International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Narcotic Adjuvants to Local Anesthetics

Dr Chandrasekhar Krishnamurti[1], Dr Mounika Jonnavittula[2]

M.D., Associate Professor (Anesthesiology), NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam-531162, A.P., India

MBBS, House Surgeon, GITAM Institute of Medical Science and Research, Rushikonda, Visakhapatnam-530045, A.P., India

Abstract: ***The use of local anesthetics is limited by their duration of action and the dose dependent adverse effects on the cardiac and central nervous system. Hence a multimodal approach to pain management is recommended whenever possible using a combination of two or more drugs that act by different mechanisms to provide safe analgesia with minimal adverse effects. Anesthesiologists now prefer to add adjunctive drugs to local anesthetics to improve the quality of regional blocks and also ensure good residual analgesia post operatively for better patient comfort. Opioids are the most frequently used local anesthetic adjuvant. A wide range of opioids ranging from morphine, fentanyl, sufentanyl, hydromorphone, buprenorphine and tramadol have been used with varying success. The opioids potentiate anti-nociception of local anesthetics by G protein coupled receptor mechanisms, causing hyperpolarisation of the afferent sensory neurons. Their efficacy is determined by their dose, site of injection, lipophilicity and also the acid-base status at the site of drug deposition. Opioid use is limited by adverse effects like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use.***

Keywords: Adjuvants, local anesthesia, narcotics

1. Introduction

William Stewart Halsted first reported the use of cocaine to block upper extremity nerves in 1884 and performed the first brachial plexus block in 1885. Regional nerve blocks avoid the unwanted effect of anaesthetic drugs used during general anaesthesia and the stress for laryngoscopy and tracheal intubation. It provides complete muscle relaxation, intraoperative haemodynamic stability, effective postoperative analgesia, early ambulation, early resumption of oral feeding, avoids the use of multiple drugs and decreases the stress response. Thus, the incidence of postoperative cardiovascular, pulmonary, gastrointestinal and thromboembolic complications is decreased.

Pain transmission in the CNS (Central Nervous System) and PNS (Peripheral Nervous System) is by a complex group of neurotransmitters and pathways that are not always easily blocked by any one drug type or technique alone. Local anesthetics have a multifactorial action at the neuromuscular junction that may involve depressed conduction of the presynaptic motor fiber, inhibiting ACh release during nerve stimulation, binding to different specific ACh sites, resulting in desensitization of receptors, temporary occlusion of nicotine receptors, stabilization of the postjunctional membrane, and interference with the excitation-contraction coupling mechanism of the skeletal muscle fiber. The use of local anesthetics is limited by their duration of action and the dose dependent adverse effects on the cardiac and central nervous system. Hence a multimodal approach to pain management is recommended whenever possible using a combination of two or more drugs that act by different mechanisms to provide safe analgesia with minimal adverse effects. Anesthesiologists now prefer to add adjunctive drugs to local anesthetics to improve the quality of regional blocks and also ensure good residual analgesia post operatively for better patient comfort.

Single-shot peripheral nerve blocks as an alternative to general anesthesia and an opioid-sparing analgesic have become a portion of standard anesthesia practice throughout the world. A broad cross section of surgical patients consistently rank postoperative pain as their highest concern, highlighting the necessity for prolonged postoperative analgesia. (1,2) While perineural catheters for postoperative analgesia for the days after surgery have increased, their utility is limited by technical challenges with placement, inherent secondary failure rate, difficulties with catheter removal, or rarely infection. Furthermore, not all anaesthetists have the subspecialty training required to perform advanced indwelling catheter techniques nor is there universal capability to administer and manage an outpatient perineural catheter programme. (3)

The majority of anesthesiologists still perform single-shot blocks. Commercially available local anesthetic have a limited duration of analgesia that frequently leaves patients complaining of pain for the first time during their first postoperative night when they are likely most vulnerable. While there are longer acting formulations and new concepts on the horizon, there are limits to what local anesthetics alone can provide.

Definition of an Adjuvant: Adjuvants are those drugs which, when co-administered with local anesthetic agents, may improve the speed of onset and duration of analgesia and counteract disadvantageous effects of local anesthetics.

Advantages of Adjuvants

1) Adjuvants to local anesthetics speed onset, prolong effect, and reduce total required dose.
2) They enhance postoperative analgesia with minimal adverse effects of local anesthetics used.
3) Their action is predominantly peripheral and without central effects, so that analgesia is optimal while side effects like myocardial depression, hypotension, bradycardia, heart block, , ventricular arrhythmias and CNS side effects are minimized.

Types of Adjuvants Used: A wide variety of drugs have been used for both neuraxial and peripheral nerve blocks and broadly divided into:

a) Opioids : The opioids used are lipophilic (buprenorphine, fentanyl and sufentanyl) and hydrophilic (morphine
b) Non Opioids: The non-opiods being epinephrine, α_2-adrenoceptor agonists (clonidine and dexmedetomidine), acetylcholine esterase inhibitors (neostigmine), adenosine, ketorolac, midazolam, magnesium, sodium bicarbonate and hyaluronidase.

A. OPIOIDS

History: The first published report of intrathecal 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. After the discovery of opioid receptors by Pert and Snyder in 1973 and the subsequent identification of dorsal horn opioid receptors by radio-ligand techniques in 1977, Wang et al described the efficacy of intra thecal (IT) morphine for postoperative analgesia in a group of eight patients with genitourinary malignancy in 1979. Since then, the use of IT morphine has become widely acceptable technique and became the first opioid approved by the United States Food and Drug Administration (FDA) for its neuraxial use and perhaps it is the most widely neuraxially used opioid.

Clinical use: Opioids are the most frequently used local anesthetic adjuvant. A wide range of opioids ranging from morphine, fentanyl, sufentanyl, hydromorphone, buprenorphine and tramadol have been used with varying success. The opioids potentiate anti-nociception of local anesthetics by G protein coupled receptor mechanisms, causing hyperpolarisation of the afferent sensory neurons. Their efficacy is determined by their dose, site of injection, lipophilicity and also the acid-base status at the site of drug deposition. (Table 1) Opioid use is limited by adverse effects like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use.

Table 1: Pharmacokinetics of commonly used opioids

	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil
pKa	8.0	8.5	8.4	6.5	7.1
Unionised at pH 7.4 (%)	23	5	9	90	68
Plasma protein bound (%)	30	40	84	90	70
Terminal half life (hrs)	3	4	3.5	1.6	0.06
Clearance ($ml.min^{-1}.kg^{-1}$)	15-30	8-18	0.8-1.0	4-9	30-40
Volume of distribution ($l.kg^{-1}$)	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative lipid solubility	1	28	580	90	50

Pharmacology: Opioids are weak bases (pKa 6.5-8.7). In solution, they dissociate into ionized and unionized fractions, the relative proportions of each depends upon the pH of the solvent and their pKa. The unionized fraction is more diffusible than ionized form. In the acidic environment, opioids are highly ionized and therefore poorly absorbed. Conversely, in the alkaline medium, they are predominantly unionized and are readily absorbed. High lipid solubility facilitates opioid transport into the biophase or site of action. Consequently, high lipid solubility confers a more rapid onset of action. Drugs with high lipid solubility, high unionized fraction or low protein binding in the plasma, demonstrate large volumes of distribution. Small doses of short- acting opioids (like alfentanil, sufentanil or fentanyl) produce a short duration of action because plasma (and brain) concentrations remain above the threshold for therapeutic action for only a brief period as the drug rapidly redistributes from the CNS to other tissues. Larger doses produce longer durations of action because plasma concentrations remain above the threshold at the completion of drug redistribution and depend upon the slower elimination process to be reduced below the threshold level.

Mechanism of Action: Intrathecal opioids bind with a family of G-protein linked pre- and postsynaptic opioid receptors in laminae I and II of the dorsal horn. This leads to opening of potassium channels and closure of calcium channels. This reduction in intracellular calcium levels reduce the release of excitatory transmitters (glutamate and substance P) from pre synaptic C fibers, but not from A fiber terminals. This reduces nociceptive transmission. Another mechanism of action involved is an adenosine mediated hyper-polarization of nerve fibers and reduced release of GABA from the dorsal horn. The concentration of the drug needed for such effects cannot be achieved by the standard parenteral and non-parenteral doses used in clinical practice, but a direct delivery to the intrathecal space provides the required high concentrations with ease. 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." The distribution of intra thecally administered opioids occurs between water (cerebrospinal fluid) and fat (nervous structures, membranes) phase and determined by the hydrophilicity or lipophilicity of the drug and the magnitude of the ionized fraction. Highly water-soluble drugs with large ionized fraction will linger in the water phase (CSF) and ascend rostrally. Lipid solubility 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. (4, 5, 6, 7, 8)

Comparison of intrathecal morphine with hydrophilic opioids

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	01-Apr	5-20 min	6-30 mcg
Sufentanil	10-20:1	< 10	02-Jun	5-20 min	2.5-10 mcg

IT: Intrathecal; *iv*: Inravenous.

(a) Morphine: Morphine is a naturally occurring phenanthrene derivative. Morphine is extensively metabolized by the gut wall and the liver to morphine-3-glucuronide (M3G) (70%), morphine-6 glucuronide (M6G) (10%) and to sulphate conjugates. M6G is 10-20 times more potent than morphine and is normally excreted in urine. It accumulates in renal failure and accounts for increased sensitivity to morphine. Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity. In the elderly, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger patient. (9,10,11)

Effects: The main effects are mediated through MOP receptors. It is a potent analgesic with good sedative and anxiolytic properties. It may cause euphoria, dysphoria and hallucination. It produces respiratory depression and cough suppression. It has minimal effect on cardiovascular system and may produce bradycardia and hypotension. Nausea and vomiting are common side-effects. Histamine release may lead to rash, itching and bronchospasm (in susceptible patients). Meiosis is common. Tolerance and dependence may develop.

Pharmacokinetics: 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. This hydrophilic property of morphine minimizes the spinal cord capillary loss. This results in a higher concentration of available morphine in the CSF, leading to a wider band of analgesia.

Hence the site of administration and the dose given have an important role to play in the extent of spread of desired analgesic effects. 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 intrathecal administration, CSF concentrations of morphine gradually decline over 12 h by slow diffusion into the epidural space with a consequent slow increase in plasma concentrations. Cephalad spread may occur as early as 30 min, when the drug is detectable in cisternal CSF. 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. Radio labelled (14C) morphine persists for 2 h with 4.5% of the injected dose remaining 3 h post injection. The removal of drug from CSF is facilitated *via* a glycoprotein carrier transport system located in the choroid plexus. Because of its poor lipid solubility, IT morphine remains in the cerebrospinal fluid (CSF) for a prolonged period of time. It is circulated through cerebral spinal bulk flow and eventually rises rostrally to supraspinal levels. IT morphine, therefore, has bimodal analgesic effects. The first peak is soon after administration and is due to spinal opiate receptor binding. The second peak occurs 12 to 24 hours later and is due to supraspinal binding as the drug is circulated. (12, 13,14)

Therapeutic Use: The use of preservative free intra thecal morphine with or without local anesthetics in a dose range of 100-200 µg has good analgesic effect lasting 12-24h. The use of IT morphine at doses < 0.3 mg, the rate of episodes of respiratory depression was not higher compared to the placebo group who received systemic opioids. (15,16) IT morphine in the dose range of 0.05-0.2 mg has been used for effective post-caesarean section analgesia. The 0.2 mg dose but not the 0.1 mg dose carries an increased risk or respiratory depression. Severe hypercarbia has been reported in patients who receive 0.4 mg IT morphine. A dose of 0.02 mg/kg of IT morphine reduces the requirements of supplemental analgesia in the first 12 h of the postoperative period. (17, 18, 19) A much lower dose of 0.002-0.004 mg/kg IT morphine may be equally effective. 0.2 mg for THR 0.3 mg for TKR 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.(20,21) Small doses of 0.05 mg have been used to treat detrusor muscle spasms in patients undergoing transurethral resection of prostate (TURP). One study compared 0.075 and 0.150 mg IT morphine for postoperative analgesia after TURP under spinal anesthesia. 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. (22, 23) Intrathecal morphine administration in doses < 100 µg limits adverse effects in elderly patients.

Epidural morphine is about 5 to 10 times more potent than its intravenous form, with epidural doses of 30 to 100 mcg/kg as a bolus or 0.2 to 0.4 mg/hour as a continuous infusion. Lower doses of morphine are recommended in patients with hepatic or renal dysfunction due to its significantly altered pharmacokinetics. 2-mg doses of epidural morphine give good analgesia of long duration despite low plasma levels. After upper abdominal and thoracic surgery higher doses (4 mg) may be necessary in healthy patients. Elderly and frail patients appear to be sensitive to epidural morphine and doses in excess of 2 mg should be avoided regardless of the type of surgery.The hydrophilic nature of neuraxial morphine aids its cephalad spread and results in a larger area of analgesia. (24,25) The adverse effects of its use in neuraxial blocks includes respiratory depression (early and late), nausea, vomiting, pruritus and urinary retention. (26) The use of morphine in peripheral nerve blocks is presently not recommended as studies have failed to show any advantage over intravenous (IV) and intramuscular (IM) routes.

Side Effects

(i) **Postoperative nausea and vomiting** (PONV): This is a common adverse effect of IT morphine. Incidence ranges from 25 to 50% in patients who received between 0.2 and 0.8 mg morphine IT. Various drugs have been used for prevention and treatment of nausea and vomiting after IT morphine. 0.1 mg IT atropine. *iv* ondensetron 4 mg, combination of *iv* dexamethasone 4 mg and *iv* droperidol 0.625 mg, transdermal 1.5 mg scopolamine, *iv* 50 mg cyclizine and oral 30 mg mirtazapine have been found to be effective in preventing IT morphine induced PONV. For intractable PONV some researchers have recommended low dose naloxone infusion. Nalmefene 0.020 mg *iv* after vaginal delivery in patients who received IT morphine decreased the incidence of PONV remarkably. Naltrexone 6 mg is an effective oral prophylaxis against IT morphine induced PONV but it shortens the duration of analgesia. (27, 28, 29, 30, 31, 32, 33, 34)

(ii) Pruritus: Although pruritus is one of the most common side effects of IT morphine administration, severe pruritus occurs only in 1% of patients. Pruritus occurs most frequently in pregnant females where gestational hormones may cause alterations in the opioid receptor population. The distribution of pruritus is mainly in the upper half of the body, probably due to the cephalad spread of the drug in the

CSF interacting with the trigeminal nucleus, where mu opioid and 5-HT3 receptors are collocated. The interaction of morphine with trigeminal nucleus stimulates the substantia gelatinosa of the dorsal horn initiating the itch reflex. There is no associated histamine release with opioid induced itching. Multiple drugs have been used in the treatment of IT morphine induced pruritus. Naloxone at a rate of 5 mcg/kg per hour *iv* can be used in the treatment of pruritus and this does not reverse analgesia. Other drugs such as ondansetron, nalbuphine have also use in the treatment of pruritus.(36,37)

κ-opioid receptor agonists have antipruritic activity. 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. 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.

Low dose 10-20 mg *iv* propofol is effective for IT morphine-induced pruritus in humans by up-regulating the expression of cannabinoid-1 [CB (1)] receptors in anterior cingulate cortex (ACC).

(iii) Urinary retention: The inability to micturate spontaneously is considered as one of the most distressing non-respiratory complication of IT morphine. Meta-analysis of the relevant studies has shown an increased incidence of urine retention amongst the patients who received IT morphine. 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. 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.

(iv) Neurotoxicity: There is no evidence that administration of IT morphine in single, repeated or as continuous infusion causes neurotoxicity. Morphine does not have any neurotoxicity.Neuraxial morphine may trigger transient motor dysfunction after a non-injurious interval of spinal cord ischemia. 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. 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.

(b) Fentanyl:

Pharmacology: Fentanyl is a synthetic phenylpyperidine derivative (N-phenyl-N-(1-Phenethyl-4-piperi-dinyl) propanamide) is an opioid analgesic with potency eighty times that of morphine. Fentanyl is lipophilic with an octanol-water partition coefficient of 955. The higher lipophilicity of fentanyl that makes it rapid onset of action, lower incidence of side effects, and reduced risk of respiratory depression Intrathecal fentanyl in the dose range of 10-25 μg prolongs the duration and extent of sensory block with a more favorable adverse effect profile when compared to morphine. The addition of epinephrine 2 μg/mL to neuraxial local anesthetic-fentanyl mixtures does not reduce any opioid related adverse effects. The efficacy of fentanyl as an adjuvant in peripheral nerve blocks is equivocal.

Mechanism of action: Three possible mechanisms of action for the improved analgesia produced by the peripheral application of fentanyl:-

a) First, fentanyl could act directly on the peripheral nervous system. Primary afferent tissues (dorsal roots) have been found to contain opioid-binding sites. Because of the presence of bidirectional axonal transport of opioid-binding protein , fentanyl may penetrate the nerve membrane and act at the dorsal horn. This could also account for its prolonged analgesia. Fentanyl has a local anesthetic action in higher concentrations above 50 μg/mL *in vitro*.
b) Secondly, fentanyl may diffuse from the plexus sheath into epidural and subarachnoid spaces and then bind with the opioid receptor of the dorsal horn.
c) Thirdly, fentanyl may potentiate local anesthetic action via central opioid receptor–mediated analgesia by peripheral uptake of fentanyl to systemic circulation.

Therapeutic use: Fentanyl 2.5 μg/mL, in combination with bupivacaine 0.25%, almost doubles the duration of analgesia after axillary brachial plexus block. The same concentration of fentanyl, administered with lidocaine 1.5%, significantly increases the success and prolongs the duration of sensory brachial plexus block, but delays the onset of analgesia. However, brachial plexus block quality is not improved when fentanyl 1 μg/mL is added to ropivacaine 0.75%. The conflicting findings are attributed to differences in liposolubility, concentrations and doses of both opioids and local anesthetics used, sites of administration and techniques of nerve blockade chosen, as well as methodological differences in study design. (38)

Higher concentrations of fentanyl (3.3 μg/mL) results in better penetration of the drug into nerve roots and, improves the success of nerve blockade of perineurally deposited drug solution. Peripheral analgesic effects of low concentrations of opioids may be masked by high local anesthetic concentrations required for adequate anesthesia. The duration of analgesia is significantly longer (695±85 min) than those without fentanyl addition I (415±78 min). The addition of fentanyl to local anesthetics causes an improved

success rate of sensory blockade but may cause a delayed onset of analgesia, perhaps by the decreased pH caused by fentanyl. At room temperature, the pH of local anesthetic is 6.2±0.1 and decreased to 5.2±0.1 (n=4) by adding 100 μg fentanyl.

The addition of 25 µg of fentanyl to 10 mg of bupivacaine prolongs and intensifies the motor block. Of interest, 5 mg of bupivacaine with the 25 µg of fentanyl results in short-acting motor block but the same level of sensory analgesia as the dose of 7.5 or 10 mg of bupivacaine with the addition of fentanyl or the 10-mg dose of bupivacaine without fentanyl. (39, 40, 41, 42)

Pethidine

Pharmacology: It is a synthetic phenylpyperidine derivative ethyl 1-methyl-4-phenylpiperidine-4-carboxylate with intermediate lipid solubility, 30 times more lipid soluble than morphine and originally developed as an antimuscarinic agent. The drug is metabolized in the liver by ester hydrolysis to norpethidine and pethidinic acid that are excreted in the urine and therefore accumulate in renal failure. At higher concentration, norpethidine can produce hallucination and convulsions. Pethidinic acid is an inactive compound. Pethidine readily crosses the placenta, and a significant amount reaches to the foetus over several hours.

Mechanism of Action

Meperidine blocks conduction in 61.5% of 39 myelinated and unmyelinated axons, and significantly reduces conduction velocity in the unblocked axons. These effects are not naloxone reversible. The site of conduction block may occur at the proximal end of the dorsal root as it passes through the dorsal root entry zone, an anatomically unique segment of the primary sensory pathway with decreased conduction safety for action potential propagation. (43, 44, 45)

Therapeutic use: Meperidine 1.5 mg/kg provides a longer duration of sensory block than 1.2 mg/kg. Increasing the dose further has no effect on the duration of sensory block. The 78-min duration of spinal block after the administration of 1.2 mg/kg meperidine is similar to the 40-77 min duration after the administration of 1 mg/kg reported by other authors. In doses below 1 mg/kg the duration of surgical anesthesia is too short and may need convertion to general anesthesia.(46,47,48,49)

Cesarean delivery can be successfully performed under spinal meperidine alone when local anesthetics are not available Side effects included moderate hypotension (decrease in arterial blood pressure > 30 mm Hg in 36% of the cases), nausea (32%), and pruritus (10.7 %). No respiratory depression was documented in mothers and newborns.

Side effects are common after intrathecal meperidine. The incidence of itching can be 10%-35% and fatigue has often been observed . In our study, the incidence of these side effects was similar and was not dose-related. The incidence of respiratory depression is controversial: some authors reported none, whereas others reported hypoxia in up to 10% of patients. Respiratory depression a common and potentially serious complication and can occur as late as 40 min after intrathecal injection, possibly a result of the systemic reabsorption of meperidine from the cerebrospinal fluid or intrathecal cephalic spread. The peak plasma concentration of meperidine occurs 90 min after an intrathecal injection of 1 mg/kg . (50,51,52,53,54)

©Sufentanil:

Pharmacology: Sufentanil, an opioid known for its rapid onset of pain relief, while its duration of action is relatively short. Sufentanil is 3 to 5 times more potent an analgesic than fentanyl due to the strong affinity for opioid receptors.

Therapeutic use: Intrathecal sufentanil in the dose of 5 µg as an adjuvant to local anesthetics has good efficacy. Adverse effects are significantly less when a lower dose of 1.5 µg is used. The epidural dose of sufentanyl is 0.75-1 µg/mL and very effective in ameliorating pain in various patient subsets.

A combination of sufentanil and ropivacaine has a relative shorter onset time compared with the sole ropivacaine. Combination of 0.125% ropivacaine with 0.3 µg/mL sufentanil produced a statistically analgesic advantage over only 0.125% ropivacaine as demonstrated by a lower pains score during the 1st stage of labor. Sufentanil supplement exerts significant impact on neonatal 1-min Apgar scores ratings. However, the common doses of fentanyl and sufentanil used with an epidural/spinal techniques in labor analgesia are safe for neonates with a similar incidence of 1-min Apgar <7. In addition, the use of sufentanil in the combined spinal-epidural labor analgesia does not change Apgar scorings of the newborns. Neonates with parenteral opioid exposure have a higher incidence of poor 1-min Apgar scorings and may need more naloxone. Considering the effect of sufentanil exposure on neonatal Apgar scoring, it is necessary to consider the neonatal risk of sufentanil supplement for labor analgesia. A single bolus of ropivacaine plus sufentanil produced longer (124.0±36.2 minutes) duration than only ropivacaine (117.4±29.9 minutes; P=0.004). Onset of analgesia in both groups are similar, 10.2±3.1 versus 9.8±3.7 minutes (P=0.419). Sufentanil has a slightly longer duration of action than fentanyl. Intrathecal sufentanil 2.5-10 mcg, when administered together with hyperbaric bupivacaine 0.5% 12.5 mg for cesarean section are equally effective. Sufentanil has a slightly longer duration of action than fentanyl. (55-65)

Pruritus is the most common side effect and almost always attributed to the use of sufentanil. The pruritic effect of sufentanil is dose-dependent.

(d) Alfentanil: Alfentanil is a synthetic phenylpiperidine derivative structurally related to fentanyl; it has 10-20% of its potency. Although it has much lower lipid solubility than fentanyl, thE lower pKa of alfentanil (6.5 versus 8.4 for fentanyl) means that more alfentanil is present in the unionized form compared to fentanyl (89% compared to 9%). Consequently, its onset of action is more rapid.

Because of its lower lipid solubility, less alfentanil is distributed to muscles and fat. Hence, its volume of distribution is relatively small and more of the dose remains in blood from which it can be cleared by the liver. Even though alfentanil has a lower clearance rate, this is more than offset by its reduced volume of distribution and its half life is relatively short.

Effects: Most effects of alfentanil are similar to fentanyl but with quicker onset and shorter duration of action.

(e) Hydromorphone:

Pharmacology: Hydromorphone (Dilaudid) has an octanol-water coefficient of 525 and an opioid with intermediate lipid solubility between morphine and fentanyl. This improves its ability and results in a rapid onset of analgesia, low incidence of side effects, and a low risk of delayed respiratory depression. Hydromorphone (octanol-water partition coefficient of 525) provides a faster and more potent onset of action than morphine, and a longer duration of action than fentanyl

Clinical use: Hydroxymorphone has been shown be an efficacious adjuvant in both intrathecal and epidural routes at the dosages of 100 µg and 500-600 µg respectively. It is preferred in patients with renal insufficiency and has a better adverse effect profile when compared to morphine. Epidural administration of hydromorphone resulted in a higher incidence of pruritus, and no improvement in postoperative analgesia and does not improve postoperative recovery of gastrointestinal function within the context of accelerated recovery program that entails early enteral feeding, early ambulation, administration of ketorolac, and lack of a nasogastric tube.

Intrathecal hydromorphone appears to be not only safe but also possibly more effective than other intrathecal opioids, including morphine, in providing intraoperative and postoperative pain management for patients undergoing cesarean delivery. There are no adverse outcomes, including respiratory depression.

Hydromorphone comes close to being an optimal opioid in spinal analgesia, providing faster access to the dorsal horn neurons and faster onset of analgesia. Compared with morphine, neuraxial hydromorphone has a lower prevalence of side effects and a reduced risk for late respiratory depression. Patients receiving intrathecal hydromorphone experience significantly better postoperative pain relief compared with saline. Intrathecal hydromorphone can be used as the second-line therapy behind morphine if analgesia with morphine is ineffective. Intrathecal hydromorphone has a faster onset and shorter half-life than morphine for cancer pain. Patients with chronic malignant pain can be switched to intrathecal hydromorphone if there is failure of pain control by intrathecal morphine. This has lower pharmacologic complications, such as nausea and vomiting, pruritus, and sedation, and improved analgesic responses by at least 25% in many of the patients. Hydromorphone, compared with morphine, is the superior analgesic for managing intractable nonmalignant pain. As a result, hydromorphone is gaining popularity and acceptance with clinicians as an alternative to morphine for the treatment of chronic pain using continuous intrathecal drug delivery systems. Though morphine and fentanyl are the most frequently selected intrathecal opioids in this setting, 100 µg of intrathecal hydromorphone can be used for the pain management of patients allergic to morphine. Patients receiving intrathecal hydromorphone report significantly lower pain scores across all 3 pain assessment categories compared with patients who received intrathecal fentanyl or local anesthetic only (average pain < 4 hours postoperatively, average pain < 12 hours postoperatively, and average pain over the 24-hour postoperative period; $P < .001$. (66,67,68)

Hydrophilic opioids, such as morphine and hydromorphone, are used in continuous epidural infusions and provide more reliable neuraxial analgesia than the more lipophilic opioids such as fentanyl and sufentanil. Epidural hydromorphone in combination with dilute bupivacaine, 0.06% provides excellent analgesia for postoperative pain following orthopedic surgery.

(f) Buprenorphine:

Pharmacology: Buprenorphine is a semi-synthetic, oripavine alkaloid derived from thebaine. It is a long-acting, highly lipid-soluble, mixed agonist-antagonist opioid analgesic first synthesized in 1966.

Mechanism of action: The analgesic effect of buprenorphine appears to depend on the integrity of descending fibers from the rostral ventromedial medulla. Residual analgesic effects of opioids after inactivation of descending fibers may be caused by peripheral effects in the presence of inflammation. Buprenorphine is shown to be fully efficacious with an antinociceptive potency 20-70 times higher than morphine. It binds to mu, kappa, and delta opioid receptors and dissociates slowly from these receptors. Buprenorphine acts as a partial mu opioid agonist and a kappa opioid antagonist

Clinical use: The low abuse liability of the drug in humans soon turned it into a widely used therapeutic agent in patients with opioid dependence. The principal clinical application of buprenorphine is as an analgesic for moderate-to-severe pain in perioperative setting.. The parenteral formulation of buprenorphine has an onset time of 5-15 min, and duration of action is about 8 h after administration. It is metabolized by the gut and liver.

Being a partial mu opioid agonist, buprenorphine has a wider safety profile as compared to full mu agonists. Further, the slow dissociation of buprenorphine from the receptor result in prolonged duration of analgesia fewer signs and symptoms of opioid withdrawal upon termination of buprenorphine therapy than those which occur with full mu opioid agonists such as morphine, heroin, and methadone. Antagonist effects at the kappa receptors are associated with limited spinal analgesia, dysphoria, and psychomimetic effects.

The various advantages associated with the use of buprenorphine are that it has a longer duration of analgesic

action, low addiction propensity, and a high therapeutic index. Buprenorphine at 150 µg prolongs the mean duration of sensory blockade and extends the length of analgesia when given either IM or in an ISB. The duration of sensory blockade and analgesia, however, is more prolonged in patients who received buprenorphine (856.1 and 1049.7 minutes) . None of the patients experience opioid-related side effects. Patients who receive buprenorphine in sciatic nerve blocks report lower pain scores up to 36 hours after surgery, had 6 hours longer duration of analgesia, and used fewer opioids for 24 hours compared with those who received IM administration. Although buprenorphine may enhance and prolong the analgesic effect for sciatic nerve blocks, it may not be as effective as it is in brachial plexus nerve blocks. (69-74)

The adverse effects associated with it include sedation, nausea, itching, constipation, addiction in higher doses, confusion, hallucinations, dry mouth, blurred vision, and respiratory depression with the overdose of drug. No neural damage has been reported Utorphanol, a synthetic opioid is seven times more potent than morphine.[5]

(g) Butorphanol

Pharmacology: A synthetic opioid of the phenanthrene series with mixed agonist/antagonist properties, the drug is 7 times more potent than morphine. It is a synthetic opioid that is classified as a kappa receptor agonist and mu receptor competitive antagonist. Butorphanol has high affinity for opioid receptors and is not easily displaced. Butorphanol is 2 to 3 times more potent than morphine and has a shorter duration of action (0.5 to 3 hours), with minimal sedation. The half-life of butorphanol is 1.64 h after intravenous administration in comparison with 3.16 h if the drug is given subcutaneously. The analgesic effects of butorphanol last for 2.5 h

Mechanism of action: Butorphanol is a synthetic opioid-like morphine having partial antagonistic activity at µ receptors and agonistic activity at kappa receptors. Stimulation of these receptors on central nervous system neurons causes an intracellular inhibition of adenylyl cyclase, closing of influx membrane calcium channels, and opening of membrane potassium channels. This leads to hyperpolarization of the cell membrane potential and suppression of action potential transmission of ascending pain pathways.

Clinical use: The addition of 2 mg butorphanol to 0.5% levobupivacaine produces longer duration of analgesia compared to 1 mg butorphanol in patients posted for upper limb surgeries under supraclavicular brachial plexus block. The higher dose of butorphanol also hastens the onset and prolongs the duration of sensory and motor block. Cardiovascular and respiratory side effects are minimal compared with mu receptor agonists, and butorphanol produces antitussive and antiemetic effects. Butorphanol produces minimal esophageal sphincter constriction and is less likely to depress GI motility compared to mu opioid receptor agonists. Butorphanol is used for mild-to-moderate pain and seems to be more effective for visceral pain than musculoskeletal pain.Butorphanol provides analgesia and mild sedation but does not cause respiratory depression unless high dose rates are used.. Butorphanol can be used to reverse the respiratory depressant effects of µ agonists such as fentanyl, morphine or pethidine and still retain some analgesic properties.

Butorphanol is used in combination with dexmetedomidine and ketamine to produce surgical anaesthesia. While butorphanol prolongs the length and depth of anaesthesia achieved, it also produced greater cardiovascular and respiratory depression than medetomidine and ketamine alone.

The addition of butorphanol to local anesthetic in epidural route produces earlier onset analgesia and time to reach peak analgesia. Higher dose of butorphanol hastens the onset of analgesia compared with lower dose. Butorphanol in a dose of 20mcg/kg as an adjuvant to local anesthetic agents in upper limb peripheral nerve blocks has been found effective and up to 2 mg doses has been associated with minimal side effects.
Perineural injection of butorphanol with bupivacaine can provide early onset of sensory and motor blockade. There is hardly any difference in-between the onset of action between the doses 30 µg/kg and 40 µg/kg of butorphanol, but sedation is an unavoidable side effect with 40 µg/kg. Prophylactic administration of butorphanol is recommended for prevention of such side effects produced by pure agonist opioids such as morphine, and it has also been effectively used for the treatment of intractable pruritus associated with dermatological conditions. (75-77)

(h) Tramadol.
Pharmacology: Tramadol is phenylpiperidine and a synthetic 4-phenyl-piperidine analogue of codeine and belongs to the aminocyclohexanol group. Tramadol has high oral bioavailability of 70% which can increase to 100% with repeated doses due to reduction in first pass effect. It is 20% bound to plasma proteins and metabolized in the liver by demethylation into a number of metabolites – only one of them (O-desmethyltramadol) is also a µ-opioid receptor agonist but is 6 times more potent than tramadol itself. Its elimination half-life is 4-6 hours. After oral administration, tramadol demonstrates 68% bioavailability, with peak serum concentrations reached within 2 hours. The elimination kinetics can be described as 2-compartmental, with a half-life of 5.1 hours for tramadol and 9 hours for the M1 derivative after a single oral dose of 100mg. This explains the approximately 2-fold accumulation of the parent drug and its M1 derivative that is observed during multiple dose treatment with tramadol. In equi-analgesic dose to morphine, tramadol produces less respiratory and cardiovascular depression than morphine.

Mechanism of action: Tramadol is a weak mu receptor agonist and has 6000 times lower than that of morphine at all opioid receptors. It inhibits reuptake of norepinephrine and potentiates the release of serotonin causing a descending inhibition of nociception. In contrast to other opioids, the analgesic action of tramadol is only partially inhibited by the opioid antagonist naloxone, which suggests the existence of another mechanism of action. This was demonstrated by the discovery of a monoaminergic activity

that inhibits noradrenaline (norepinephrine) and serotonin (5-hydroxytryptamine; 5-HT) reuptake, making a significant contribution to the analgesic action by blocking nociceptive impulses at the spinal level. Tramadol is a racemic mixture of 2 enantiomers, each one displaying differing affinities for various receptors. The rank order of potency was (-)-tramadol < (+)-tramadol <*O*-desmethyltramadol. (+/-)-Tramadol is a selective agonist of mu receptors and preferentially inhibits serotonin reuptake, whereas (-)-tramadol mainly inhibits noradrenaline reuptake. The action of these 2 enantiomers is both complementary and results in the analgesic effect of (+/-)-tramadol.

Clinical use: The recommended daily dose of tramadol is between 50 and 100mg every 4 to 6 hours, with a maximum dose of 400 mg/day; the duration of the analgesic effect after a single oral dose of tramadol 100mg is about 6 hours. Adverse effects, and nausea in particular, are dose-dependent and therefore considerably more likely to appear if the loading dose is high. The reduction of this dose during the first days of treatment is an important factor in improving tolerability. Other adverse effects are generally similar to those of opioids, although they are usually less severe, and can include respiratory depression, dysphoria and constipation. Tramadol can be administered concomitantly with other analgesics, particularly those with peripheral action, while drugs that depress CNS function may enhance the sedative effect of tramadol. Tramadol should not be administered to patients receiving monoamine oxidase inhibitors, and administration with tricyclic antidepressant drugs should also be avoided. Tramadol has pharmacodynamic and pharmacokinetic properties that are highly unlikely to lead to dependence.. Tramadol is a central acting analgesic which has been shown to be effective and well tolerated, and likely to be of value for treating several pain conditions (step II of the World Health Organization ladder) where treatment with strong opioids is not required.

Tramadol has local anaesthetic effect similar to lignocaine following intradermal injections. Nerve conduction blocking effects of opioids have been demonstrated in both clinical and animal studies. Tramadol 2 mg/kg has local anesthetic and post-operative analgesic effect equal to lidocaine 1 mg/kg and can be used for minor surgeries performed subcutaneously. Tramadol hydrochloride 5% possesses local anesthetic activity similar to 2% lignocaine hydrochloride.

The addition of intrathecal tramadol 25 mg to the isobaric ropivacaine does not alter the block characteristics produced by intrathecal ropivacaine alone. Caudal tramadol prolongs duration of analgesia by 4 h.

When used in PNBs, tramadol has been demonstrated to increase the duration of analgesia.Patients who received tramadol (1.5 mg/kg) either IM or in an ISB experience an increased duration of analgesia (4 and 7 hours, respectively) compared with those who receive only levobupivacaine. 100-mg dose of tramadol as an adjuvant to mepivacaine in axillary brachial plexus block increases duration of motor and sensory blockade in the axillary tramadol group that significantly ($p < .01$) outlasts both an intravenous and a placebo group. The use of tramadol in PNBs are equivocal. The 200-mg dose provides the best analgesia with no increased adverse effects. A 1.5-mg/kg dose of tramadol as an adjuvant to 0.5% levobupivacaine (0.5 mL/kg) for interscalene block experience prolonged analgesia compared to systemic tramadol (14.5 vs. 10.1 hours; $p < .001$).

Intrathecal tramadol in doses ranging from 10-50 mg has been in used different subsets with varying success].

Epidural tramadol in doses of 1-2 mg/kg presented itself as an attractive alternative to morphine for postoperative analgesia without any respiratory depressant effect. Epidural tramadol has given good results for amelioration of pain in various patient subsets ranging from obstetric patients and abdominal surgeries to pediatric patients for lower abdominal procedures. (78-88)

Remifentanyl: It is a synthetic phenylpiperidine derivative of fentanyl acting on mu-type receptors with exactly the same effects of any available fentanyl-type opioid with the same efficacy. Remifentanil has approximately the same potency as fentany and is rapidly broken down by non-specific plasma and tissue esterases resulting in a short elimination half life (3-10 minutes). Onset time is 1-3 min (IV) and the drug is excreted by the kidneys. Its metabolite has weak mu agonist action The drug is not suited as an adjuvant with local anesthetics due to its very half life, lack of residual action and incidence of hyperalgesia following its use.

References

[1] Chew ST, Tan T, Tan SS, Ip-Yam PC. A survey of patients' knowledge of anaesthesia and perioperative care *Singapore Med J* 1998,39: 399- 402
[2] Aveline C, Le Hetet H, Le Roux A , et al. Perineural ultrasound-guided catheter bacterial colonization: a prospective evaluation in 747 cases. *Reg Anesth Pain Med* 2011;36: 579
[3] Bowens C Jr, Briggs ER, Malchow RJ. Brachial plexus entrapment of interscalene nerve catheter after uncomplicated ultrasound-guided placement. *Pain Med 2*011; 12: 1117
[4] Fields HL, Emson PC, Leigh BK, et al. Multiple opiate receptor sites on primary afferent fibres. Nature (Lond) 1980;284:351–3
[5] Yaksh KL. Multiple opioid receptor systems in brain and spinal cord. Eur J Anaesthesiol. 1984;1:171–3.
[6] Stein C. Peripheral mechanisms of opioid analgesia. Anesth Analg. 1993;76:182–91
[7] Stein C, Millan MJ, Shippenberg TS, Peter K, Herz A. Peripheral opioid receptors mediating antinociceptionc in inflammation.
[8] Evidence for involvement of mu, delta and kappa receptors. J Pharmac Exp Ther. 1989;248:1269–75
[9] Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology. 1979;50:149-51
[10] Nordberg G, Hedner T, Mellstrand T, Dahlström B. Pharmacokinetic aspects of intrathecal morphine analgesia. *Anesthesiology*. 1984;60:448-454.
[11] 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* 2002; **27**:535-537.
[12] 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
[13] Neustein SM, Cottone TM. Prolonged respiratory depression after intrathecal morphine. *J Cardiothorac Vasc Anesth*. 2003; 17:230- 231.
[14] Law CL, Visser EJ. Unconsciousness and severe respiratory depression following intrathecal morphine analgesia for lumbar spinal surgery. *Acute Pain*. 2007;9:163-167.
[15] 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.
[16] 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
[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
[18] 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.
[19] 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.
[20] 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.
[21] 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.
[22] Martinez-Velez A, Singh P. Epidural Morphine. Stat Pearls Publishing; 2020
[23] Rawal N, Sjostrand U, Dahlstrom B. Post operative pain relief by epidural morphine. Anesth Analg 1981;60(10):726-31
[24] Chaney MA. Side effects of intrathecal and epidural opioids. *Can J Anaesth*. 1995;42:891-903
[25] 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.
[26] 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.
[27] 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.
[28] 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.
[29] 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.
[30] 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.
[31] 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.
[32] 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.
[33] 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.
[34] 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.
[35] 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.
[36] Nishikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesth Analg 2000;91:384-7
[37] Gissen AJ, Gugino LD, Datta S, Miller J, Covino BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. Anesth Analg. 1987;66:1272–6.
[38] Gissen AJ, Gugino LD, Datta S, Miller J, Covino BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. Anesth Analg 1987;66:1272–6
[39] Power I, Brown DT, Wildsmith JA. The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. Reg Anesth 1991;16:204–8
[40] Nishikawa K, Kanaya N, Nakayama M, et al. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesth Analg. 2000;91(2):384–387.
[41] Grace D, Fee JPH. Anaesthesia and adverse effects after intrathecal pethidine hydrochloride for urological surgery. Anaesthesia 1995;50:1036-40.
[42] Kafle SK. Intrathecal meperidine for elective caesarean section: a comparison with lidocaine. Can J Anaesth 1993;40:718-21.

[43] Conway F, Critchley LAH, Stuart JC, Freebairn RC. A comparison of the haemodynamic effects of intrathecal meperidine, meperidine-bupivacaine mixture and hyperbaric bupivacaine. Can J Anaesth 1996; 43:23-9.
[44] Sangarlangkarn S, Klaewtanong V, Jonglerttrakool P, Khankaew V. Meperidine as a spinal anesthetic agent: a comparison with lidocaine-glucose. Anesth Analg 1987; 66:235-40.
[45] Acalovschi I, Bodolea C, Manoiu C. Spinal anesthesia with meperidine: effects of added alpha-adrenergic agonists-epinephrine versus clonidine. Anesth Analg 1997; 84:1333-9.
[46] Famewo CE, Naguib M. Spinal anaesthesia with meperidine as the sole agent. Can Anaesth Soc J 1985; 32:533-7.
[47] Patel D, Janardhan Y, Merai B, et al. Comparison of intrathecal meperidine and lidocaine in endoscopic urological procedures. Can J Anaesth 1990; 37:567-70.
[48] Nguyen Thi TV, Orliaguet G, Ngu TH, Bonnet F. Spinal anaesthesia with meperidine as the sole agent for cesarean delivery. Reg Anesth 1994; 19:386-9.
[49] Naguib M, Famewo CE, Absood A. Pharmacokinetics of meperidine in spinal anaesthesia. Can Anaesth Soc J 1986; 33:162-6.
[50] Cheun JK, Kim AR. Intrathecal meperidine as the sole agent for cesarean section. J Korean Med Sci 1989;4:135-8.
[51] Cozian A, Pinaud M, Lepage JY, et al. Effects of meperidine spinal anesthesia on hemodynamics, plasma catecholamines, angiotensin I, aldosterone, and histamine concentrations in elderly men. Anesthesiology 1986;64:815-9.
[52] Ong B, Segstro R. Clinical reports: respiratory depression associated with meperidine spinal anaesthesia. Can J Anaesth 1994;41:725-7.
[53] Li B, Wang H, Gao C. Bupivacaine in combination with fentanyl or sufentanil in epidural/intrathecal analgesia for labor: a meta-analysis. J Clin Pharmacol. 2015;55:584–91.
[54] Coleman L, Carvalho B, Lipman S, Schmiesing C, Riley E. Accidental intrathecal sufentanil overdose during combined spinal-epidural analgesia for labor. Int J Obstet Anesth. 2009;18:78–80
[55] Golfam P, Yari M, Bakhtiyari HR. Minimum appropriate dose of lidocaine with a fixed dose of sufentanil epinephrine used for spinal anesthesia in caesarian section. *Anesth Pain Med*. 2013**;2**(3):123-6
[56] Derakhshan P, Imani F, Koleini Z S, Barati A. Comparison of Adding Sufentanil and Low-Dose Epinephrine to Bupivacaine in Spinal Anesthesia: A Randomized, Double-Blind, Clinical Trial, Anesth Pain Med. 2018 ; 8(5):e6960
[57] Li B, Wang H, Gao C. Bupivacaine in combination with fentanyl or sufentanil in epidural/intrathecal analgesia for labor: a meta-analysis. *J Clin Pharmacol* 2015; 55:584–591
[58] Li BS, Wang W, Wang ZQ, et al. Efficacy and safety of local anesthetics bupivacaine, ropivacaine and levobupivacaine in combination with sufentanil in epidural anesthesia for labor and delivery: a meta-analysis. *Curr Med Res Opin* 2014; 30:2279–2289.]
[59] Polley LS, Columb MO, Wagner DS, et al. Dose-dependent reduction of the minimum local analgesic concentration of bupivacaine by sufentanil for epidural analgesia in labor. *Anesthesiology* 1998; 89:626–632.
[60] Ortner CM, Posch M, Roessler B, et al. On the ropivacaine-reducing effect of low-dose sufentanil in intrathecal labor analgesia. *Acta Anaesthesiol Scand* 2010; 54:1000–1006
[61] Cicarelli DD, Silva RV, Frerichs E, et al. Combined spinal-epidural for labor analgesia: does the addition of sufentanil to the local anesthetic influence Apgar scores of the newborns? *Rev Bras Anestesiol* 2007; 57:272–279
[62] Courtney MA, Bader AM, Hartwell B, et al. Perioperative analgesia with subarachnoid sufentanil administration. Reg Anesth 1992;17:274-8.
[63] Umenhoffer WC, Arends RH, Shen DD, et al: Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil and sufentanil. Anesthesiology 2000; 92:739-753
[64] Liu SS, Bieltz M, Wukovits B, et al: Prospective survey of patientcontrolled epidural analgesia with bupivacaine and hydromorphone in 3,736 postoperative orthopedic patients. Reg Anesth Pain Med 2010;35:351-354
[65] Liu S, Carpenter RL, Mulroy MF, et al: Intravenous versus epidural administration of hydromorphone. Effects on analgesia and recovery after radical retropubic prostatectomy. Anesthesiology 1995;82:682-688
[66] Chaplan SR, Duncan SR, Brodsky JB, Brose WG: Morphine and hydromorphone epidural analgesia. Anesthesiology 1992;77:1090-1094
[67] Mehta TR, Parikh BK, Bhosale GP, Butala BP, Shah VR. Post operative analgesia after incisional infiltration of bupivacaine v/s bupivacaine with buprenorphine. J Anaesthesiol Clin Pharmacol. 2011;27:211–4
[68] Dobkin AB. Buprenorphine hydrochloride: Determination of analgesic potency. Can Anaesth Soc J. 1977;24:186–93.
[69] Johnson RE, Fudala PJ, Payne R. Buprenorphine: Considerations for pain management. J Pain Symptom Manage. 2005;29:297–326.
[70] Vadivelu N, Hines RL. Buprenorphine pharmacology and clinical applications. Semin Anesth Perioper Med Pain. 2004;23:281–90.]
[71] Modi M, Rastogi S, Kumar A. Buprenorphine with bupivacaine for intraoral nerve blocks to provide postoperative analgesia in outpatients after minor oral surgery. J Oral Maxillofac Surg. 2009;67:2571–6.
[72] Viel EJ, Eledjan JJ. Brachial plexus block with opioids for postoperative pain relief: Comparison between buprenorphine and morphine. Reg Anesth 1989; 14: 274 - 278.
[73] Wajima Z, Shitara T, Nakajima Y, Kim C, Kobayashi N, Kadotani H, *et al.* Comparison of continuous brachial plexus infusion of butorphanol, mepivacaine and mepivacaine-butorphanol mixtures for postoperative analgesia. Br J Anaesth 1995;75:548-51
[74] Wajima Z, Shitara T, Nakajima Y, Kim C, Kobayashi N, Kadotani H et al. Continuous brachial plexus

infusion of butorphanol mepivacaine mixtures for analgesia after upper extremity surgery. Br J Anaesth 1997; 78: 83-85

[75] Dhimar AA, Patel MG, Swadia VN, Desai DJ. Epidural butorphanol: Comparison of two different doses for lower limb orthopedic surgery. J Anaesth Clin Pharmacol 2006;22:47-52.

[76] Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. Br J Anaesth. 2003;91:536–54053.

[77] Chakraborty S, Chakrabarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. Indian J Pharmacol. 2008;40:180–18254.

[78] Parthasarathy S, Ravishankar M. Single dose intrathecal tramadol in the management of post appendicectomy pain. J Anaesthesiol Clin Pharmacol. 2002;18:419–42255.

[79] Jung JI, Kang PS. The effect of intrathecal tramadol and clonidine on saddle block with heavy bupivacaine. Korean J Anesthesiol. 1999;37:227–232]

[80] Mostafa MG, Mohamad MF, Farrag WSH. Which has greater analgesic effect: intrathecal nalbuphine or intrathecal tramadol? J Am Sci. 2011;7:480–484. 57. Subedi A, Biswas BK, Tripathi M, Bhattarai BK, Pokharel K. Analgesic effects of intrathecal tramadol in patients undergoing caesarean section: a randomised, double-blind study. Int J Obstet Anesth. 2013;22:316–321.

[81] Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia. Can J Anaesth. 1993;40:308–313.

[82] Prakash S, Tyagi R, Gogia AR, Singh R, Prakash S. Efficacy of three doses of tramadol with bupivacaine for caudal analgesia in paediatric inguinal herniotomy. Br J Anaesth. 2006;97:385–388.

[83] Chrubasik J, Warth L, Wust H, Zindler M. Analgesic potency of epidural tramadol after abdominal surgery. Pain. 1987;30(Suppl 4):S154.

[84] Gunduz M, Ozcengiz D, Ozbek H, Isik G. A comparison of single dose caudal tramadol, tramadol plus bupivacaine and bupivacaine administration for postoperative analgesia in children. Paediatr Anaesth. 2001;11:323–326.

[85] Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. Anaesthesia. 1993;48:328–331.

[86] Singh AP, Singh D, Singh Y, Jain G. Postoperative analgesic efficacy of epidural tramadol as adjutant to ropivacaine in adult upper abdominal surgeries. Anesth Essays Res. 2015;9:369–373.