Chapter 4

Spinal Additives in Subarachnoid Anaesthesia for Cesarean Section

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Additional information is available at the end of the chapter

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1. Introduction

Cesarean section is among the most commonly performed surgeries in women and neuroaxial anaesthesia is the technique of choice for this procedure. Although numerous side effects related to obstetric anaesthesia had been described, [1, 2, 3, 4] subarachnoid anaesthesia has a clear tendency to be used more often than epidural and combined spinal-epidural technique. It is safe, easy to perform, effective, low failure rate, no systemic local anaesthetic toxicity, inexpensive, prevents aspiration pneumonia, and has a high rate of maternal satisfaction. [5, 6, 7] Produces a deep anaesthesia, inhibits the stress response to surgery, blunts the autonomic and somatic responses to pain, and facilitate breathing, coughing, sighing and early ambulation [8, 9] Finally, efferent sympathetic blockade results in increased blood flow to the blocked area resulting in better wound healing. It also reduces the risk of deep vein thrombosis and thromboembolism.

The main limitations of spinal anaesthesia are its short duration of action and do not provide prolonged postoperative analgesia when it is performed only with local anaesthetics. Adding adjuvants drugs to intrathecal local anaesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. It is also possible to reduce dose of local anaesthetics, as well as total amount of systemic postoperative analgesics. Several spinal adjuvants have been used to improve spinal anaesthesia quality and to prolong postsurgical analgesia. Intrathecal opioids are the most commonly utilized; fentanyl and sufentanil improve neuroaxial anaesthesia, decrease trans operative pain and moderately prolong sensory block, while morphine prolongs postoperative analgesia. Alpha2 adrenergic agonists clonidine and dexmedetomidine shorten onset of action, and prolong duration of spinal anaesthesia.

Ketamine, midazolam, neostigmine, magnesium sulphate and others spinal drugs are still under investigation.

This chapter is an up to date of spinal additives currently used to enhance subarachnoid anaesthesia for cesarean section and to produce subarachnoid postcesarean analgesia.

2. Spinal additives drugs for cesarean delivery

The use of subarachnoid additives in spinal anaesthesia for cesarean section has two main objectives: to enhance spinal block and to produce effective and prolonged postoperative analgesia. Reducing the dose of local anaesthetics used in spinal anaesthesia can decrease some of the side effects such as maternal hypotension, high spinal block, and prolonged motor block. By inducing better analgesia after cesarean section with intrathecal additives, the recently given birth mother is better able to take care of her newborn, which immediately improves mother-baby relationship, decreases prelacteal feeds (feeding any other substance before first breastfeeding), which is closely related to urban residency, first-time motherhood, and cesarean delivery. Prelacteal feed has been reported as high as 26.5%. It has several harmful effects on the mother-newborn binomia. [10, 11] Immediate proper breast feeding even favor neonatal analgesia for minimum invasive procedures like heel prick. [12]

Postoperative pain after cesarean section is common and more intense compared to postvaginal delivery pain. [13] When this kind of pain is not prevented nor treated properly, it can evolve to chronic pain which means a serious health problem. [14] Therefore, intrathecal adjuvants play an important role not only in maternal analgesia, but in the future of the newborn.

There are several adjuvant drugs used to enhance spinal anaesthesia; morphine is the most frequently used and also many other opioid agonists such fentanyl, sufentanyl, hydromorphone, diamorphine, and meperidine have been well studied and are part of our daily armamentarium in this clinical scenario, as are some non-opioid drugs such clonidine. There is a heterogeneous group including midazolam, neostigmine, magnesium, that needs more research before they can be part of daily use as intrathecal adjuvants for C-section anaesthesia.

Table 1 summarizes the most commonly used spinal additives and some drugs under clinical research in parturients undergoing cesarean delivery with spinal anaesthesia.

3. Spinal opioids

Opioids are the most commonly used analgesics to treat perioperative pain. Since the isolation of morphine in 1804 by Friedrich Sertürner, a pharmacist´s apprentice in Germany, morphine became widely used after 1815. Since then, a large number of opioids have been developed modifying the 4, 5-epoxymorphinan ring structure. Opioids have a narrow therapeutic index

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with a large inter patient analgesic response variability; from poor analgesia to dangerous side effects.

Morphine was the first spinal drug used to relieve pain, [15] Pert and Snyder [16] discovered the opioid receptors in 1973, and three years after Yaskh and Rudy working at Yale published their famous article entitled *Analgesia mediated by a direct spinal action of narcotics*, [17] which encouraged animal and clinical research for the use of opioids and other neuroaxial additives.

Intrathecal opioids bind to opioid receptors localized in laminae I and II at the spinal dorsal horn reducing nociceptive transmission. Opioids with high lipid solubility and low pKa results in a extremely potent analgesic effect, rapid onset and short duration of action, conversely opioids with diminished lipophilicity such is morphine, have a slow onset and prolonged analgesia. Pharmacokinetically, subarachnoid injection of opioids follows a complex multi compartmental model influenced by opioid properties and cerebro spinal fluid (CSF) dynamics. From the lumbar CSF they move inside the spinal cord binding dorsal horn opiate receptors and also enter the bloodstream through the posterior radicular artery. Spinal opioids also penetrate the dura mater into the epidural cavity and hence can reach the venous plexus of Baston and reach the systemic circulation. They can also move in a cephalad-caudal direction as a drug bulk flow. [18] This rostral migration is probably the most important factor to explain the side effects of opioids, especially deleterious properties of morphine. There are other possible sites where spinal opioids act to produce local anaesthetic effects blocking nerve conduction, [19] or by reducing the release of GABA and glycine by a calcium independent process from dorsal horn neurons. [20]

After local anaesthetics, opioids are the most commonly used drugs by this route providing segmental analgesia. Clinicians have used them for more than 30 years in anaesthesia, for acute pain, postoperative analgesia, and to treat cancer pain. [21, 22] Although spinal opioids are used frequently, there are many unresolved disputes on the neurotoxicity of opioids injected into the subarachnoid space. [23, 24, 25, 26]

In obstetrics patients, neuroaxial opioids use is a significant therapy for labour pain, in cesarean section anaesthesia, and for postoperative pain. A very small dose of almost any opioid delivered into the lumbar spinal space provides significant pain relief with virtually no risk to mother or the fetus-neonate.

Morphine. It is the basic reference opioid to which all analgesics of its kind are compared. It is a phenanthrene derivative, the prototypical agonist opiate at mu and kappa opioid receptors. Has a benzene ring with a phenolic hydroxyl group at position 3 and an alcohol hydroxyl group at position 6 and at the nitrogen atom. Its chemical formula is $C_{17}H_{19}NO_3$. This opioid can be administered by mouth, intravenously, intramuscular, subcutaneously, rectally, intranasal, and through the neuraxial route. Has a significant amount first-pass liver metabolism and about 40 to 50% of the absorbed morphine reach the central nervous system. Most morphine is eliminated by the kidneys. Its poor lipid solubility-a physical characteristic that favors its behavior when injected into the intrathecal space-producing slow analgesic onset with long duration and rostral migration that facilitates some of its side effects such as pruritus, emesis, hypothermia, and respiratory depression. [27, 28]

Although there are places where spinal opioids in obstetrics are not routinely used, [29] at present time, neuraxial morphine is considered as the gold standard to treat pain after C-section and has become a conventional practice in many countries. It is mentioned in textbooks on obstetric and neuroaxial anesthesia [30, 31, 32] as a conventional method. Most authors have reported that 100 to 200 μg of spinal morphine plus regular or low doses of a PPX local anaesthetic or lidocaine are enough to provide an excellent block, high quality postcesarean analgesia, decreased needs of rescue postoperative analgesics, with few side effects. [33-37]

Weigl and coworkers [38] compared intrathecal morphine 100 μg versus spinal fentanyl 25 μg added to 0.5% hyperbaric bupivacaine 7.5 to 15 mg in 60 parturients. Intrathecal morphine drastically prolonged the time for first rescue analgesic, and also reduce postoperative meperidine [47 mg versus 130 mg) when compared to fentanyl. Itch was more often observed in patients treated whit morphine. There was no significant difference in the incidence of postoperative nausea and vomiting between both groups. There were few patients in the morphine group who required additional intravenous opioids during surgery. Bejar et al from Argentina [39] demonstrated that intrathecal morphine 100 μg were better than systemic morphine, although the former had more incidence of itching. In a Brazilian study [40] the authors found that 50 μg of intrathecal morphine produced equal analgesia after cesarean section as 100 μg, but with less incidence of pruritus. Cortes-Blanco et al from México [36], compared morphine 100 μg versus 200 μg added to intrathecal ropivacaine 15 mg in 80 women undergoing cesarean delivery. The analgesic effect lasted 24 to 30 hours, with a low need of postoperative rescue analgesic; ketorolac was used in equal dose in both groups ($p>0.05$]. However side effects were more frequent in those women receiving morphine 200 μg: pruritus 30% versus 55%, nausea 10% versus 30%, and vomiting 5% versus 12.5%. The authors recommended 100 μg as the ideal dose in Mexican parturients undergoing C-section.

Morphine can be coadministered with sufentanil. Draisci et al [41] compared spinal administration of morphine 150 μg plus sufentanil 5 μg versus spinal sufentanil 5 μg plus a single subcutaneous morphine 10 mg in 64 pregnant women undergoing elective cesarean under spinal anaesthesia with hyperbaric bupivacaine 10 mg. Both groups received 1 g acetaminophen every 6 hours and intravenous tramadol was used if VAS was superior to 4. Coadministration of two opioids resulted in prolonged analgesia, less need of tramadol, and less incidence of nausea and no difference in pruritus incidence. Using a combination of spinal morphine 100 μg plus sufentanil 2.5 μg, Bouvet et al [42] determined that the ED_{50} and ED_{95} of intrathecal levobupivacaine is 12.9 mg. For less levobupivacaine dose, the authors recommended to use spinal-epidural combined technique for C-section anaesthesia.

Notwithstanding the multiple investigations to determine the ideal dose, a recent study questioned the best dose of intrathecal morphine for postcesarean analgesia. Wong and coworkers [43] compared the most used doses; 100 versus 200 μg and concluded that the higher dose produce better analgesia but with more nausea, so morphine dosing has to be based on patient preference for analgesia versus emesis.

Recently, in order to avoid spinal morphine side effects, some authors compared ultrasound guided tranversus abdominis plane block versus intrathecal morphine; although ultrasound-guided transversus abdominis plane block is an effective method to supply pain relief after

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cesarean delivery, 100 μg and 200 μg subarachnoid morphine provided superior analgesia, but emesis and itching were more frequent. This block could be a reasonable alternative when morphine cannot be used. [44, 45]

Hydromorphone. Also known as dihydromorphinone, is a semi-synthetic opioid widely used to treat pain. It is 5 to 11.1 times more potent than morphine, highly soluble in water, with intermediate lipid solubility. The chemical name is 4, 5α-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride, with a molecular formula $C_{17}H_{19}NO_3$ and molecular weight 285.33766. Has a similar pharmacokinetics and duration of action than morphine, is extensively metabolized by the liver to hydromorphone-3-glucoronide with no analgesic effects, 62% of the oral dose is eliminated by this gland on the first pass. Hydromorphone cross the blood brain barrier and reach concentrations in the CNS faster than morphine. Is better tolerated in patients with kidney failure due to a lack of an active metabolite, but its half life can increase to as much as 40 hours. [28, 46]

In a retrospective research, Rauch [47] found that 100 μg of spinal hydromorphone produced a comparable onset of pain relief to 25 μg of subarachnoid fentanyl, with a prolonged analgesia ($p<.001$] and proposed this opioid as a substitute of intrathecal morphine. Beatty et al [48] compared intrathecal hydromorphone 40 μg versus intrathecal morphine 100 μg in 114 parturients undergoing cesarean section. They found no statistical differences regarding opioid related side effects, rescue analgesics needs or postoperative pain intensity during the first 24 hours. In non obstetric patients [49] nausea is related significantly in a dose-dependent manner. In patients with known allergy to intrathecal morphine, hydromorphone can be used spinally with better analgesic results. [50]

Diamorphine. Also known as heroin, is an pure agonist opioid analgesic 1.5 to 2 times more potent than morphine. In 1874 Charles Write boiled morphine and created heroin. Its chemical name is 4, 5-Epoxy-17-methylmorphinan-3, 6-diyldiacetate hydrochloride monohydrate or [5α, 6α)-7, 8-Didehydro-4, 5-epoxy-17-methylmorphinan-3, 6-diol diacetate (ester), with a molecular formula $C_{21}H_{23}NO_5$. After oral ingest, diamorphine undergoes extensive liver first pass metabolism via deacetylation, transforming into a 6-monoacetylmorphine and morphine. Injected diamorphine, promptly cross the blood-brain barrier and is transformed into morphine by deacetylation, acting over the μ opioid receptors. This opioid can be given by the same routes as morphine in approximately half dose. Its high liposolubility [200 times more liposoluble than morphine) is against rostral migration, consequently reduces the possibility of side effects due to its action on the CNS, especially late respiratory depression. Diamorphine is associated with more euphoria than morphine. [51, 52] This opioid is used for the treatment of pain; severe physical trauma, myocardial infarction, post-surgical pain, and chronic pain, including end-stage cancer and other painful terminal illnesses. Although diamorphine is used for the cure of pain, it is also used illegally by addicts. [51]

Diamorphine had been used neuroaxialy for intraoperative and postcesarean analgesia. Epidural 5 mg produces similar analgesia to 250 μg injected into the subarachnoid space, but with less emesis. [52] Equal doses of diamorphine and intrathecal morphine produce similar postcesarean analgesia but the former has lower frequency and intensity of emesis and pruritus, which is attributed to its greater lipophilicity. [53] Most studies have compared

intrathecal doses from 125 up to 375 μg, with similar analgesic results, but a wide outcome regarding incidence of pruritus, nausea and vomit. [54] In a double blind randomized controlled investigation Wrench and coworkers [55] compared spinal diamorphine 0, 100, 200, and 300 μg added to spinal block and systemic diclofenac-paracetamol plus subcutaneous diamorphine for breakthrough pain. They found that 300 μg resulted in better analgesia, but a dose related increase in the incidence of pruritus. In this study, nausea and vomit did not have a dose dependent effect. Spinal diamorphine 300 μg was comparable to intrathecal fentanyl 20 μg regarding needs of intraoperative analgesics supplementation, but the former opioid produced longer postoperative analgesia. [56] Diamorphine 250 μg combined with fentanyl 15 μg as additive to spinal bupivacaine were not superior to diamorphine alone. [57] Sarvan et al [58] found in 200 cesarean done under spinal anaesthesia with 12.5 mg hyperbaric bupivacaine that the ED [95] of 400 μg subarachnoid diamorphine is needed to prevent intraoperative analgesic supplementation. This high dose increased time for first request postoperative analgesic, but also augmented the incidence of nausea, vomiting and pruritus. The addition of intrathecal diamorphine does not appear to influence block height. [60]

Fentanyl. Is the oldest synthetic piperidine opioid agonist, 100 to 80 times more potent than morphine, chemically identified as N-[1-phenethyl-4-piperidyl) propionanilide citrate [1:1] with a molecular weight of 528.60. The empirical formula is $C_{22}H_{28}N_2O \bullet C_6H_8O_7$. The pharmacokinetics of fentanyl can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg. It is primarily transformed in the liver, demonstrates a high first pass clearance and releases approximately 75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. It has a rapid onset of action when the drug is given intravenously or intrathecally. Fentanyl has less emetic activity than either morphine or petidine. [27, 28, 30, 32]

After intrathecal morphine, fentanyl is probably the most widely used opioid in patients undergoing cesarean section; improves quality of spinal anaesthesia, reduces dose of local anaesthetics, but has little impact on prolonging postoperative analgesia. [60, 61, 62] Most used doses of intrathecal fentanyl range from 15 to 25 μg, although this opioid had been investigated in a wide range as of 2.5 up to 50 μg for cesarean delivery. It can be safely mixed with lidocaine, bupivacaine, levobupivacaine, ropivacaine, or mepivacaine. [63, 64, 65, 66] The first study using intrathecal fentanyl was done by Hunt at [67] from Brigham and Women´s Hospital in Boston USA; they evaluated 0, 2.5, 5, 6.25, 12.5, 25, 37.5 and 50 μg of fentanyl added to spinal hyperbaric bupivacaine 0.75% in 56 parturients undergoing cesarean delivery. Sixty seven percent of patients in the control group needed supplemental intraoperative opioids. None of the parturients who received more than 6.5 μg fentanyl required transoperative opioids. Time for first analgesic request was 33.7±30.8 min (mean±SD) in the control group and increased to 130±30 min ($p<0.05$] in those women treated with 6.25 μg fentanyl. Duration of effective analgesia was significantly longer in this group 192±74.9 min versus 71.8±43.2 min ($p<0.05$]. Bigger doses had no effect on effective analgesia. Itching was increased with 25 and 50 μg. There were no side effects in the neonates. They concluded that the optimal dose of spinal fentanyl is 6.5 μg. Most authors reported that higher doses from 12.5 to 25 μg [68, 69] are safe

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and enhance spinal blockade, trans cesarean analgesia and immediate postsurgical analgesia, without increasing side effects.

The optimal dose of 12 mg 0.5% hyperbaric bupivacaine for C-section was reduced to 8 mg adding 10 μg of spinal fentanyl. [71] The addition of fentanyl 20 μg to 10 mg hyperbaric bupivacaine 0.5% did not alter significantly spirometric parameters in 40 parturients after cesarean delivery compared with bupivacaine alone. [72]

In summary, the addition of intrathecal fentanyl to local anaesthetics used in cesarean section reduces the need for intraoperative analgesics, improves postoperative analgesia for a brief period of time of 2-4 hours, has no effect on the subsequent analgesic doses. The aforementioned doses are very safe for the mother and newborn, and its side effects are minimal.

Sufentanil citrate. Synthesized in mid-1970s, was introduced into clinical practice 10 years later. Sufentanil is a potent pure agonist opioid, 6-10 times more potent than fentanyl, chemically designated as N-{4-(Methoxymethyl)-1-[2-[2-thienyl)ethyl]-4-piperidinyl}-N-phenylpropanamide, with a molecular weight of 578.68. The molecular formula is $C_{22}H_{30}N_2O_2S$. [73, 74]

This opioid is a fundamental part of daily anaesthesia armamentarium. As spinal additive for cesarean section, sufentanil had been used in doses ranging from 1.5 to 20 μg. The initial clinical research by Courtney et al [75] compared 0, 10, 15 and 20 μg as spinal adjuvant to 0.75% hyperbaric bupivacaine 10.5 mg in 37 women undergoing elective cesarean delivery. Analgesia was prolonged significantly in all patients treated with sufentanil, but pruritus incidence was notably increased. Apgar score and Early Neonatal Neurobehavioral Scale were within normal limits. The most recommended dosages range from 2.5 to 5 μg improving spinal anaesthesia and postoperative analgesia, with mild side effects. [28, 76, 77, 78, 79] Braga and coworkers [78] compared sufentanil 0, 2.5, 5 and 7.5 μg added to spinal hyperbaric bupivacaine 12.5 mg. Onset block was significantly shorter in women treated with the opioid and postoperative analgesia was longer in patients receiving 5 and 7.5 μg sufentanil. Those women who received higher doses had more incidences of sedation and pruritus. A prospective, randomized, double-blind, controlled trial [79] found that smaller doses also produced excellent operative analgesia and prolonged postcesarean analgesia; the authors compared 0, 1.5, 2.5 and 5 μg sufentanil added to hyperbaric bupivacaine 0.5% 12.5 mg in 100 pregnant women undergoing elective C-section. Women treated with the opioid had no operative pain, postoperative analgesia was prolonged and rescue analgesic was similar in those women treated with sufentanil. Itch was more frequent in the 2.5 and 5 μg sufentanil groups than in placebo or 1.5 μg sufentanil. There were no differences in the newborn evaluation. Bang et al [80] compared a placebo group versus 2.5 versus 5 μg sufentanil added to spinal hyperbaric bupivacaine and reported no significant differences among the 3 groups regarding the maximum sensory levels and motor block. Patients receiving 5 μg sufentanil had slower recovery of the sensory block. Intrathecal sufentanil enhanced intraoperative analgesia, muscle relaxation and duration of effective analgesia in a dose related response. Occurrence of hypotension, sedation, and itching were also opiate dose related. The addition of 2.5 μg sufentanil to 0.5% levobupivacaine produced faster onset time for sensory and motor block than levobupivacaine alone. It also prolonged postoperative analgesia and reduced analgesic needs. These results were similar to the addition of intrathecal 10 μg fentanyl. [81] Sufentanil 5 μg added to spinal local anaesthetics

produce similar results as spinal morphine 200 μg regarding anaesthesia quality, operative analgesia, incidence of maternal emesis as well as newborn safety, but morphine postoperative analgesia was longer 19.5± 4.7 hours versus 6.3±5.2 hours p< 0.05]. [28, 82]

Adding 5 μg sufentanil to ropivacaine appears to be optimal, as it increases the efficacy of spinal analgesia without increasing the incidence of side effects, and ropivacaine dose can be reduced up to 28% of ED50 for C-section. [83, 84, 85] Mixing 5 or 10 μg sufentanil with 75 mg lidocaine 5% in parturients undergoing cesarean delivery prolonged spinal anaesthesia compared to placebo, but also produced mild to moderate respiratory depression, which was more important with 10 μg 46.7% (p<0.001]. [86]

Several authors had compared fentanyl versus equianalgesic doses of intrathecal sufentanil administered concurrently with hyperbaric bupivacaine 0.5% for cesarean delivery; both opioids abolished intraoperative opioid requirements, and discreetly prolonged postcesarean analgesia although sufentanil produced more prolonged analgesia without significative side effects on the parturient and neonate. [87, 88, 89]. Bremerich et al [90] reported that the association of sufentanil-levobupivacaine was better than fentanyl added to intrathecal bupivacaine o levobupivacaine. A study from Brasil [91] showed that intrathecal sufentanil 2.5 μg combined with morphine 80 μg during anaesthesia with hyperbaric bupivacaine decreased significantly the immediate incidence of postcesarean shivering from 62.5% to 32.5% (p<0.007].

*Meperidine (Pethidine).*Meperidine is a synthetic opioid agent, and is the only opioid that has significant local anaesthetic activity in the dose range normally used for analgesia. Was synthesized in 1939 as an anticholinergic agent, but was soon discovered to have analgesic properties. It belongs to the phenylpiperidine family; it is ethyl 1-methyl-4-phenylisonipecotate hydrochloride, readily soluble in water. Molecular formula is $C_{15}H_{21}NO_{2,}$ and has a molecular weight 247.33274. Meperidine is quickly hydrolyzed in the liver to petidinic acid, and is also demethylated to norpetidine, a neurotoxic metabolite. Meperidine metabolites are further conjugated with glucoronic acid and excreted into the urine. [28, 30, 92, 93].

There are reports using intratecal meperidine mixed with local anaesthetics in several clinical settings; in obstetric patients, meperidine has been used as spinal adjuvant, as a single agent for epidural or subarachnoid for labor pain, and also for anaesthesia-analgesia in cesarean delivery. As spinal sole drug for cesarean section, meperidine had been uses with good results. [94, 95, 96]. Cheun and Kim [96] studied 182 parturients undergoing cesarean delivery; they used meperidine 50 mg combined with 10% dextrose 0.5 mL injected in the lumbar spinal space achieving sensory and motor blockade in all patients, prolonged analgesia [453±158.1 min) and motor recovery [75.9±17.2 min). Side effects were minimum and included nausea, hypotension and pruritus. Eighteen patients had mild pain at the end of surgery. There were no side effects on the newborns.

Yu and coworkers [97] compared meperidine 10 mg plus intrathecal 0.5% hyperbaric bupivacaine 10 mg versus hyperbaric bupivacaine alone. They found prolonged postcesarean analgesia (mean 234 min, 95% confidence interval 200-269 min) versus control group (mean 125 min, 95% confidence interval 111-138 min; p<0.001]. Woman receiving meperidine had

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more incidence of intraoperative emesis [11 versus 3; p=0.02]. Reducing meperidine dose to 7.5 mg also produces similar results, enhancing local anaesthetics spinal block and prolonging postcesarean analgesia. [98, 99] Meperidine is a good substitute in patients with allergy to local anaesthetics. [100, 101]

Nalbuphine. Is a synthetic agonist-antagonist opioid belonging to the phenanthrene group. Chemically is 17-(cyclobutylmethy1]-4, 5a-epoxymorphinan-36a, 14-triol hydrochloride, molecular weight 393.91, soluble in water [35.5 mg/mL at 25°C) and ethanol [0.8%), Pka 8.71 and 9.96. The molecular formula is $C_{21}H_{27}NO_4$ HCl. It is structurally related to naloxone, an antagonist of the opiate receptors, and to oxymorphone, an analgesic agonist of the opiate receptors. It has an elimination half-life (t1/20] of about 5 hours in normal people. Because nalbuphine is mainly eliminated from the body by biotransformation, nalbuphine undergoes an extensive first-pass metabolism. [102, 103]

Rawal and coworkers studied several spinal opioids in sheep, including nalbuphine; [104] although spinal nalbuphine was not the less neurotoxic, the authors found that this opioid was associated with relative minor behavioral and EEG changes, sedation, spinal cord mild inflammatory and neuronal changes. Following intrathecal nalbuphine, the above-mentioned changes were similar to those seen in control animals. One animal developed motor impairment during 60 minutes. The analgesic effect of spinal nalbuphine can be reverted by naloxone. [105] To date, no clinical reports of this opioid have mentioned secondary neurological damage, although this observation has not enough clinical evidence. There is little clinical research with this opioid injected intrathecally. Nalbuphine been used as additive for spinal anaesthesia in several clinical settings in doses from 200 to 1600 μg. [106, 107, 108]

The first study with intrathecal nalbuphine in obstetric patients was conducted by Culebras et al; [109] in a double blind study they injected nalbuphine 200, 800, 1600 μg mixed with hyperbaric 0.5% bupivacaine versus morphine 200 μg with bupivacaine in 90 parturients undergoing cesarean delivery. Only women receiving morphine and nalbuphine 200 μg reported transoperative pain. In the nalbuphine groups, postoperative analgesia lasted longest with the 0.8 mg dose, but postoperative analgesia was significantly prolonged in the morphine group (p<0.0001]. Itching incidence was superior with spinal morphine as well as postcesarean nausea and vomiting. There was no maternal or newborn respiratory depression. Culebra´s article was accompanied by an editorial written by Yaksh; [110] most of his commentaries were regarding the lack of solid evidence about the neurotoxicity of nalbuphine and emphasized that benefits does not outweigh the risks to use this the opioid by the spinal route.

Yoon et al [111] found that an intrathecal mixture of nalbuphine 1000 μg, morphine 100 μg and hyperbaric 0.5% bupivacaine 10 mg for cesarean delivery strengthen intraoperative analgesia compared with morphine alone, but this combination reduce postcesarean duration of complete analgesia and had no effect on the incidence of itch. In a recent randomized, double blind article using intrathecal nalbuphine for postcaesarean analgesia there were no differences between nalbuphine 800 μg versus 25 μg fentanyl associated with hyperbaric 0.5% bupivacaine 10 mg; both opioids produce transoperative analgesia and early postoperative analgesia. [112]

4. Spinal opioids side effects

As described in the preceding paragraphs, intrathecal opioids as adjuncts to local anaesthetics are very safe in spinal anaesthesia for cesarean section, although may have sporadic potentially life-threatening events. There is variety of side effects which are worth to be discussed briefly. These side effects are due to different factors such as pharmacological and pharmacodynamic characteristics of each opioid, the injected dose, and type of patient. Opioids with high liposolubility have less risk of rostral migration and lower incidence of CNS side effects. Larger doses will have higher incidence and severity of CNS deleterious effects.

Respiratory depression is a deleterious side effect which may have serious consequences like respiratory arrest and even death. Fortunately, it is a very rare event. This complication can occurs as quickly as 15 to 20 minutes after injection of lipophilic opioids, but with water soluble opioids the event is late. [113, 114, 115] Morphine intrathecal doses higher than 300 μg are associated with more episodes of respiratory depression. [116] It is mandatory to closely monitor all patients receiving neuroaxial opioids. Besides clinical surveillance, pulse oximetry monitors are used by most clinicians, although the use of transcutaneous carbon dioxide monitor has been recommended recently. [117] It is prudent to give prophylactic nasal oxygen. When respiratory depression is detected, it should be managed with intravenous naloxone. Also intravenous nalbuphine has been used with excellent results. On rare occasions it is necessary to use ventilatory support with endotracheal intubation.

Emesis and pruritus are the most frequent side effects. Nausea and vomiting are similar, but pruritus increased in direct proportion to the dose of intrathecal morphine (linear regression, p=0.0001]. Although emesis due to spinal morphine do not interfere with early feeding after surgical delivery, [118] it is an unpleasant nuisance that can be prevented by various drugs administered immediately after the umbilical cord is ligated; ondansetron 4-8 mg, ganisetron 3 mg, tropisetron 5, droperidol 1.25 mg, dexamethasone 4-8 mg and diphenydramine 30 mg. [119, 120] Metoclopramide 10 mg does not appear to be effective for emesis prophylaxis in this patient population. Serotonin [5-HT3] receptors antagonists had poor effect preventing itching, while the prophylactic or therapeutic administration of droperidol 1.25. mg, nalbuphine 5-10 mg, pèntazocine 15 mg, butorphanol 1 mg followed by intravenous infusion of 0.2 mg/h. [121, 122, 123]

Severe postoperative hypothermia has been described in a variety of surgical procedures, including cesarean section done under epidural or spinal therapeutic doses of morphine. The mechanism is not well known but it is said that could be mediated by morphine cephalad spinal spread reaching opioid receptors and altering the temperature set point in the hypothalamus. It can be treated effectively with naloxone or lorazepam. [124-129]

5. Non opioids spinal additives

As we reviewed, spinal opioids side effect profiles may have some limitation to be used as adjuvants in cesarean delivery; pruritus, nausea, vomiting, and urinary retention are non fatal

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deleterious side effects but bother most patients. Late respiratory arrest and hypothermia after usual opioid doses has been seldom reported in the literature. There are several non-opioide adjuvants that have been studied for the purpose to enhance spinal anaesthesia and to prolong and augment postcesarean analgesia [130], being alpha2 agonists the most promising agents. [131, 132] Spinal adjuvants like magnesium, ketamine, neostigmine are mostly used for clinical research, and nowadays is no prudent to recommend these drugs as a routine practice. *Clonidine.* Eisenach et al demonstrated that epidural/spinal clonidine did not affect sheep fetus, but fetal bradycardia may limit the efficacy of spinal clonidine if used more than 10 μg/kg in obstetrics. [133, 134] Many clinical studies have been done using neuroaxial clonidine mixed with local anaesthetics and/or opioids, and as solo drug in obstetrics patients. Low doses of spinal clonidine in subarachnoid anaesthesia for cesarean delivery are reported to enhance the anaesthetic block, to reduce dose of local anaesthetics, and to extend postoperative analgesia. There are studies mixing clonidine with intrathecal opioids, as there is a synergic effect.

In a double blind study Filos et al [135] carried out their investigation to evaluate the analgesic effect of sole clonidine in women undergoing elective cesarean delivery, 150 μg were injected 45 minutes after general anaesthesia and compared to intrathecal saline as control group. Pain intensity was lower in clonidine treated parturients 20 to 120 minutes after spinal injection ($p<0.05$], request for first analgesic was also longer in the clonidine group 414±128 minutes versus 181±169 minutes ($p<0.01$]. Clonidine side effects were severe; hypotension with a maximal reduction of systolic [15±9%), diastolic [22±12%) and mean arterial pressure [18±12%). Sedation was significantly more intense compared to saline ($p<0.05$]; also dried mouth was more commonly ($p<0.01$]. Although these data suggest that 150 μg subarachnoid clonidine is effective to treat acute pain after cesarean section, it has side effects such as hypotension, sedation, and dryness of mouth. Two years later, the same authors [136] performed a different study comparing 150, 350 and 450 μg of spinal clonidine to evaluate the dose-response hemodynamic and analgesic responses in the immediate postoperative period of cesarean section under general anaesthesia. They found less pain in all groups in a dose dependent mode: request for first analgesic 402±75 min, 570±76 min, and 864±80 minutes respectively ($p<0.01$-0.001]. Clonidine reduced mean arterial pressure compared with baseline only in those patients treated with 150 μg [21±13%, $p<0.05$]. Sedation was evident in all groups. Respiratory rate and motor activity of the lower extremities were unaffected in all three groups. The hemodynamic stability after 300 and 450 μg suggested a pressor consequence at peripheral sites. This investigation demonstrated a dose related analgesia after spinal clonidine at doses as great as 450 μg. Studies with lower doses of clonidine has shown satisfactory results. Peach et al [137] in a randomized, double blind trial compared intrathecal clonidine mixed with fentanyl 15 μg and morphine μg versus clonidine plus morphine in 240 women undergoing cesarean delivery with hyperbaric 0.5% bupivacaine. Using a dose finding analysis the authors found similar comparable postoperative efficacy and side effects for groups receiving morphine 100 μg with clonidine 60, 90, or 150 μg and concluded that a multimodal approach for postcesarean analgesia, using subarachnoid bupivacaine, fentanyl, morphine 100 μg, and clonidine 60 μg, improves pain relief compared with morphine 100 μg or clonidine 150 μg alone, but increases intraoperative sedation and may increase perioperative vomiting. Other

investigators have found that clonidine 75 μg is a safe dose; prolong the anesthetic block and enhance postoperative analgesia, with minimal side effects and no harm to the newborn [132, 138, 139] Van Tuijl et al [140] compared 15 μg, 30 μg and 60 μg of clonidine added to hyperbaric bupivacaine 0.5%; the authors found a dose dependent variability of analgesia duration and sedation. Duration of analgesia was significantly higher in those patients who received clonidine 60 μg as compared to the other two groups [598.7±140.47 versus 436.65±149.84 and 387.1±97.05 min respectively). Sedation was also more in the highest dose. In this study the authors recommended 15 μg and 30 μg doses due to good postoperative analgesia and less sedation.

It has been mentioned that mixture of hyperbaric local anaesthetics with clonidine should not be done in one syringe before injection into the subarachnoid space, but to inject each drug in separate syringes in order to avoid syringe interactions, in particular changes in the density of local anaesthetics. Sachan et al [141] studied the differences between hyperbaric bupivacaine mixed with clonidine in the same syringe just prior to subarachnoid injection versus separate administration in 60 parturient undergoing cesarean deliveries. Those women who received clonidine 75 μg plus hyperbaric bupivacaine 0.5% 10 mg contained in one syringe had shorter analgesia time [337±18.22 min) versus those patients receiving same drugs but applied in separated syringes [474.33±20.79 min), p=0.000. Moreover, time to reach highest sensory level and complete motor block was significantly less, without any major haemodynamic instability in those women injected in a sequentially manner. As a single drug, subarachnoid clonidine is not recommended for anaesthesia neither for postcaesarean analgesia.

Should we administer intrathecal clonidine in obstetric patients? Under the results of clinical investigations done by many authors in different countries, intrathecal clonidine is a safe drug in obstetric patients when recommended doses are observed, but more clinical studies are needed to adequately respond to this question. [131] Moreover, we have to keep in mind that the FDA maintains its recommendation not to use epidural clonidine in obstetrics. This organization does not mention the use of intrathecal clonidine in this clinical scenario. For more information about intrathecal clonidine please read the chapter entitled *Intrathecal clonidine as spinal anaesthesia adjuvant. Is there a magical dose?* included in this book.

Midazolam. A water soluble imidazobenzodiazepine, highly liposoluble in vivo, with a rapid onset of action and high metabolic clearance. Chemically is 8-chloro-6-[2-fluorophenyl)-1-methyl-4*H*-imidazo [1, 5-a] [1, 4] benzodiazepine hydrochloride, and the molecular formula $C_{18}H_{13}ClFN_3 \bullet HCl$, with a molecular weight of 362.25. [142] For an extended information on midazolam, we refer you to the chapter included in this book entitled *Midazolam in spinal anaesthesia: intrathecal or intravenous?* written by Beyazit Zencirci.

A preservative free midazolam administered by continuous intrathecal infusion to sheep and pigs in doses from 5 to 15 mg/day during 43 days demonstrated that behavior, neurological function, and vital signs were normal. There were no data of neurological damage, except mild inflammation surrounding the catheter tract that was also observed in animals treated with placebo. [143] There are few articles using intrathecal midazolam for cesarean section. In a prospective, randomized, double-blind, placebo controlled study [144] the authors compared

1 and 2 mg of midazolam added to subarachnoid bupivacaine 10 mg versus plain bupivacaine. Request for first analgesic was 4.3±0.7 versus 6.1±1.0 versus 3.8±0.5 hours, respectively. Supplemental diclofenac were significantly less in those women treated with midazolam 2 mg [93±29 mg) compared with midazolam 1 mg [148±16 mg) and plain bupivacaine [145±12 mg). Time to block regression was longer in plain bupivacaine group B [182±30 minutes) compared with midazolam 1 mg [152±32 minutes) and midazolam 2 mg group B [126±20 minutes) (both p<.001]. Interesting, patient who did not receive intrathecal midazolam had higher incidence of nausea and vomiting. Arterial pressure, heart rate, oxygen saturation, sedation score, and time to first void were comparable between groups. Karbasfrushan et al [145]. compared intrathecal midazolam 2 mg added to bupivacaine 10 mg versus plain bupivacaine in women undergoing elective cesarean. Patients treated with midazolam had significant pain relieve at 15 and 120 min after surgery, but there were no significant differences between the groups regarding the intensity of pain 5, 30, 60 and 240 min after the surgery. Request for first analgesic was 178.06±77.33 versus 142.18±55.19 min. Duration of analgesia and regression for sensory analgesia was similar in both groups, but nausea and vomiting were higher in the midazolam group. Salimi et al [147] use a combination of 2 mg midazolam plus 5 μg sufentanyl intrathecally versus sufentanyl alone for labour pain in 80 parturients. Analgesia was enhanced and prolonged significantly [185±15.2 min versus 92±12.7 min p=0.001]. No significant side effects were observed in both groups.

Magnesium sulfate. Is a chemical compound containing magnesium, sulfur and oxygen. Magnesium sulphate is a noncompetitive antagonist of the N-methyl-d-aspartate (NMDA) receptor, therefore can interfere nociceptive modulation. There is controversy about the neurotoxicity of magnesium sulfate injected into the neuraxis. [148, 149] In a contemporary study conducted in Sprague-Dawley rats, Ozdogan and coworkers [149] were able to demonstrate on electron microscopic examinations, that single or repeated spinal injection of magnesium sulphate 0.15% produced significant neurodegeneration. Nonetheless, there are clinical studies that support the use of this ion via neuraxial-epidural or subarachnoid-in diverse clinical scenarios, [150, 151, 152] including in the obstetric field, showing to prolong analgesia without important side effects in healthy and pathologic parturients.

It has been used through epidural [153, 154] and spinal via for cesarean delivery, with highly variable results. Ghrab et al [155] studied 105 women undergoing cesarean section with spinal anaesthesia. They found that adding magnesium sulphate 100 mg to morphine 100 μg improved the quality and duration of postcesarean analgesia without augmenting the incidence of harmful side effects. Jabalameli and Pakzadmoghadam [156] compared 0, 50, 75 and 100 mg magnesium sulphate added to spinal bupivacaine in 132 parturients undergoing cesarean delivery. Magnesium produced a delay in the onset of sensory and motor blockade. Duration of sensory and motor blockade were longer in those women treated with 75 a 100 mg doses. Patients who did not receive magnesium had a shorter recovery time and needed more postoperative analgesic (p<0.001]. In patients with mild preeclampsia [157] adding magnesium sulphate 50 mg to 0.5% hyperbaric bupivacaine and fentanyl 25 μg induced a slower onset of motor and sensory block, prolonged duration of spinal anaesthesia and motor block and reduced needs of diclofenac during 24

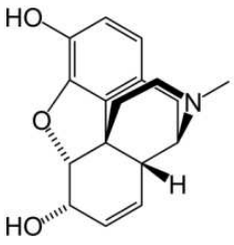
hours. No harmful side effects were noticed. As Faiz et al mentioned, spinal magnesium improved perioperative shivering in women undergoing elective caesarean delivery. [158] In a prospective, randomized, double blind study in 90 women undergoing cesarean section, Unlugenc et al [159] were unable to probe that 50 mg magnesium sulphate have any benefit over spinal anaesthesia with bupivacaine 0.5%. Adding this adjuvant to 10 mg spinal bupivacaine did not shorten onset time of sensory and motor blockade or prolonged duration of subarachnoid anaesthesia as compared to spinal fentanyl.

6. Conclusions

Across the world, subarachnoid anaesthesia is the most used anaesthetic procedure for Cesarean delivery. Compared to general and epidural anaesthesia, its main disadvantage is a short duration action and most important, the lack of prolonged postoperative analgesia. These two negative factors had been overcome with the addition of drugs that act enhancing quality and durability, while they managed to decrease the dose of local anaesthetic and prolong postoperative analgesia. Provision of postcesarean delivery analgesia is of great consequence since it accelerate early ambulation, decreases maternal morbidity, improves parturient outcome, decrease cost, and most important augment the quality of the mother-infant relationship from the moment of birth.

When planning spinal anaesthesia for cesarean section there are different local anaesthetics and various adjuvants that enhance the technique and favor better outcome of our patients. It is vital that the choice of adjuvants drugs be rationally and according to each clinical condition and local availability of these drugs. Although there is no gold standard for a perfect spinal anaesthesia and postcesarean analgesia, in this millennium is mandatory to provide the best available care. As reviewed, there is a large list of options and the choice is mostly determined by drug safety and accessibility, the experience of anaesthesiologists, and monetary factors.

When adjuvants are selected for neuroaxial anaesthesia, it is mandatory to use drugs that are not neurotoxic and are free of preservatives.

Spinal Adjuvants	Dose range in μg	Effects	Side effects
Morphine 	50-400 Recommended dose 100	Reduce DE_{50} and DE_{95} of spinal LA Prolonged POA Reduce analgesics	PONV dose related Pruritus moderate to severe Urinary retention Respiratory depression (rare) Hypothermia (very rare)

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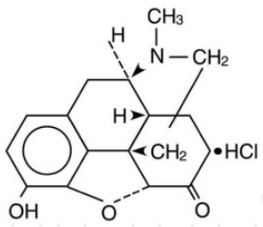
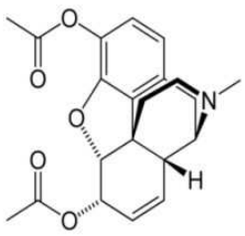
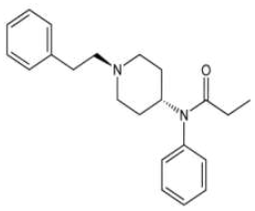
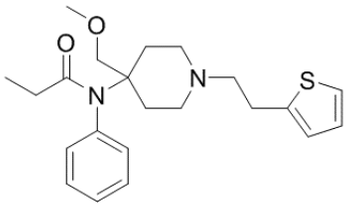
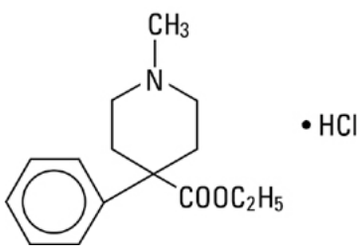
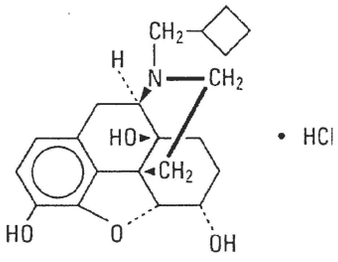
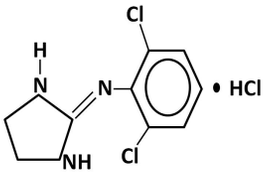
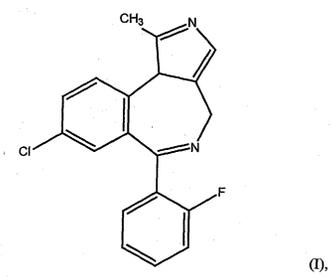
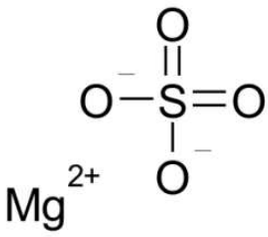
Spinal Adjuvants	Dose range in µg	Effects	Side effects
Hydromorphone 	40-100	Prolonged POA Reduce POP analgesics doses	PONV similar no morphine Less itching than morphine
Diamorphine (Heroine) 	125-400 Recommended dose 300	Reduce intraoperative analgesics Enhance POA Reduce POP analgesics doses	PONV similar no morphine Less itching than morphine
Fentanyl 	6.5 - 50 Recommended dose 12.5	Fast onset Enhace spinal anaesthesia Reduce spinal LA dose Reduce intraoperative analgesics Enhance POA for 2-4 hours	Less PONV than morphine Less itchichin tha morphine
Sufentanyl 	1.5 - 20 Recommended dose 5	Rapid onset Enhace spinal blockade Reduce spinal LA doses Improve trans cesarean analgesia Short prolongation of POA Reduce PO analgesic needs	Dose relates itchnig Posoperative sedation PONV higher than fentanyl
Meperidine 	7000 to 10, 000 D Recommended dose, 500	Rapid onset Improve spinal anaesthesia Prolongs POA	High incidence of transurgical vomitig PONV are high

Spinal Adjuvants	Dose range in µg	Effects	Side effects
Nalbufine* 	200 - 1600 Recommended dose 800	Enhance operative analgesia Prolongs arly POA No effect on itching	PONV are dose related In not better that spinal morphine
Clonidine 	15 - 450 Recommended dose 30	Improve spinal anaesthesia Reduce spinal LA dose Prolongs POA No respiratory depresion	Hypothension Sedation Dry mouth Fetal and maternal bradycardia
Midazolam* 	1000-2000 Recommended dose 2000?	Enhance POA Reduce PO analgesic doses Reduce PONV?	Augments PONV?
Magnesium sulphate* 	5, 000-100, 000 Recommended dose?	Prolongs spinal block Augments POA Reduces PO analgesic doses Reduces postoperative shivering	Delays onset of spinal anaesthesia

LA=Local anaesthetics. POA=Postoperative analgesia. POP=Postoperative. PONV=Postoeprative nausea and vomiting.

*Nalbuphine, midazolam and magnesium suphate are under clinical investigatior to determine its use in spinal anaesthesia for several clinical scenarios.

Table 1. Spinal additives and some drugs under clinical research in parturients undergoing cesarean delivery with spinal anaesthesia.

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I hope this chapter help reader and add some helpful information.

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