Chapter 5

Intrathecal Clonidine as Spinal Anaesthesia Adjuvant — Is there a Magical Dose?

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Additional information is available at the end of the chapter

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1. Introduction

Clonidine was synthesized in 1962 as nasal decongestant, and marketed as antihypertensive in 1972. Bloor and Flacke in 1982 [1] demonstrated in mongrel dogs that intravenous clonidine 5 and 20 μg/kg decreased halothane MAC by 42% and 48% respectively. Since then, clonidine has been used by anaesthesiologists as an anaesthetic adjunct to provide increased perioperative cardiovascular and sympathoadrenal stability, to enhance general and regional anaesthesia, as well as sedation and analgesia. [2, 3] In 1999, dexmedetomidine, a novel selective and specific alpha2 agonist, was approved for postoperative sedation in intensive care patients, and has also been investigated in general anaesthesia, regional anaesthesia and pain treatment. Basic research in animals and clinical studies in humans performed with epidural clonidine have shown its analgesic effects, with less side effects than any other neuroaxial anaesthesia adjuvant. Similar results were also obtained with intrathecal injection of clonidine. Due to the short duration of analgesic action by the latter route, the extradural administration is the most studied. Epidural administration of clonidine has been widely utilized; indeed, the FDA has only approved peridural use of clonidine infusion in chronic pain patients. There are many publications with epidural clonidine for intraoperative surgical pain as an adjunct to general anaesthesia and epidural anaesthesia, postoperative pain, pediatrics, and labour analgesia. It has been used alone, or in combination with local anaesthetics, opioids, in bolus, or by continuous infusion.

Intrathecal administration of clonidine is an interesting alternative route of administration. As an alpha2 agonist, spinal injected clonidine prolongs sensory and motor block, increases sedation and may potentiate hypotension and bradycardia. It has been used in high (> 150 μg), low (< 150 μg) and small (< 75 μg) doses. High doses 150, 300 and 450 μg produce dose

dependent analgesia, enhance spinal anaesthesia, with relative hemodynamic stability. Furthermore, doses of 15 and 30 μg in addition to spinal local anaesthetics provide better sensory and motor block compared to local anaesthetics alone. [4, 5]

The optimal dose of spinal clonidine remains unknown. For short ambulatory procedures 15 to 75 μg added to local anaesthetics enhance spinal anaesthesia without negative impact on home discharge criteria. For short-stay or longer hospitalization surgeries, doses from 150 up to 450 μg of clonidine as adjuvant for any local anaesthetics are safe, prolongs motor and sensory block, and reduces the need of postoperative opioids.

This chapter updates current data on dose-response relationship of subarachnoid clonidine when added as adjunct to spinal local anaesthetics and/or spinal opioids in different clinical surgery scenarios, as well as for postoperative analgesia and labour pain.

2. Spinal additives

Spinal adjuvant drugs have been used since the beginning of subarachnoid anaesthesia. Adrenaline, an alpha2 agonist, was the first drug used to enhance duration of spinal anaesthesia, and morphine was the first opioid injected with eucaine in the lumbar spinal space to relieve vertebral pain. [6] After the first article on spinal analgesia using opioids written by Yaksh and Rudy in 1976, [7] the neuroaxial route to inject opioids as adjuvants drugs grew logarithmically. Morphine, fentanyl, sufentanyl and many more agonist opioids have proven their safety and efficacy to decrease the dose of local anaesthetics, to facilitate a faster recovery, and effective postoperative analgesia. There are many receptors which modulates spinal pain response; however, there are only few FDA approved drugs to be used via subarachnoid as adjuvants or sole medications.

Many drugs have being injected into the spinal or peridural space in order to provide analgesia and/or to enhance neuraxial anaesthesia. Nowadays, opioids are the more frequently used spinal additives, but their side effects may limit its use; pruritus, urinary retention and late respiratory depression. There are studies with intrathecal adjuvants that have not been approved to be used in spinal anaesthesia: midazolam, ketamine, neostigmine, magnesium sulphate, calcium channel blockers, nonsteroidal anti-inflammatory, dexmedetomidine, tizanidine, etcetera.

3. Alpha2 adrenergic agonist drugs

Alpha2 agonist medications are used as adjuvants in anaesthesia and analgesia. They can be prescribed orally, transdermally, intravenously, perineuraly, or through the neuroaxial route. Beside analgesia and sedation, they decrease sympathetic tone and attenuate the stress response to anaesthesia and surgery. Although adrenaline was the first alpha2 agonist used intrathecally, it is no longer recommended. Nowadays, clonidine is the most used alpha2

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agonist in neuroaxial anaesthesia, even though dexmedetomidine has also recently been studied for epidural and spinal anaesthesia adjuvant. Clonidine acts as a selective partial agonist with a ratio of 200:1, whereas dexmedetomidine is highly selective with a ratio of 1600:1. Tizanidine, 5-bromo-N-[4, 5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (UK-14, 304], and moxonidine are other alpha2 agonists with a potential neuroaxial use. [8, 9, 10, 11] More than 90 patents have been deposited recently regarding different methods of alpha2 modulation (use of agonists or antagonists, nucleic acids and polypeptides) for diagnosis, prognosis and treatment of disorders involving this receptors.

4. Clonidine

This prototypical alpha2 adrenergic receptor agonist was developed in the early 1960s. It is an imidazoline derivative that exists as a mesomeric compound. It has a molecular weight of 266.56, chemical name is Benzenamine, 2, 6-dichloro-N-2-imidazolindinylidene monohydrochloride and 2-[[2, 6-dichlorophenyl) imino] imidazolidine monohidrochloride. Figure 1 shows its structural formula (C9H9Cl2N3 HCl). Clonidine stimulates alpha2 adrenoreceptors in the brain and spinal cord, resulting in reduction of sympathetic outflow from the central nervous system and in decreased in peripheral resistance, renal vascular resistance, plasma renin activity, heart rate, cardiac output, and blood pressure. Normal postural reflexes are intact; therefore, orthostatic symptoms are mild and infrequent. Plasmatic level of clonidine peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe renal impairment. Following oral administration, approximately 75% is bioavailable in men, about 40-60% of the absorbed dose recovered unchanged in the urine in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Severe adverse side effects are infrequent, and well tolerated in most patients. Sedation and dry mouth are the most common side effects, and are usually related to dose and length of administration. [12, 13]

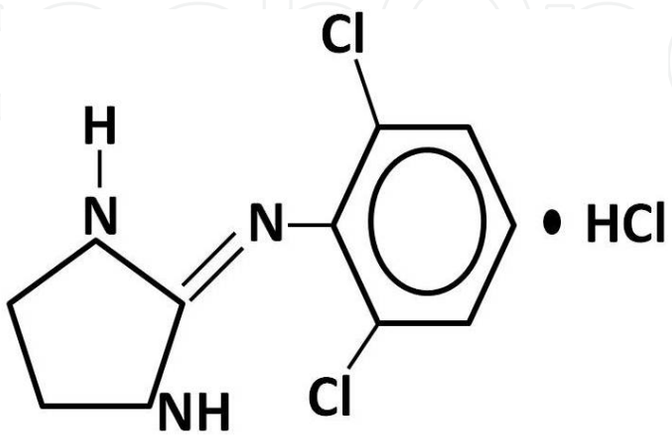

Figure 1. Structural formula of clonidine

5. Mechanisms of action of spinal clonidine

It has been shown that epidural and spinal administration of clonidine in surgical patients enhances quality and duration of neuroaxial anaesthesia, reduces dose of local anaesthetics as well as others neuroaxial additives such opioids. It also produces a short period of postoperative analgesia, and lowers the dose of systemic postoperative analgesics.

G-protein-coupled receptors (GPCRs) are the largest and most diverse superfamily of membrane receptors responsible for signaling between cells and tissues, mediating most cellular responses to hormones and neurotransmitters, playing important physiological roles in homeostasis. They are a major drug targets. The alpha2 adrenoceptors are membrane proteins belonging to these superfamily GPCRs, that form a group of 3 to 4 gene polymorphic products, that mediate major central nervous system actions of norepinephrine and epinephrine, including control of mood state, arousal, endocrine function, autonomic and somatic motor outflows, and modulation sensory inputs, including pain. The alpha2 adrenoceptors are located presynaptically and regulates the release of the neurotransmitter; they are also present in postsynaptical locations.

Three distinct subtypes have been described, characterized and cloned; alpha2A, alpha2B, and alpha2C. [14, 15, 16, 17] There is a fourth receptor called alfa2D that has been described and their functions are still not known, although it appears that this receptor alfa2D is in fact, an alpha2A-D subtype; the alpha2A in humans and the alpha2D in rats. [18]

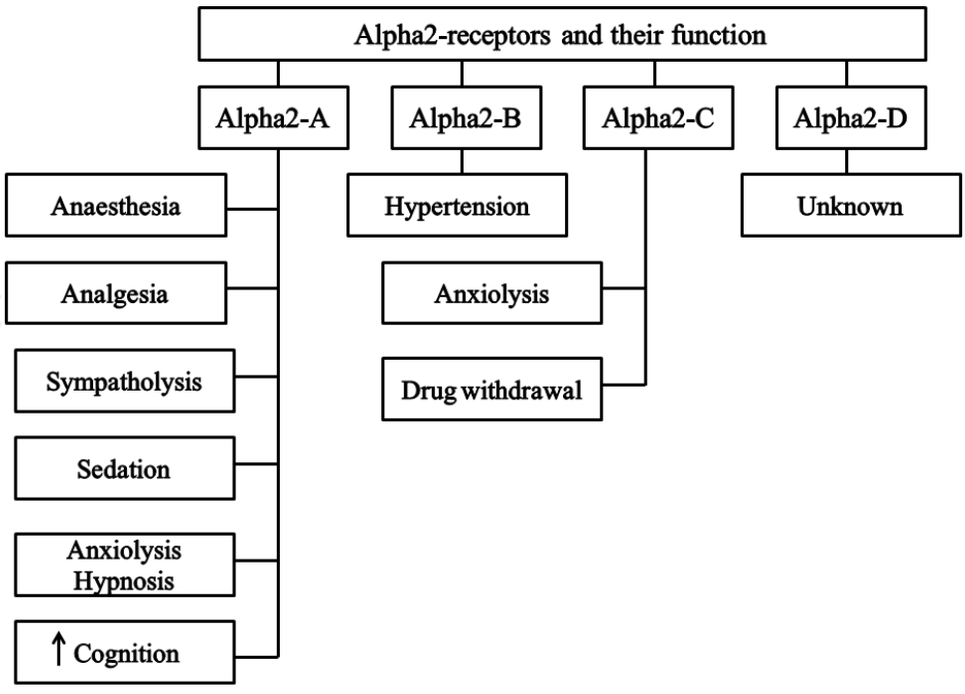

Figure 2. Alpha2 adrenoceptors are membrane proteins belonging to the super family GPCRs. There are four subtypes. Their stimulation has wide therapeutic effects.

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The anatomic site of action of the alpha2 agonists involves specific receptors of the spinal dorsal horn and supraspinaly in the nucleus coereleus in the pons. [19, 20, 21, 22] While the mechanism and location of action of the sedative effect of these compounds are due to the hyperpolarization of excitable neurons localized in the nucleous coereleus, the analgesic effect of these drugs is not completely understood, and have a complex mechanism. Alpha 2 agonists induce analgesia by acting in different places; brain, brain stem, spinal cord and peripheral nerves. Their supraspinaly analgesic mechanism in the locus coereleus is probably by transduction, while in the spinal cord is likely related to activation of the descending medullospinal noradrenergic pathways or to the reduction of spinal sympathetic outflow at presynaptic ganglionic sites. Clonidine suppresses the generation of action potentials in tonic-firing spinal dorsal horn neurons. This may be explained, in part, by an interaction with voltage-gated $Na^+$and K^+currents.

Clonidine also acts synergistically with local anaesthetics because of its action of opening potassium channels.

6. Spinal interactions between alfa2 agonists and opioids

It is an uncommon clinical practice to combine alpha2 agonists and opioids in spinal anaesthesia to either enhance local anaesthetic effects or to provide postoperative analgesia. This technique is based on the spinal synergism between these two drugs. When morphine and clonidine are co-administered intrathecally, the resulting antinociception is greater than expected if the drug responses were additive; thus, a synergistic interaction is present. [23, 24] For the most part, the underlying molecular synergy mechanisms are not known, although some studies have identified both the delta and the mu-opioid receptors as candidate receptors capable of interacting synergistically with alpha 2A agonists. Roerig et al [25] found in rats that interactions between opioid and adrenergic agonists in mouse spinal cord were mediated by delta and alpha2 receptor subtypes, the synergistic interaction between morphine and alpha2 adrenergic agonists may involve action at delta opioid receptors, and antagonist action on these drug interactions is intrincated. Stone and coworkers, [26] in a genetically modified mouse line expressing a point mutation (D79N) in the alpha2A adrenergic receptor investigated the role of the alpha2A receptor in alpha2 agonist-evoked analgesia and adrenergic-opioid synergy. They were able to demonstrate that the alpha2A subtype receptor is the primary mediator of alpha2 adrenergic spinal analgesia and is necessary for analgesic synergy with opioids, and concluded that combination therapies targeting the alpha2A receptor and opioid receptors may be useful in maximizing the analgesic efficacy of opioids while decreasing total dose requirements. Although others have found that the alpha2C adrenergic receptor subtype contributes to this synergy, [27] Chabot-Doré and coworkers [28] confirmed that although other opioid receptors can interact synergistically with alpha2 receptors agonists, Delta opioid receptor is sufficient for spinal opioid-adrenergic interactions. Protein kinase is needed for this analgesic synergy. [29]

Analgesic synergy between opioid and alpha2 adrenergic agonists is potentially beneficial by increasing efficacy and/or reducing the total drug required to produce sufficient pain relief, and undesired side effects can be minimized.

7. Safety of spinal clonidine

Neurotoxicity has not been reported following the use of intrathecal clonidine and generally the drug is considered to be safe in this regard. Although subarachnoid administration of clonidine has not been approved by the FDA or any other regulatory agency in the world, there are experimental studies that have demonstrated its safety and efficacy when used by this route. Continuous administration of spinal clonidine in Wistar rats during 14 days failed to demonstrate neurotoxic damage. [30] Erddivanli and coworkers injected male Sprague-Dawley rats [31] with 3 μg and 10 μg of intrathecal dexmedetomidine added to bupivacaine; they found no apparent pathohistological changes 24 hours after a single injection. In male Kunming mice 1 to 3 μg of dexmedetomidine displayed a robust analgesia via a alpha2-receptor in a dose dependent manner and no significant pathological impacts on the spinal cord were noticed, with a potential protective effects of lidocaine induced neural cell damage. [32] In postnatal rats spinal clonidine produces age and dose-dependent analgesia, without signs of spinal cord toxicity, even at doses bigger than required for analgesia. [33]

8. Clinical use of spinal clonidine

To enhance spinal anaesthesia and postoperative pain control clonidine can be injected in the subarachnoid space as an adjuvant drug to opioids or local anaesthetics. A systematic review by Elia et al [34] including 1, 445 patients using a wide variety of spinal clonidine doses as adjuvant to subarachnoid bupivacaine, mepivacaine, prilocaine, or tetracaine found that 15 to 150 μg prolonged in a linear, dose-dependent manner, the time to 2 segment regression (range of means, 14 to 75 minutes) and also delayed the regression time to L2 dermatome (range of means, 11 to 128 minutes). The time to first analgesic request (median 101 minutes, range 35 to 310] and motor block (median 47 minutes, range 6 to 131] was extended with no relation to dose. There were fewer episodes of intraoperative pain with clonidine (relative risk, 0.24; 95% confidence interval [CI], 0.09-0.64; number needed to treat, 13] but more episodes of arterial hypotension (relative risk, 1.81; 95% CI 1.44-2.28; number needed to harm, 8] without evidence of dose-responsiveness. The risk of bradycardia was unchanged.

Side effects of intrathecal clonidine include sedation, hypotension and a reduction of the heart rate. Especially in post-surgical patients these circumstance warrants specific attention.

The following paragraphs discuss spinal clonidine use in different anaesthetic and surgical scenarios, as well as in the management of postoperative and labour pain.

http://dx.doi.org/10.5772/58712

9. Ambulatory settings

Spinal anaesthesia side effects are a major concern in some patients and physicians and may be reluctant to use this technique in ambulatory surgery. [35] Nowadays there are many articles showing that spinal anaesthesia is a safe and effective technique in this clinical scenario. There is an special interest to use adjuncts drugs such clonidine in order to decrease local anaesthetic dose to promptly achieve a recovery profile. [36]

Several investigations in patients undergoing knee arthroscopy have shown that low doses of clonidine [15 up to 45 μg) added to low doses of intrathecal hyperbaric bupivacaine [5-6 mg) improves the quality of anaesthesia, prolong the motor block, without affecting time to home discharge in outpatients. [37] In 60 ambulatory patients undergoing knee arthroscopy Marrivirta et al [38] added 75 μg clonidine to 6 mg spinal hyperbaric bupivacaine vs. 6 mg bupivacaine alone. These researchers found that motor block was prolonged in those patients who received clonidine without affecting home-readiness. Also these patients needed more vasopressors and had less postoperative pain. Adding clonidine 15 μg to 8 mg of isobaric spinal ropivacaine [39] did not prolonged motor or sensory blockade, but enhanced anaesthesia quality for knee arthroscopy. Bigger doses such 75 μg produced significantly longer sensory and motor blockade [195 ± 40 min and 164 ± 38 min; $p < 0.05$], but associated with sedation and hypotension.

In our practice we have good results with doses of 45-150 μg. These doses of spinal clonidine favor the reduction of local anaesthetics doses and do not prolong the recovery time of our outpatients.

10. General surgery and urologic procedures

Numerous surgical procedures of the abdominal wall, abdominopelvic cavity, and retroperitoneum can be performed under single injection of local anaesthetics in the spinal space. For prolonged cases the use of adjuvant drugs improves the quality and increases the duration of the subarachnoid block. Clonidine has been used successfully in various surgical procedures of the abdomen and pelvis. Intrathecal clonidine 15, 30, 45 and 75 μg alone, or added to opioids expand spinal anaesthesia sensory block and duration of motor block, and also provided prolonged postoperative analgesia. In a randomized study [40] of 73 patients ASA physical status I and II undergoing gynecological abdominal surgery with spinal bupivacaine 15 mg, the authors compared clonidine 30 μg, sufentanyl 10 μg, clonidine 15μg plus sufentanil 15 μg versus a control group. Sensory block to pinprick at 10 min was higher for clonidine and sufentanil/clonidine groups compared to the control group ($p < 0.02$]. Anaesthetic time (Bromage score 2] was also longer for clonidine and sufentanil/clonidine groups compared to the control and sufentanil groups ($p < 0.05$]. Time to first rescue analgesics was shorter in the control group compared to the other groups ($p < 0.02$]. The dose of intramuscular diclofenac in 24 hours was higher in the control group compared to all other groups ($p < 0.05$]. The incidence of adverse effects and ephedrine consumption were similar among groups. Cloni-

dine 75 μg associated with 17.5 mg hyperbaric bupivacaine 0.5% for lower abdominal surgeries [41] with high level spinal anaesthesia (T4] induced a higher incidence of arterial hypotension but prolongs sensory block and postoperative analgesia similar to clonidine 45 μg. In lower abdomen surgeries, Yoganarasimha and coworkers [42] compared intrathecal clonidine 75 μg versus intrathecal neostigmine 50 μg as adjuvant drugs for spinal anaesthesia 0.5% hyperbaric bupivacaine 12.5 mg; analgesia was prolonged significantly with clonidine [362 ± 36 min) compared with neostigmine [300 ± 25 min)($p < 0.05$]. No serious adverse effects were noted perioperatively in either group. In an interesting clinical study with 60 patients undergoing right colon resection under general anaesthesia, preoperative intrathecal clonidine was superior to bupivacaine to prevent postoperative secondary hyperalgesia; [43] the authors compared the effect of clonidine 300 μg versus bupivacaine 10 mg intrathecally versus saline (control group): morphine needs patient controlled postoperative analgesia were less in the clonidine group [31.5±12 versus 91±25.5 and 43±15 mg, respectively, in groups clonidine, saline, and bupivacaine: $p < 0.05$ at 72 postoperative hours). The area of mechanical hyperalgesia at 72 h was 3±5 cm^2 in the clonidine group versus 90±30 and 35±20 cm^2 in the saline and bupivacaine groups ($p < 0.05$]. After 6 months, fewer patients in the clonidine group experienced residual pain than in the saline group [0 of 20 versus 6 of 20, $p < 0.05$]. In laparoscopic procedures done under bupivacaine spinal anaesthesia, clonidine 30 μg produced good sedation, intra and postoperative analgesia, and abolished shoulder tip pain during the procedures. [44] For inguinal hernioplasthy [45, 46] adding clonidine 15 or 30 μg to small doses of hyperbaric bupivacaine enhance spinal anaesthesia, prolongs the time to first analgesic request, and decreases postoperative pain, compared with bupivacaine alone. Thirty μg clonidine was associated with higher incidence and duration of hypotension than 15 μg of clonidine.

Some research has shown the usefulness of intrathecal clonidine in urology procedures, although there are some controversies. In a controlled, prospective, double-blind investigation with patients undergoing elective transurethral resection of bladder tumours under spinal anaesthesia [47] the authors found that adding clonidine 75 μg to prilocaine 75 mg increased the duration of sensory and motor block and reduced the need for additional postoperative analgesics by providing excellent analgesia for about 8 hours during recovery period. In a similar study, 25 μg spinal clonidine improved bupivacaine spinal anaesthesia: shorter time to achieve complete motor block and sensory block at T9 level, with longer postoperative analgesia. [48] In 60 patients undergoing transurethral resection of prostate or bladder tumors Kanazi et al [49] compared clonidine 30 μg, versus dexmedetomidine 3 μg added to 12 mg spinal hyperbaric bupivacaine, versus bupivacaine alone. Patients treated with alpha2 agonists had a significantly shorter onset time of motor block and significantly longer sensory and motor regression times than patients who only received local anaesthetic. The mean time of sensory regression to the S1 segment was 303 ±75 min for those injected with dexmedetomidine, 272 ±38 min in the group who received clonidine and 190±48 min in patients with bupivacaine alone (bupivacaine versus dexmedetomidine and bupivacaine versus clonidine, $p< 0.001$]. The regression of motor block to Bromage 0 was 250 ±76 min, 216±35 min, and 163±47 min respectively (bupivacaine versus dexmedetomidine and bupivacaine versus clonidine, $p< 0.001$]. The onset and regression times were not significantly different between patients treated

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with the alpha2 agonists. The mean arterial pressure, heart rate and level of sedation were similar in the three groups intra-operatively and post-operatively. Andrieu and his group [50] compared intrathecal morphine 4μg/kg without or with clonidine 4μg/kg, or PCA in patients undergoing radical retropubic prostatectomy under general anaesthesia with sevorane-N2O. Adding clonidine to spinal morphine reduced intraoperative use of sufentanil, prolonged time until first request for PCA rescue, and added prolonged analgesia at rest and during coughing.

In contrast with previous mentioned studies, Larsen et al [51] compared 75 μg versus 150 μg of clonidine added to 80 mg mepivacaine 4%, versus spinal mepivacaine alone in patients who had transurethral surgery and found that clonidine had no effect on the onset time, spread or intensity of subarachnoid anaesthesia. The higher dose prolonged the duration of sensory block by 50 minutes and the duration of motor block by 40 minutes, while 75 μg had no significant effect. Heart rate and mean arterial pressure were significantly reduced in both clonidine groups when compared to plain mepivacaine. There was no significant reduction in postoperative analgesic demand. They do not recommend the routine addition of clonidine for spinal anaesthesia with local anaesthetics. There is a reported case of late respiratory depression (16 h after spinal block) in a 70 year old man undergoing prostatic adenomectomy done under spinal anaesthesia with 10 mg bupivacaine, 30 μg clonidine and 100 μg morphine. Intrathecal mixture of morphine-clonidine in older patients must be careful monitored. [52]

10.1. Orthopaedic

Postoperative pain following orthopaedic surgeries has been shown to be a significant negative factor that delay patient recovery and contributes to serious complications. It may also result in larger use of healthcare resources and ultimately lead to poor outcomes. The utilization of multimodal pain management following large orthopaedic surgeries like total joint arthroplasty, total knee replacement, or spinal surgery has positively affected the quality of postoperative care, reduced surgical pain, and decreased the magnitude of opioid consumption and subsequent dose-related complications. Multimodal spinal anaesthesia-analgesia including spinal clonidine is safe and may reduce hospital stay, decrease postoperative complications, and increase patient satisfaction.

In a dose-response prospective study, Strebel et al [53] compared three doses of clonidine (37.5, 75 and 150 μg) added to spinal 0.5% bupivacaine 18 mg in 80 orthopaedics patients. Duration of sensory block (regression below level L1) was increased in patients receiving intrathecal clonidine: 311±101 min in 37.5 μg (+8%), 325 ±69 min in 75 μg (+13%), and 337±78 min in those patients who received 150 μg (+17%) (estimated parameter for dose 0.23 [95% confidence interval-0.05-0.50]). versus control group 288 ±62 min. Time to first analgesic request was also prolonged: 343 ±75 min (+16%), 381±117 min (+29%), and 445±136 min (+51%) (estimated parameter for dose 1.02 [95% confidence interval 0.59-1.45]), respectively compared to control group 295±80 min. Hemodynamic stability was maintained and they found no differences in sedation level. van Tuijl and coworkers [37] investigated the effect of 0, 15 and 30 μg of clonidine added to 5 mg hyperbaric bupivacaine on the duration of motor block, analgesia and ability to void after knee arthroscopy. They found that clonidine increased motor block duration by 25 and 34 min respectively. They also found better analgesic quality, and the mean

time for spontaneous voiding was increased up to 18 and 44 min respectively. Amaranto and Berrío demonstrated that spinal clonidine 2 μg/kg added to hyperbaric lidocaine in orthopaedic cases enhance anaesthesia quality, significantly prolonged post operative analgesia, with early motor recovery and minimal side effects. [54] In adolescents scheduled for lower extremities orthopaedic surgery under spinal anaesthesia with isobaric 0.5% bupivacaine added with clonidine 1 μg/kg prolonged duration of sensory and motor block, produced extended spinal postoperative analgesia by 120 min, without severe side effects. [55] Spinal sufentanil 75 μg alone, or added with epinephrine 200 μg, or clonidine 30 μg after total hip replacement results in good analgesia with similar onset and duration of action, and minor side effects. [56] Compared with intrathecal dexmedetomidine, clonidine had a similar results in patients undergoing lower limb surgery with spinal bupivacaine; Mahendru et al [57] conducted a prospective study adding clonidine 30 μg, vs. dexmedetomidine 5 μg, vs. fentanyl 25 μg to 12.5 mg spinal hyperbaric bupivacaine in cases of lower limb surgeries. They discovered that dexmedetomidine prolonged significantly sensory and motor block compared to clonidine, fentanyl and bupivacaine alone. The mean time of two segment sensory block regression was 147±21 min with dexmedetomidine, 117±22 with clonidine, 119±23 in those patients receiving fentanyl, and 102±17 in bupivacaine alone ($p > 0.0001$). The regression time of motor block to reach modified Bromage 0 was 275±25, 199±26, 196±27, 161±20 respectively ($p > 0.0001$). Hemodynamic stability was conserved. In patients 60 years or older undergoing lower extremity orthopaedic surgeries, intrathecally clonidine 15 μg or 30 μg with 9 mg hyperbaric bupivacaine, significantly potentiated the sensory block levels and duration of analgesia without affecting the trend of systolic blood pressure as compared to bupivacaine alone. Clonidine in doses of 30 μg however facilitated the ascent of sensory level block to unexpectedly higher dermatomes for a longer time. [58] Spinal postoperative analgesia can be improved by epidural infusion of 40 $\mu g/h^{-1}$ mixed with ropivacaine 4 mg/h^{-1} in patients undergoing hip arthroplasty. [59]

Some studies have found conflicting data which showed that spinal clonidine is not a useful adjuvant for postoperative analgesia in orthopedic major surgery. Gehling et al [60] evaluated 45 patients undergoing hip or knee replacement under 15 mg bupivacaine spinal anaesthesia and found a mean time until first opioid request was for placebo 10.3±7.9 h, for 0.1 mg morphine 23.0±3.9 h and for 0.1 mg morphine+50 μg clonidine 21±6.9 h, respectively. Co-administration of pethidine 0.75 mg/kg^{-1} and clonidine 75 μg provided good intraoperative anaesthesia for total hip replacement, but similar to plain isobaric 0.5% bupivacaine. [61]

11. Obstetrics

The role of the anesthesiologist in obstetrics has many responsibilities; labour analgesia, anesthesia for vaginal delivery, anaesthesia for cesarean section, anaesthesia for non-obstetric surgeries during pregnancy, and postoperative analgesia. A comprehensive labour analgesia program has to include newer procedures and ajuvant drugs to facilitate ambulation, excellent pain relief, patient comfort and safety for the mother-fetus binomial. [62, 63, 64] Spinal clonidine has been used for labour analgesia, to enhance spinal anaesthesia during cesarean

http://dx.doi.org/10.5772/58712

section, and for postoperative pain relief. Its use tends to be more frequent in this field, since it reduces opioids doses, and thus the side effects such as emesis and maternal pruritus, and the possibility of respiratory depression secondary to rostral opioid distribution. Theoretically, it could also reduce the fetal bradycardia.

Labour analgesia. There are many advances in the pharmacology of labour analgesia focused on alternatives mechanisms to target spinal pain receptors, and the efficacy and safety of old and new drugs and techniques; i.v. remifentanyl for patient controlled analgesia, low dose of diluted local anaesthetics, addition of neuraxial adjuvants like opioids, neostigmine, and clonidine. [65, 66, 67, 68]

Most studied doses of intrathecal clonidine for labour analgesia range from 15 to 45 μg mixed with opioids and/or local anaesthetics. In a preliminary open-label protocol done in France by Mercier and coworkers [69] comparing sufentanil 5 μg+clonidine 30 μg versus sufentanil 5 μg alone injected intrathecally to alleviate pain during the first stage of labour, the authors demonstrated that clonidine potentiate labour analgesia and side effects such hypotension, maternal pruritus and sedation were similar in both groups. In a second research, the same group [70] studied 53 nulliparous women in painful labour using the same doses, but followed by 5 mg of epidural bupivacaine. In this study the duration of analgesia was longer in the sufentanil-clonidine group versus sufentanil alone [125±46 versus 97±30 min, p=0.007]. There were more incidents of hypotension and ephedrine needs in those patients who received sufentanil and clonidine. The incidence of fetal heart rate abnormalities during the first 30 min after spinal injection was similar in both groups [17% versus 19%). No parturient had motor blockade. Gautier et al [71] found that 30 μg of intrathecal clonidine plus 2.5 or 5 μg intrathecal sufentanil increased the duration of labour analgesia during the first stage without undesirable maternal or fetal effects. Labbene et al. [72] added clonidine 15 μg to 2.5 mg isobaric bupivacaine and 5 μg sufentanil during combined spinal-epidural analgesia resulting in extended duration of analgesia without increasing side effects. In nonobstetrical patient doses of 25 to 30 μg of clonidine augmented duration of postoperative analgesia, so smaller dose of clonidine may be effective in the obstetric population.

Chiari et al from Austria [73] did the first study using spinal clonidine as a sole drug for labour analgesia; in 36 parturients with < 6 cm cervical dilation; they compared 50, 100, and 200 μg intrathecal clonidine and found that labour pain was significantly reduced in all patients, analgesia duration was significantly longer with 200 μg (median 143; range 75-210 min), with 100 μg (median 118; range 60-180 min) and using 50 μg (median 45; range 25-150 min). Hypotension was associated with 200 μg and the need of intravenous ephedrine more often than in the other groups.

There are controversies in the use of spinal clonidine for labour analgesia as some researchers have found a higher frequency of maternal hypotension, foetal arrhythmia, and worse neonatal umbilical artery pH. Therefore, some of them do not recommend its use. [74, 75, 76] The study done by Paech et al [77] with subarachnoid fentanyl 20 μg+bupivacaine 2.5 mg, plus either saline or clonidine 15, 30 or 45 μg found that addition of clonidine to fentanyl-bupivacaine reduced maternal blood pressure and did not significantly augment the duration of spinal

labour analgesia. To avoid hypotension due to the combination of spinal clonidine-opioids-diluted local anaesthetics, epidural clonidine can be used in doses of 75 μg. [78]

When low doses of clonidine with or without opioids are used for spinal labour analgesia, we must remember that at the end of pregnancy there is a degree of autoanalgesia mediated by endorphins [79] Even though neuraxial analgesia is the most efficient and safest mode of labour analgesia, the use of spinal clonidine mixed with opioids and/or local anaesthetics must be used cautiously to avoid hypotension.

Cesarean section. Nowadays, spinal anaesthesia is the most used technique for cesarean section. [80] Currently, opioids are the drugs most commonly used as adjuvants in this clinical scenario, but its side effects are troubling. Low doses of spinal clonidine in cesarean section are used to improve the anaesthetic block, to reduce the dose of local anaesthetics, and to prolong postoperative analgesia. It can also be combined with intrathecal opioids, as there is a synergic effect as discussed in previous paragraph.

In a recent study, 37.5 μg of clonidine added to hyperbaric bupivacaine was suggested as the optimal dose for emergency cesarean surgery, allowing reduction of up to 18% of the total dose of hyperbaric bupivacaine. [81] Adding clonidine 75μg to hyperbaric bupivacaine prolongs spinal anaesthesia and improves early postoperative analgesia after cesarean section, but does not diminish morphine needs during the first 24 hours of the postoperative period. [82] Other studies have found that 75 μg is a safe dose; prolong the anaesthetic block and enhance postoperative analgesia, with minimal side effects and no harm to the newborn. [83, 84, 85] In a randomized, double blind, dose finding study, Peach et al [86] compared intrathecal clonidine mixed with fentanyl and morphine versus clonidine plus morphine in 240 women undergoing cesarean section with hyperbaric 0.5% bupivacaine. A dose-finding analysis showed similar postoperative efficacy and side effects for groups receiving morphine 100μg with clonidine 60, 90, or 150 μg and concluded that a multimodal approach to 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. In another dose finding study [87] comparing 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 minutes 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.

As a single drug, subarachnoid clonidine is not recommended neither for anaesthesia or post cesarean analgesia. In order to evaluate the analgesic effect of clonidine, a double blind study was carried out in 20 patients undergoing elective cesarean section; [88] 150 μg of spinal clonidine were injected 45 min after general anaesthesia and compared to intrathecal saline as control group. Pain intensity was lower in clonidine treated patients from 20 to 120 min after intrathecal injection ($p< 0.05$), request for first analgesic was also longer in the clonidine group 414±128 min versus 181±169 min ($p< 0.01$). Clonidine side effects were severe; hypotension with a maximal reduction of systolic (15±9%), diastolic (22±12%) and mean arterial pressure

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(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.

In a research [4] using 150, 350 and 450 μg of spinal clonidine performed to evaluate the dose-response hemodynamic and analgesic profiles in the immediate postoperative period of cesarean section under general anaesthesia. The authors found that pain was less in all groups in a dose dependent mode: request for first analgesic 402±75 min, 570±76 min, and 864± 80 min 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 stabilility after 300 and 450 μg suggested a pressor consequence at peripheral sites. In an unpublished research we found that 75 μg of spinal clonidine was not enough to perform curettage in patients with incomplete abortion.

12. Pediatrics

Spinal anaesthesia is safe and effective in children, with many advantages like minimal cardiorespiratory disturbances. Its major limitation is its short duration, which can be extended, as in adults, with the mixture of adjuvants drugs. [90, 91] In postnatal rats, spinal clonidine did not produce signs of neurotoxicity, [33] and has been used in all pediatric age groups, from newborns to teenagers. In newborns, Rochette and coworkers [92] studied 75 patients which were injected with increasing doses of clonidine (0.25, 0.5, 1 y 2 μg/kg) with plain spinal bupivacaine 0.5% (1 mg/kg) and concluded that clonidine 1 μg/kg produces improvement in spinal anaesthesia duration without significant side effects. Dose of 2 μg/kg produced transient hypotension. In a randomized investigation with 45 children aged 6 to 15 years, clonidine 2 μg/kg prolonged motor block and improved postoperative analgesia. Hypotension and bradycardia were 54% and 30% respectively. [93] In children aged 6-8 year undergoing spinal anaesthesia with 0.5% bupivacaine for orthopedic surgery, the addition of clonidine 1 μg/kg prolonged significantly the time to regression of the sensory block and recovery of motor block, also delayed time for first rescue analgesia. Sedation was augmented and propofol requirement were reduced. [94] Batra et al [95] also demonstrated that intratecal clonidine 1 μg/kg reduces propofol dose for sedation in children.

13. Postoperative pain

The term balanced spinal analgesia refers to the antinociceptive effect produced by the interaction between several drugs that injected inside the subarachnoid space would abolish or reduce the intensity of postoperative pain. Spinal non opioids adjuvants compounds have moderate to low analgesic potency, but combined with opioids allow a decrease of opioids

dose for postoperative pain control, resulting in less opioids side effects, promoting recovery and faster home readiness. Spinal alpha2 agonist drugs are not used routinely as a single analgesic in the postoperative period. A single dose of spinal clonidine as a sole postoperative analgesic has poor effect. When clonidine is added to spinal local anaesthetics or spinal opioids it does extend the time to first analgesic dose and decrease the total amount of systemic postoperative opioids. Clonidine spinal synergism with other analgesics is due to antinociceptive actions that have been described in previous paragraphs. In previous sections we have discussed some aspects of postoperative analgesia produced by intrathecal clonidine in various surgical scenarios. In this section we discuss more details on the prevention of postoperative pain with spinal clonidine.

Adding clonidine 150 μg to spinal bupivacaine in patients undergoing femoral osteosynthesis prolonged significantly the first request for analgesics compared to oral clonidine and plain spinal bupivacaine (337±29 min, 313±29 versus 236±27 min respectively), and reduced the total dose of morphine. [96] Combining 50 mg of hyperbaric lidocaine, 25 μg fentanyl, and clonidine 150 μg produced excellent postoperative analgesia in proctological patients. [97] Small doses of spinal clonidine also produce postoperative analgesia without deleterious side effects. In a comparative evaluation of 15 μg versus 30 μg clonidine as analgesic adjuvant added to 15 mg of spinal 0.5% hyperbaric bupivacaine in 90 patients undergoing abdominal hysterectomy, the authors [98] found a prolonged first pain complaint time for those women treated with clonidine compared with patients who did not received spinal clonidine (315.37+50.3, 387.07+83.19 versus 204.8+34.8 minutes). Hemodynamic parameters were alike in all patients.

A recent meta-analysis by Engelman and Marsala [99] found that clonidine increased the duration of postoperative analgesia by 1.63 h [95% confidence interval (CI): 0.93-2.33]. There was a 90% probability that clonidine increases the duration of postoperative analgesia by more than 75 min compared with morphine alone. They also found that spinal clonidine decrease the need for postoperative morphine by a mean of 4.45 mg. (95% CI: 1.40-7.49 mg). Hypotension was the only side effect increased by clonidine (odds ratio 1.78; 95% CI: 1.02-3.12). In patients undergoing transurethral surgery, 25 μg clonidine plus 7.5 mg of subarachnoid isobaric bupivacaine significantly delayed time for first request supplemental analgesia compared to bupivacaine alone (434.1±78. 3 min versus 263.97±40.38 min p=0.000) respectively. [48] In a recent study done with clonidine 30 μg added to intratecal bupivacaine-fentanyl, the authors demonstrated that the incidence of intraoperative pain and postoperative analgesic requirements were significantly less compared with the patient who did not received the alfa2 agonist for vaginal hysterectomy. [100]

Chest pain after coronary artery bypass surgery has been relieved with intrathecal clonidine in doses 1 μg/kg or 100 μg, with or without spinal opioids. Adding clonidine to neuraxial opioids improves the quality of analgesia postoperatively and expedites the process of weaning from mechanical ventilation, allowing earlier extubation. No serious side effects have been described. [101, 102, 103]

Baker and coworkers [104] hypothesized that hyperbaric clonidine avoid its rostral migration, and consequently reduced some of its side effects such as hypotension, bradycardia and sedation. They use 150 μg of either isobaric or hyperbaric clonidine in 30 elderly patients found

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that patients in the first group needed more intravenous fluid administration, have more bradycardia, but duration of analgesia was significantly larger than in the hyperbaric clonidine group (median, 400 min; range, 115-400 min versus median 265 min; range, 205-400 min. $p < 0.05$). Sedation scores did not differ between groups.

In conclusion, for postoperative pain the addition of clonidine to intrathecal local anaesthetics and/or opioids extends the time to first analgesia and decreases the amount of opioids used. Severe hypotension and bradycardia are seldom observed, and sedation is not an important side effect.

14. Controversy over spinal clonidine dose

As reviewed, there is no universal agreement on recommended dose for the various clinical uses of spinal clonidine. Recently, Ginosar, Riley and Angst [105] did a nice study in volunteers and found out a clonidine dose dependant effect. Significant analgesia to experimental heat pain was detected above 25 μg. After 50 μg the heat pain tolerance increased by that ~1°C, similar to the analgesic effect of 5 mg epidural morphine or 30 μg epidural fentanyl observed in studies using this experimental heat pain model.

Table 1 shows the different doses of intrathecal clonidine in different clinical scenarios of subarachnoid anaesthesia and analgesia. It can be seen that the dose range is wide as already discussed in this chapter. Up until today, there is not a standard recommended dose of subarachnoid clonidine. Doses range from 15 up to 450μg. It is necessary to adjust the dose to several factors: age, type of patients, time of surgery, type of surgery and dose of local anaesthetic and intrathecal opioids used.

Type of surgery	Dose range μg	Effects	Reported side effects	References
Ambulatory	15 to 150	Enhance anaesthesia quality Postoperative analgesia	Prolongs motor block Hypotension	[37, 38, 39]
General surgery	15 to 75	Enhance sensory and motor block Decrease trans operative pain incidence Postoperative analgesia Prevents postoperative hyperalgesia and chronic pain Decreases postoperative analgesic consumption	Hypotension Sedation	[41, 42, 43, 44, 45, 46]
Urology	25 to 150 4 μg/kg	Shortens latency time Retrace regression 2 segments/S1 segment	Bradycardia Hypotension	[47, 48, 49, 50, 51]

Type of surgery	Dose range μg	Effects	Reported side effects	References
		Longer postoperative analgesia		
		Reduce intraoperative opioids		
Orthopaedics	15 to 150	Increases regression to L1 segment and motor block duration	Facilitates high spinal block	[37, 53, 54, 55, 56, 57, 58, 60, 61]
	1-2 μg/kg	Enhance quality anaesthesia	Prolongs time to void	
		Prolongs time for first analgesic		
Obstetrics				
Labour analgesia	15 to 45	Potentiates opioid spinal analgesia	Maternal hypotension	[69, 70, 71, 72, 73, 74, 75, 76]
	50 to 200*	Reduce labour pain	Maternal dry mouth	
			Fetal arrhythmias	
		Prolongs analgesia	Fetal acidosis	
Cesarean	37.5 to 450	Enhance anaesthesia	Maternal hypotension	[81, 82, 83, 84, 85, 86, 87, 88]
		Postoperative analgesia	Sedation	
		Prolongs time for first analgesic request		
Pediatrics	1 to 2 **	Prolongs spinal blockage	Sedation ***	[92, 93, 94, 95]
		Reduces propofol dose	Hypotension***	
			Respiratory depression***	
Post operative analgesia	30 to 450	Enhance spinal anaesthesia	Sedation	[48, 96, 97, 98, 99, 100, 102, 103]
		Prolongs time for first analgesic request	Bradycardia	
		Prolongs postoperative analgesia in a dose response manner	Dose below 150 μg may induce more hypotension	
		Decrease postoperative opioids doses		
* Sole analgesic, ** μg/kg, *** Only with 2 μg/kg				

Table 1. Use of spinal clonidine

15. Conclusions

Spinal anaesthesia was described over 100 years ago. Since then, neuroaxial drug administration has advanced exponentially and nowadays includes a large variety of medication that provides not only anaesthesia, but analgesia as well. The growing interest in alpha2 agonists

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for intrathecal use has motivated innumerable research due to its ability to improve anaesthesia and neuraxial analgesia without the side effects of opioids such as respiratory depression, pruritus and urinary retention. Their analgesic effect is due to their binding on alpha2 adrenoreceptors localized in the brainstem nuclei and spinal substantia gelatinosa linked to analgesic mechanisms. A synergistic action between opioids and clonidine at the level of the spinal cord has been suggested. Clonidine also acts synergistically with local anaesthetics because of its action of opening potassium channels. Side effects of intrathecal clonidine include sedation, hypotension and a reduction of the heart rate. Spinal clonidine doses from 15 up to 450 μg are used in diverse clinical scenarios as adjuvant drug to local anaesthetics and/or opioids with the main goal to enhance spinal analgesia-anaesthesia. Clonidine and dexmedetomidine side effects are sedation, dose related bradycardia and hypotension, but rarely reach critical levels and are easy to treat. The largest evidence about the effectiveness of intrathecal clonidine is provided by studies on post-surgical pain. Although intratecal clonidine is safe, in obstetrics patients we still need to use the smallest dose based on current recommendations.

This chapter may serve as a review to help clinicians decide whether or not to use spinal clonidine as adjuvant drugs in their daily practice.

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