests that spinal lipophilic opioids significantly reduce MAC.

The 17-Nation European Survey showed that most anaesthesiologists thought that spinal administration of opioids affect postoperative outcome, decreases hospitalization time, and decreases morbidity. In this respect, morphine was considered superior to other opioids (table-6).

<table>
<thead>
<tr>
<th>Table - 6 : Opinion of European Anaesthesiologists regarding the role of opioids given epidurally in decreasing postoperative morbidity and hospitalization time.</th>
</tr>
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<tbody>
<tr>
<td>Role of opioid</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Affect outcome</td>
</tr>
<tr>
<td>Decreases hospitalization time</td>
</tr>
<tr>
<td>Decreases morbidity**</td>
</tr>
</tbody>
</table>

*Fentanyl, Sufentanil & Pethidine
**Major operation, high-risk patients, trauma patients and old patients.

(b) **Demerits :** Some of the reported side effects of neuraxial opioids such as nausea, vomiting, hypotension, somnolence, and early respiratory depression, are dose-related and are thought to result from the vascular uptake of opioids. The effects of neuraxial opioids on gastrointestinal functions have also received attention. The nonsystemic and characteristic adverse effects are pruritus, urinary retention, and late-onset respiratory depression.

(i) **Pruritus**

Most consistent side effect is pruritus. It is generally mild and occasionally very distressing to the patient and
In general, early onset respiratory depression is a minor problem. It occurs within 1 hour with morphine and within minutes with lipophilic opioids. Late onset respiratory depression is more problematic and predisposing factors for its development are summarized in table-9.

Table - 9 : Predisposing factors for development of late onset respiratory depression after spinal administration of opioids.

- Advanced age
- High risk patients
- Large doses of opioids
- Use of water soluble opioids
- Intrathecal administration of opioids (compared with epidural)
- Concomitant use of parenteral administration of opioids or sedatives or both
- Opioid-naive patient (lack of tolerance to opioids)
- Thoracic epidural administration of opioids

Early and late onset respiratory depression have also been reported after epidural administration of fentanyl, sufentanil, pethidine, diamorphine and hydromorphone. Otherwise generally risk of late onset respiratory depression is higher with morphine than with lipophilic opioids (considered safer because of segmental localization). Epidural administration of fentanyl has been associated with a decrease in the CO2 response curve that lasted 30 to 120 min after a single injection of 200 g in healthy volunteers and throughout the 18 hour study period in patients undergoing orthopaedic procedures who received 1 kg⁻¹ bolus followed by 1 gkg⁻¹hr⁻¹.

Data obtained over a two year period showed that opioids administered as I.V. PCA or epidurally carry an equally low risk of respiratory depression. Over 15,000 patients were treated either with I.V. morphine (n=10,019), I.V. fentanyl (n=529), PCA or epidural morphine (n=3,165) and epidural fentanyl (n=1,943). The average duration of treatment was 2.48 days for I.V. PCA opioid and 3.76 days for epidural opioids.

The incidence is as depicted in table-8.

Table - 8 : Incidence of respiratory depression after epidural administration of morphine.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Dose (mg)</th>
<th>No. of cases</th>
<th>Incidence (%)</th>
<th>Ref (see text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6000-9000</td>
<td>2-4</td>
<td>23</td>
<td>0.25-0.4</td>
<td>[49]</td>
</tr>
<tr>
<td>1085</td>
<td>4-6</td>
<td>10</td>
<td>0.9</td>
<td>[50]</td>
</tr>
<tr>
<td>14000</td>
<td>4</td>
<td>13</td>
<td>0.09</td>
<td>[51]</td>
</tr>
<tr>
<td>4880</td>
<td>2-5</td>
<td>12</td>
<td>0.25</td>
<td>[52]</td>
</tr>
</tbody>
</table>

Prophylactic administration of opioid antagonists such as naloxone, naltrexone, nalbuphine and butorphanol has been recommended for prevention of pruritus, nausea, vomiting and other adverse effects.

ii) Respiratory Depression

Results from large surveys involving thousands of patients suggest that the risk of late onset respiratory depression following epidural morphine is <1% and this can be reduced further if certain risk factors are avoided. The risk of respiratory depression following other opioids may or may not be less, current data being inconclusive. What is clear is that respiratory depression following spinal opioids is unpredictable and may be associated with any opioid.

The incidence is as depicted in table-8.

Table - 7 : Incidence of pruritus after epidural administration of opioid.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose</th>
<th>Incidence*</th>
<th>Duration of analgesia (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5 mg</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>50 g</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>1 mg</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

*Fifteen patients were in each group.
and Intensive Care issued guidelines in 1992, that irrespective of age, all patients who receive spinal opioids can now be nursed in regular wards. This guideline is based on the use of morphine, the observation time is 12 hrs. after injection. Similar guidelines have been issued by ESRA (European Society of Regional Anaesthesia) in 1996.56

Pregnant women have decreased anaesthetic requirements and are particularly susceptible to significant respiratory depression with IT sufentanil.18-20 The risk of respiratory depression appears to be increased by antecedent I.V. opioid agonist administration.18,19 If a systemic analgesic is needed in early labour, mixed agonist-antagonist opioid (e.g. nalbuphine) may offer some protection against IT sufentanil induced respiratory depression.20

iii) Nausea

Although nausea is generally considered a significant side effect of opioid administration, IT opioids may actually protect against intraoperative nausea and vomiting. Dahlgren et al observed a reduction in requirement for intraoperative antiemetic medication when spinal opioids were added to LA spinal for cesarean delivery.32 Cooper et al also reported a statistically significant reduction in intraoperative nausea with the addition of IT fentanyl (25 g) to a standardized spinal anaesthetic for cesarean delivery.57

iv) Urinary Retention

Urinary retention is a problem mainly with hydrophilic spinal opioids (e.g. morphine) and has not been observed with lipophilic opioids. Ben-David et al reported no significant difference in time to urination with the addition of IT fentanyl to spinal bupivacaine for outpatient knee arthroscopy.28 Also Liu et al observed no increase in time to first void in a crossover volunteer study using a hyperbaric lidocaine 5% spinal with or without 20 g fentanyl.16 Intrathecal sufentanil has been used alone for lithotripsy, and time to voluntary micturition was less than that after spinal lidocaine.59 On the other hand IT epinephrine clearly increases the time until voluntary micturition.59

Cytometric studies of volunteers injected epidurally with 2, 4 or 10 mg of morphine demonstrated a decrease in the strength of the detrusor contraction, which leads to a corresponding increase in larger capacity. These urodynamic changes are noticed within 15 to 30 minutes, last an average of 15 hours after epidural injection, and are unrelated to the morphine dose.

v) Neurotoxic potential of Neuraxial Opioids

As regards spinal toxicity of spinal opioids, there is paucity of information in the literature. Rawal et al, working on sheep model, reported no neural toxicity with 1.5 g kg\(^{-1}\) of IT sufentanil, but did note neuronal histopathological changes with 7.5 g kg\(^{-1}\) IT sufentanil.60 Obviously this was an exceptionally high dose of IT sufentanil and as there are no reports of neural toxicity despite widespread clinical use of fentanyl and sufentanil neuraxially, it is clear cut that typical, small doses of IT lipophilic opioids are safe.

Even unintentional massive doses of 50 to 100 mg of morphine given epidurally produce no serious physiological effects other than predictable naloxone reversible respiratory depression. Patients with cancer pain receiving daily doses of 480 mg of morphine epidurally or 60 mg intrathecally showed no evidence of any physiologic or neurologic changes.51

Prophylactic antagonist for spinal opioid induced respiratory depression

Naloxone is effective in reversing respiratory depression associated with spinal opioids, but it has a shorter duration of action than that of most opioids and there is risk of recurrence of respiratory depression after a single dose. Its short elimination half life necessitates repeated I.V. injections. This can be overcome by administration of continuous infusion of low-dose naloxone. It has been observed by Gan et al that low dose naloxone infusion (0.25 g kg\(^{-1}\) hr\(^{-1}\)) not only attenuates side effects but may also reduce postoperative opioid requirements.62

Mixed agonist antagonist drugs such as nalbuphine or butorphanol have also been used. Both naloxone and nalbuphine require careful dose titration to achieve satisfactory reversal of respiratory depression without reversal of analgesia or precipitating hemodynamic adverse effects. Recently synthetic analogues of naloxone such as naltrexone and nalmefene have been developed. Nalmefene has a considerably longer elimination half-life than naloxone, so its reversal effects after a single injection can be expected to outlast the analgesic effects of most opioids. Increasing the dose of nalmefene from 0.5 to 2 mg results in four fold prolongation of the antagonist effect. In contrast, increasing the usual 0.4 mg dose of naloxone has little effect on its duration of action.

Patient-controlled epidural fentanyl following spinal fentanyl at cesarean section

There has been a concern that acute spinal opioid tolerance induced by giving spinal fentanyl at cesarean section may make subsequent epidural fentanyl patient controlled analgesia ineffective.64 However, Cooper et al have confirmed that epidural fentanyl can produce effective analgesia following the use of 25 g of spinal fentanyl at cesarean section.
Feasibility of premixed solutions for epidural anaesthesia

Since opioids are mixed with local anaesthetics to provide analgesia, the stability of such solutions has to be assured. Ready-made mixtures give greater assurance of stability, availability as well as decrease the incidence of drug administration errors. Recently, Sanchez et al.,\(^{58}\) (using diamorphine in ropivacaine) have shown that such solutions can be manufactured in pharmacy aseptic units and can be stored up to one month for routine use in epidural infusions.

Neuraxial Non-Opioids

i) Enhancement of analgesic effect of intrathecal clonidine on bupivacaine spinal anaesthesia:

Intrathecal injection of clonidine, an alpha-2 agonist, provides effective relief of pain.\(^{56-70}\) However, the clinical use of intrathecal clonidine is hampered by the side effects of sedation, bradycardia, and hypotension.\(^{66-68}\)

Basic Pharmaceutics of Clonidine

Clonidine, an imidazole compound, is a selective partial agonist for \(\alpha_2\) adrenoceptors with a ratio of approximately 200:1 (\(\alpha_2:\alpha_1\)). It is thought to inhibit nociceptive impulses by activating postsynaptic \(\alpha_2\) adrenoceptors in the dorsal horn of the spinal cord.\(^{71}\) Yohimbine, a selective \(\alpha_2\) adrenergic antagonist, effectively reverses clonidine induced analgesia. Neuraxial administration of clonidine also has a local effect on sympathetic nerves in the spinal cord.

Clinical Neuraxial application of Clonidine

Rockmann et al. compared the analgesic effects of epidural clonidine (8 g kg\(^{-1}\)) alone, with a lower dose (4 g kg\(^{-1}\)) in combination with morphine (2 mg) or morphine (50 g kg\(^{-1}\)) alone in patients undergoing pancreatocleotomy.\(^{72}\) Epidural clonidine group had an earlier onset of a longer duration of analgesia than when morphine alone was used. Haemodynamically, the clonidine treated patients had a rate dependent decrease in cardiac output. It has also been observed that addition of clonidine (1 g kg\(^{-1}\)) to a caudal epidural solution of bupivacaine, improved the duration of postoperative analgesia\(^{73}\) without comprising ventilation.\(^{74}\)

Thirty-six geriatric patients, undergoing knee replacement using continuous spinal anaesthesia, were randomly assigned to receive bupivacaine alone or combined with either clonidine or morphine and the duration of surgical anaesthesia was assessed.\(^{69}\) Only 1/9 patients in the clonidine group received re-injection of bupivacaine for surgical pain compared with 8/11 patients in the morphine and 8/10 patients in the bupivacaine alone groups. In another study, patients undergoing cesarean section were randomized to receive spinal anaesthesia with bupivacaine alone or supplemented with either clonidine or clonidine plus fentanyl intrathecally.\(^{75}\) The addition of clonidine improved the spread of sensory block and prolonged postoperative analgesia, but moderately increased sedation.

Very recently Lena et al.\(^{51}\) have shown that following IT morphine (4 g kg\(^{-1}\)) along with IT clonidine (1 g kg\(^{-1}\)) in a group of patients undergoing coronary artery bypass grafting (CABG) (IT injection performed before induction of G.A.), time to extubation was significantly lower, VAS scores were significantly lower and morphine dosage was significantly lower as compared with control group.

Research on ST-91, a polar analogue of clonidine

Recent experimental work by Duffo et al.,\(^{75}\) with 2-(2,6-diethylphenylamine 2-imidazoline) (ST-91), a polar analogue of clonidine (acts on a 2-non A adrenoceptors) in rats have shown that intrathecal ST-91, seems to be an attractive alternative to clonidine as it produces analgesia in normal rats and in rats after nerve injury without significant hypotension, bradycardia, and sedation which are significant with clonidine. But human trials must await proper preclinical chemistry and toxicity studies.

ii) Enhancement of analgesic effect of intrathecal neostigmine on bupivacaine spinal anaesthesia:

Intrathecal administration of neostigmine, a cholinesterase inhibitor, has been shown to produce analgesia without neurotoxicity in animals.\(^{76,77}\) and humans, but also produced adverse effect of motor block, dizziness, nausea or vomiting.\(^{78,79}\) Gordh et al. have shown a relationship between the alpha-adrenergic and the cholinergic systems in the spinal cord to produce analgesia.\(^{80}\) Hence combining cholinergic and alpha adrenergic agents will produce improved analgesia by reducing the dose of each individual drug, therefore minimizing their adverse effects. Abram and Winne,\(^{81}\) showed in a rat model that IT neostigmine did indeed potentiate morphine analgesia. Hood et al.\(^{82}\) had shown in human volunteers that a neostigmine clonidine combination produced improved analgesia, while side effects were related solely to the dose of the individual drug. Recently Pan et al.\(^{83}\) have shown that combining IT clonidine (150 g) and neostigmine (50 g) enhanced bupivacaine spinal anaesthesia and produced prolonged postoperative analgesia compared with adding either drug alone to bupivacaine. However, this combination also produced significantly more adverse effects. The neostigmine 50 g dose could still be too large and a more favourable effect and adverse effect profile might be achieved with a smaller dose, such as 25 g, as suggested by others.\(^{54,85}\)
Another recent study by Almeida et al. showed that low dose intrathecal neostigmine (1-5 g) enhanced the analgesic action of 100 g intrathecal morphine used for postoperative pain relief following intra abdominal gynaecologic surgery. This enhancement of analgesia results from an increase in concentration of neurotransmitter acetylcholine and consequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors, in the cholinergic interneurons at laminae III and V of the dorsal horn of spinal cord coincident with opioid and adrenergic sites.

Very recently Turan et al. have shown that neostigmine 2 mg kg\(^{-1}\) when added to caudal 0.2% ropivacaine 0.5 mg kg\(^{-1}\) prolonged the period of analgesia by nearly 3 times without increasing the incidence of adverse effects in children aged 1-5 years undergoing inguinal hernia and hypospadias repair.

Neostigmine has also been successfully used through the caudal epidural route in pediatric patients.

It has also been shown by Gabriela et al. in patients undergoing vaginoplasty that the combination of I.V. ketamine (0.2 mg kg\(^{-1}\)) and IT neostigmine (50 g) results in less nausea and vomiting than the combination of I.V. fentanyl in prolonged postoperative analgesia and less intraoperative adverse effects in children aged 1-5 years undergoing inguinal hernia and hypospadias repair.

I.V. fentanyl (1 g kg\(^{-1}\)) and IT neostigmine.

The first clinical use of Somatostatin given intrathecally was reported in 1984. Effective analgesia was achieved in cancer patients who were tolerant to opioids. The analgesia was not reversed by naloxone, suggesting a non opioid mechanism of analgesia. The rationale for using somatostatin given neuraxially was the localization of specific somatostatin receptors in the spinal cord and demonstration of an inhibitory effect of somatostatin on nociceptive neurons. Octreotide is a stable analogue of somatostatin. It is a potent analgesic for cancer pain. The main problem with somatostatin is the risk of neurotoxicity which appears to be dose and species related.

Another problem is neurotoxic potential of intrathecal ketamine. Focal degeneration with loss of myeline and axoplasm has been observed in spinal nerve roots of monkeys after ketamine was given intrathecal. Large doses of ketamine given intrathecally may have neurotoxic potential in humans.

v) Intrathecal somatostatin and octreotide

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vi) Epidural methylprednisolone and P300 Event-related potentials (ERPs) in chronic low back pain

We have shown that following epidural methylprednisolone therapy in chronic mechanical low back pain patients, the absolute peak latency of P300 ERPs significantly decreased, thereby suggesting that significant improvement in cognitive functions (as P300-ERPs reflects cognitive functions) and pain relief go hand in hand.

vii) Intrathecal adenosine

Adenosine is an endogenous nucleoside with various effects on the peripheral and central nervous system whose actions are mediated through specific cell surface associated receptors. The adenosine A1 receptor agonist R-phenyl-isopropyl adenosine effectively reduces pain behaviour probably by a spinal site of action. Based on a background of the antinociceptive effects of intrathecally administered
Adenosa in animals Rane et al\textsuperscript{101} studied the side effects and analgesic effects of intrathecal adenosa (500-2000 g) on experimental pain in human volunteers. They demonstrated that an intrathecal adenosa injection of 1000 g lack side effects and attenuated different types of experimental pain.

**Augmentation of peripheral nerve blockade and ganglion blockade\textsuperscript{102}**

Epinephrine has routinely been used to potentiate and prolong action of local anaesthetic solutions specifically lignocaine for peripheral nerve block. Advantage being 2 fold. First, it reduces the local anaesthetic plasma concentration and thus minimizes the possibility of systemic toxicity,\textsuperscript{103} and secondly, enhanced quality and prolonged duration of nerve block.

Epinephrine by stimulating a-adrenergic receptors in the neural vasculature mediates contraction of vascular smooth muscle,\textsuperscript{104} reduces local blood flow and thereby slows clearance of lidocaine from the nerve. Potentiation of effect of local anaesthetic at sub maximal doses could result from pharmacokinetic factors that ultimately increase the intraneural LA concentration in the effector compartments. Also pharmacodynamic action of epinephrine on nerve membrane affecting various factors that regulate excitability such as potassium channel, Cl\textsuperscript{-} channel and Na\textsuperscript{+}/K\textsuperscript{+} pumps may contribute to potentiation effect.

Role of epinephrine apart, the description of multiple opiate receptor sites on primary afferent fibers by Fields et al\textsuperscript{105} in 1980 has led researchers to study the efficacy of opioids added to LA for peripheral nerve blocks.

Candido et al\textsuperscript{106} studied the effect of buprenorphine 0.3 mg added to 40 ml of local anaesthetic for axillary brachial plexus block and found that postoperative analgesia lasted 3 times longer than local anaesthetic block alone supporting the concept of peripherally mediated opioid analgesia.

In post-thoracotomy patients, the addition of clonidine (2 gkg\textsuperscript{-1}) significantly enhanced both the postoperative analgesia obtained with an intercostal block of bupivacaine as well as arterial oxygenation.\textsuperscript{107}

In an interesting study, Fine et al have successfully demonstrated that stellate blocks with fentanyl or local anaesthetic with fentanyl provided profound and enduring pain relief in postherpetic neuralgia patients, supporting the concept of endogenous opioids on sympathetic ganglion.\textsuperscript{108}

**Conclusion**

Since their introduction into clinical practice in 1979 opioids given spinally have achieved international popularity in various clinical settings. This undoubtedly represents a major breakthrough in pain management. The use of augmentation strategies (Neuraxial Opioids or Non-opioids) in epidural and intrathecal analgesia and peripheral nerve blockade and ganglion blockade is widespread and increasing for the management of intraoperative pain, postoperative pain, labour pain, chronic non-malignant pain and cancer pain (using implantable, programmable intrathecal pumps). It is increasingly being recognized that solution to the problem of postoperative pain management lies not so much in the development of new techniques as in the development of an organization to exploit existing expertise on the use of neuraxial opioids and non-opioids. Recent experimental works on intrathecal ST-91 and intrathecal adenosa have been quite encouraging. A well organized pain service definitely ensures safe and effective pain management.\textsuperscript{109} Also extensive international experience points convincingly that patients receiving neuraxial opioids or non-opioids for postoperative analgesia can be safely nursed in regular wards, provided trained personnel and appropriate guidelines are available and followed. The identification of appropriate “augmentation strategies” using neuraxial opioids or non-opioids for labour pain, intraoperative pain, postoperative pain, chronic pain and cancer pain, and need for future “safety studies” and “outcome studies” with these augmentation techniques shall go a long way in optimizing patient safety and comfort.

**References**


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