

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,400

Open access books available

133,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Víctor M. Whizar-Lugo, Juan C. Flores-Carrillo and
Susana Preciado-Ramírez

Additional information is available at the end of the chapter

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

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 $\mu\text{g}/\text{kg}$ 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 α_2 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 α_2 agonist, spinal injected clonidine prolongs sensory and motor block, increases sedation and may potentiate hypotension and bradycardia. It has been used in high ($> 150 \mu\text{g}$), low ($< 150 \mu\text{g}$) and small ($< 75 \mu\text{g}$) 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 α_2 agonist, was the first drug used to enhance duration of spinal anaesthesia, and morphine was the first opioid injected with eucaïne 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, perineurally, 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

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 monohydrochloride. 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]

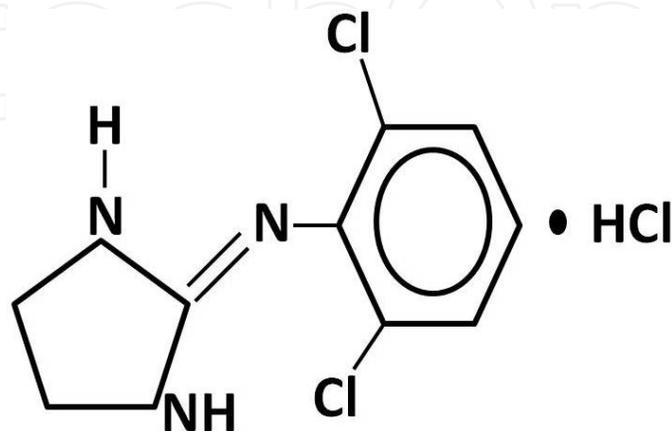


Figure 1. Structural formula of clonidine

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]

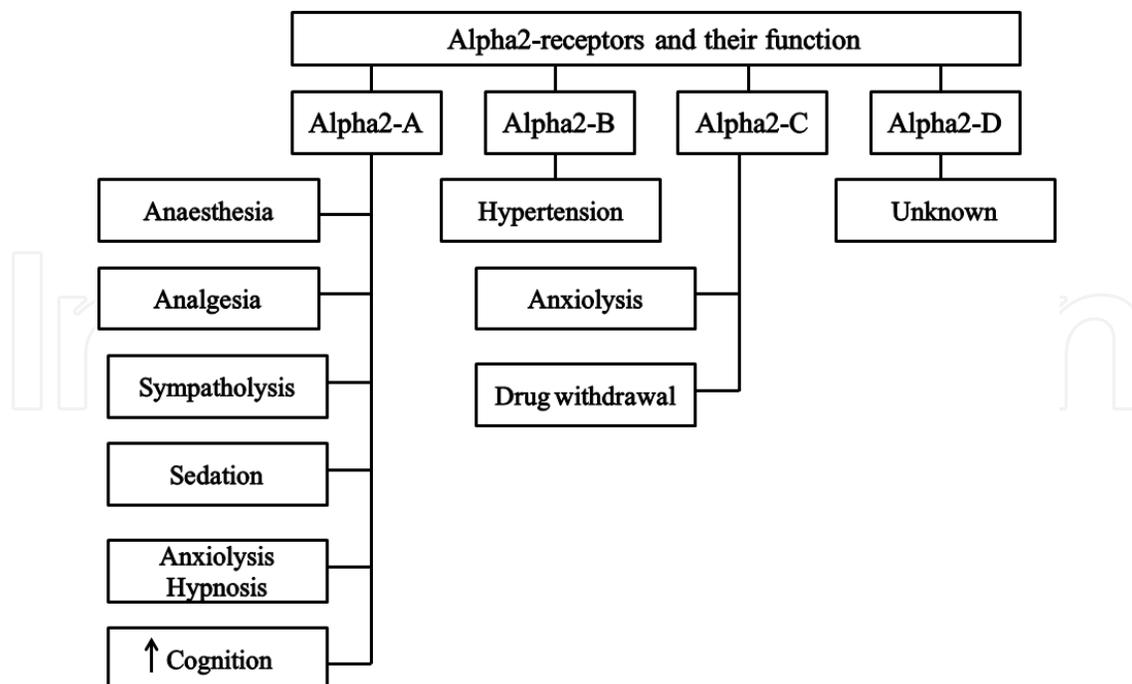


Figure 2. Alpha2 adrenoceptors are membrane proteins belonging to the super family GPCRs. There are four subtypes. Their stimulation has wide therapeutic effects.

The anatomic site of action of the alpha₂ agonists involves specific receptors of the spinal dorsal horn and supraspinally in the nucleus coeruleus 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 nucleus coeruleus, the analgesic effect of these drugs is not completely understood, and have a complex mechanism. Alpha₂ agonists induce analgesia by acting in different places; brain, brain stem, spinal cord and peripheral nerves. Their supraspinally analgesic mechanism in the locus coeruleus 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 alpha₂ 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 intricated. Stone and coworkers, [26] in a genetically modified mouse line expressing a point mutation (D79N) in the alpha_{2A} adrenergic receptor investigated the role of the alpha_{2A} receptor in alpha₂ agonist-evoked analgesia and adrenergic-opioid synergy. They were able to demonstrate that the alpha_{2A} 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 alpha_{2A} 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 alpha_{2C} 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] Erdivanli 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.

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 Marri-virta 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, sufentanil 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 cm² in the clonidine group versus 90±30 and 35±20 cm² 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 hernioplasty [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

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 sevoflurane-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 carefully monitored. [52]

10.1. Orthopaedic

Postoperative pain following orthopaedic surgeries has been shown to be a significant negative factor that delays 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 orthopaedic 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 µg/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, anaesthesia 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

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

(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 stability 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 cardio-respiratory 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

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

* Sole analgesic, ** $\mu\text{g}/\text{kg}$, *** Only with 2 $\mu\text{g}/\text{kg}$

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 α_2 agonists

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.

Author details

Víctor M. Whizar-Lugo¹, Juan C. Flores-Carrillo² and Susana Preciado-Ramírez³

1 Anaesthesiology, Pain Medicine, Internal Medicine and Critical Care Medicine, Hospital General de Tijuana, ISESALUD and Centro Médico del Noroeste, Tijuana, México

2 Anaesthesiology and Critical Care Medicine, Instituto Mexicano del Seguro Social and Centro Médico del Noroeste, Tijuana, México

3 Anaesthesiology Fundación Médica Sur, México D.F., México

References

- [1] Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. *Anesth Analg* 1982;61:741-5.
- [2] Bloor B. Clonidine and other alpha₂ adrenergic agonists: and important new drug class for the perioperative period. *Sem Anesth* 1988;7:170-77.
- [3] Eisenach JC, De Kock M, Klimscha W.alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). *Anesthesiology* 1996;85:655-74.

- [4] Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans. A dose-response study. *Anesthesiology* 1994;81:591-601.
- [5] Mavropoulos G, Minguet G, Brichant JF. Interest for alpha-2 adrenoreceptor agonists in anaesthesia and intensive care medicine. *Rev Med Liege* 2014;69:97-101.
- [6] Matsuki A. Noting new under the sun-A Japanese pioneer in the clinical use of intrathecal morphine. *Anesthesiology* 1983;58:289-90.
- [7] Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. *Science* 1976;192:1357-1358.
- [8] Kroin JS, McCarthy RJ, Penn RD, Lubenow TJ, Ivankovich AD. Continuous intrathecal clonidine and tizanidine in conscious dogs: analgesic and hemodynamic effects. *Anesth Analg*. 2003;96:776-82.
- [9] Ochs G, Loew M, Tonn J, Toyka K. Distribution, tolerability and tissue compatibility of intrathecal tizanidine in the sheep. *Acta Anaesthesiol Scand* 1998;42:786-93.
- [10] Asano T, Dohi S, Ohta S, Shimonaka H, Iida H. Antinociception by epidural and systemic alpha(2)-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. *Anesth Analg*. 2000;90:400-7.
- [11] Stone LS, Fairbanks CA, Wilcox GL. Moxonidine, a mixed alpha(2)-adrenergic and imidazoline receptor agonist, identifies a novel adrenergic target for spinal analgesia. *Ann N Y Acad Sci* 2003;1009:378-85.
- [12] Pettinger WA. Pharmacology of clonidine. *J Cardiovasc Pharmacol* 1980;2 Suppl 1:S21-8.
- [13] Houston MC. Clonidine hydrochloride. *South Med J* 1982;75:713-9.
- [14] Robinson ES, Nutt DJ, Hall L, Jackson HC, Hudson AL. Autoradiographical and behavioural effects of a chronic infusion of antisense to the alpha2D-adrenoceptor in the rat. *Br J Pharmacol* 1999;128:515-22.
- [15] Flordellis C, Manolis A, Scheinin M, Paris H. Clinical and pharmacological significance of alpha2-adrenoceptor polymorphisms in cardiovascular diseases. *Int J Cardiol* 2004;97:367-72.
- [16] Odagaki Y, Toyoshima R. Pharmacological characterization of alpha2D-adrenergic receptor-mediated [35S]GTPgammaS binding in rat cerebral cortical membranes. *Pharmacol Res* 2008;57:435-44.
- [17] Quaglia W, Del Bello F, Giannella M, Piergentili A, Pignini M. α 2C-adrenoceptor modulators: a patent review. *Expert Opin Ther Pat* 2011;21:455-81.
- [18] Civantos Calzada B, Aleixandre de Artiñano A. Alpha-adrenoceptor subtypes. *Pharmacol Res* 2001;44:195-208.

- [19] Lee A, Rosin DL, Van Bockstaele EJ. Ultrastructural evidence for prominent postsynaptic localization of alpha₂C-adrenergic receptors in catecholaminergic dendrites in the rat nucleus locus coeruleus. *J Comp Neurol* 1998;394:218-29.
- [20] Pan HL, Wu ZZ, Zhou HY, et al. Modulation of pain transmission by G-protein-coupled receptors. *Pharmacol Ther* 2008;117:141-61.
- [21] Valenzuela-Harrington M, Negrete-Díaz V, Rodríguez-Moreno A. Núcleo coeruleo. *Neurotransmisores, funciones y patología. Anest Mex* 2007;19:155-66.
- [22] Whizar-Lugo V. El núcleo coeruleus, receptores alfa₂ adrenérgicos y anestesia. *Anest Mex* 2007;19:130-34.
- [23] Wei ZY, Karim F, Roerig SC. Spinal morphine/clonidine antinociceptive synergism: involvement of G proteins and N-type voltage-dependent calcium channels. *J Pharmacol Exp Ther* 1996;278:1392-407.
- [24] Wilcox GL, Carlsson KH, Jochim A, Jurna I. Mutual potentiation of antinociceptive effects of morphine and clonidine on motor and sensory responses in rat spinal cord. *Brain Res* 1987;405:84-93.
- [25] Roerig SC, Lei S, Kitto K, Hylden JK, Wilcox GL. Spinal interactions between opioid and noradrenergic agonists in mice: multiplicativity involves delta and alpha-2 receptors. *J Pharmacol Exp Ther*. 1992;262:365-74.
- [26] Stone LS, MacMillan LB, Kitto KF, Limbird LE, Wilcox GL. The alpha_{2a} adrenergic receptor subtype mediates spinal analgesia evoked by alpha₂ agonists and is necessary for spinal adrenergic-opioid synergy. *J Neurosci*. 1997;17:7157-65.
- [27] Fairbanks CA, Stone LS, Kitto KF, et al. alpha₂C-Adrenergic receptors mediate spinal analgesia and adrenergic-opioid synergy. *J Pharmacol Exp Ther* 2002;300:282-90.
- [28] Chabot-Doré AJ, Millicamps M, Stone LS. The delta-opioid receptor is sufficient, but not necessary, for spinal opioid-adrenergic analgesic synergy. *J Pharmacol Exp Ther* 2013;347:773-80.
- [29] Schuster DJ, Kitto KF, Overland AC, et al. Protein kinase C ϵ is required for spinal analgesic synergy between delta opioid and alpha-2A adrenergic receptor agonist pairs. *J Neurosci*. 2013;33:13538-46.
- [30] Guevara-López U, Aldrete JA, Covarrubias-Gómez A, Hernández-Pando RE, López-Muñoz FJ. Absence of histological changes after the administration of a continuous intrathecal clonidine in Wistar rats. *Pain Pract*. 2009;9:122-9.
- [31] Erdivanli B, Altun M, Sezen OK, Colakoğlu SA. Anti-nociceptive, analgesic and pathohistological effects of intrathecal dexmedetomidine and bupivacaine in rats. *Rev Bras Anestesiología*. 2013;63:183-7.

- [32] Zhang H, Zhou F, Li C, et al. Molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and its neurotoxicity evaluation: an in vivo and in vitro experimental study. *PLoS One*. 2013;8:e55556.
- [33] Walker SM, Grafe M, Yaksh TL. Intrathecal clonidine in the neonatal rat: Dose-dependent analgesia and evaluation of spinal apoptosis toxicity. *Anesth Analg* 2012;115:450-460.
- [34] Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med*. 2008;33:159-67.
- [35] Whizar-Lugo VM, Martínez-Gallegos N, Torres-Chávez J. Polémicas en anestesia subaracnoidea. *Anest Mex* 2004;16:109-123.
- [36] Salinas FV, Liu SS. Spinal anaesthesia: local anaesthetics and adjuncts in the ambulatory setting. *Best Pract Res Clin Anaesthesiol*. 2002;16:195-210.
- [37] van Tuijl I, Giezeman MJ, Braithwaite SA, Hennis PJ, Kalkman CJ, van Klei WA. Intrathecal low-dose hyperbaric bupivacaine-clonidine combination in outpatient knee arthroscopy: a randomized controlled trial. *Acta Anaesthesiol Scand* 2008;52:343-9.
- [38] Merivirta R, Kuusniemi K, Jaakkola P, Pihlajamäki K, Pitkänen M. Unilateral spinal anaesthesia for outpatient surgery: a comparison between hyperbaric bupivacaine and bupivacaine-clonidine combination. *Acta Anaesthesiol Scand*. 2009;53:788-93.
- [39] De Kock M, Gautier P, Fanard L, Hody JL, Lavand'homme P. Intrathecal ropivacaine and clonidine for ambulatory knee arthroscopy: a dose-response study. *Anesthesiology* 2001;94:574-8.
- [40] Julião MC, Lauretti GR. Low-dose intrathecal clonidine combined with sufentanil as analgesic drugs in abdominal gynecological surgery. *J Clin Anesth*. 2000;12:357-62.
- [41] Braz JR, Koguti ES, Braz LG, Croitor LB, Navarro LH. Effects of clonidine associated to hyperbaric bupivacaine during high-level spinal anesthesia. *Rev Bras Anesthesiol* 2003;53:561-72.
- [42] Yoganarasimha N, Raghavendra T, Amitha S, Shridhar K, Radha M. A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries. *Indian J Anaesth*. 2014;58:43-7.
- [43] De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. *Anesth Analg* 2005;101:566-72.
- [44] Ghodki PS, Sardesai SP, Thombre SK. Evaluation of the effect of intrathecal clonidine to decrease shoulder tip pain in laparoscopy under spinal anaesthesia. *Indian J Anaesth* 2010;54:231-4.

- [45] Dobrydnjov I, Axelsson K, Thörn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. *Anesth Analg* 2003;96:1496-503.
- [46] Thakur A, Bhardwaj M, Kaur K, et al. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomized double-blinded study. *J Anaesthesiol Clin Pharmacol* 2013;29:66-70.
- [47] Santiveri X, Arxer A, Plaja I, Metje MT, Martínez B, Villalonga A, López M. Anaesthetic and postoperative analgesic effects of spinal clonidine as an additive to prilocaine in the transurethral resection of urinary bladder tumours. *Eur J Anaesthesiol* 2002;19:589-93.
- [48] Gecaj-Gashi A, Terziqi H, Pervorfi T, Kryeziu A. Intrathecal clonidine added to small-dose bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery. *Can Urol Assoc J* 2012;6:25-9.
- [49] Kanazi GE, Aouad MT, Jabbour-Khoury SI, et al.. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. *Acta Anaesthesiol Scand* 2006;50:222-7.
- [50] Andrieu G, Roth B, Ousmane L, et al. The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. *Anesth Analg* 2009;108:1954-7.
- [51] Larsen B, Dorscheid E, Macher-Hanselmann F, Büch U. Does intrathecal clonidine prolong the effect of spinal anesthesia with hyperbaric mepivacaine? A randomized double-blind study. *Anaesthesist* 1998;47:741-6.
- [52] Ouro-Bang'na Maman AF, Sama HD, Alassani F, Egbohou P, Chobli M. Severe differed respiratory depression after intrathecal administration of morphine and clonidine on a 70-year-old patient. *Ann Fr Anesth Reanim* 2009;28:701-3.
- [53] Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal clonidine and isobaric bupivacaine for orthopedic surgery: a dose-response study. *Anesth Analg* 2004;99:1231-8.
- [54] Amaranto MA, Berrío C. Clonidina por vía subaracnoidea en pacientes de traumatología. *Rev Colomb Anestesiología* 2000;28:149-56.
- [55] Kaabachi O, Zarghouni A, Ouezini R, Abdelaziz AB, Chattaoui O, Kokki H. Clonidine 1 microg/kg is a safe and effective adjuvant to plain bupivacaine in spinal anesthesia in adolescents. *Anesth Analg*. 2007;105:516-9.
- [56] Fournier R, Van Gessel E, Weber A, Gamulin Z. Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement. *Br J Anaesth* 2002;89:562-6.
- [57] Mahendru V, Tewari A, Katyal S, et al. A comparison of intrathecal dexmedetomidine, clonidine, and fentanyl as adjuvants to hyperbaric bupivacaine for lower limb

- surgery: A double blind controlled study. *J Anaesthesiol Clin Pharmacol.* 2013;29:496-502.
- [58] Agarwal D, Chopra M, Mohta M, Sethi AK. Clonidine as an adjuvant to hyperbaric bupivacaine for spinal anesthesia in elderly patients undergoing lower limb orthopedic surgeries. *Saudi J Anaesth* 2014;8:209-14.
- [59] Dobrydnjov I, Axelsson K, Gupta A, et al. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: a double-blind, randomized and placebo-controlled study. *Acta Anaesthesiol Scand* 2005;49:538-45.
- [60] Gehling M, Tryba M, Lüsebrink T, Zorn A. Can the addition of clonidine improve the analgesic efficacy of low dose intrathecal morphine? A randomised double-blind trial. *Anaesthesist* 2003;52:204-9.
- [61] Grace D, Milligan KR, Morrow BJ, Fee JP. Co-administration of pethidine and clonidine: a spinal anaesthetic technique for total hip replacement. *Br J Anaesth* 1994;73:628-33.
- [62] Hong RW. Less is more: the recent history of neuraxial labor analgesia. *Am J Ther.* 2010;17:492-7.
- [63] Roelants F. The use of neuraxial adjuvant drugs (neostigmine, clonidine) in obstetrics. *Curr Opin Anaesthesiol* 2006;19:233-7.
- [64] Datta S. Spinal opiates in obstetrics. In *Obstetric anaesthesia handbook*. Fourth Edition. Springer USA. Pags 89-99. 2006.
- [65] Goudra BG, Singh PM. Remifentanil in labor. *J Obstet Anaesth Crit Care* 2013;3:74-6.
- [66] Sultan P, Murphy C, Halpern S, Carvalho B. The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis. *Can J Anaesth* 2013;60:840-54.
- [67] Pandya ST. Labour analgesia: Recent advances. *Indian J Anaesth.* 2010;54:400-8.
- [68] Van de Velde M. Neuraxial analgesia and fetal bradycardia. *Curr Opin Anaesthesiol* 2005;18:253-6.
- [69] Mercier FJ, Boulay G, Ben Ayed M, Benhamou D. Combined spinal and epidural analgesia for labor. Prolongation by addition of a minidose of clonidine to sufentanil. An initial study. *Ann Fr Anesth Reanim* 1996;15:263-5.
- [70] Mercier FJ, Dounas M, Bouaziz H, Des Mesnards-Smaja V, Foiret C, Vestermann MN, Fischler M, Benhamou D. The effect of adding a minidose of clonidine to intrathecal sufentanil for labor analgesia. *Anesthesiology* 1998;89:594-601.
- [71] Gautier PE, De Kock M, Fanard L, Van Steenberge A, Hody JL. Intrathecal clonidine combined with sufentanil for labor analgesia. *Anesthesiology* 1998;88:651-6.

- [72] Labbene I, Gharsallah H, Abderrahman A, et al. Effects of 15 mcg intrathecal clonidine added to bupivacaine and sufentanil for labor analgesia. *Tunis Med* 2011;89:853-9.
- [73] Chiari A, Lorber C, Eisenach JC, et al. Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor: a dose-response study. *Anesthesiology* 1999;91:388-96.
- [74] Missant C, Teunkens A, Vandermeersch E, Van de Velde M. Intrathecal clonidine prolongs labour analgesia but worsens fetal outcome: a pilot study. *Can J Anaesth*. 2004;51:696-701.
- [75] Dewandre PY. The right drug and dose for neuraxial labour analgesia. *Acta Anaesthesiol Belg* 2006;57:395-9.
- [76] Belhadj Amor M1, Draief A, Ouezini R, Dhahri S, Jebali A, Lamine K, Ferjani M. 30 microg intrathecal clonidine prolongs labour analgesia, but increases the incidence of hypotension and abnormal foetal heart rate patterns. *Ann Fr Anesth Reanim*. 2007;26:916-20.
- [77] Paech MJ, Banks SL, Gurrin LC, Yeo ST, Pavy TJ. A randomized, double-blinded trial of subarachnoid bupivacaine and fentanyl, with or without clonidine, for combined spinal/epidural analgesia during labor. *Anesth Analg* 2002;95:1396-401.
- [78] Van de Velde M, Berends N, Kumar A, Devroe S, Devlieger R, Vandermeersch E, De Buck F. Effects of epidural clonidine and neostigmine following intrathecal labour analgesia: a randomised, double-blind, placebo-controlled trial. *Int J Obstet Anesth*. 2009;18:207-14.
- [79] Eisenach JC, Dobson CE, Inturissi CE, Hood D, Agner PB. Effect of pregnancy and pain on cerebrospinal fluid immunoreactive enkephalins and norepinephrine in healthy humans *Pain* 1990;43:149-54.
- [80] Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. *Br J Anaesth* 2011;107:308-18.
- [81] Bajwa SJ, Bajwa SK, Kaur J, Singh A, Singh A, Parmar SS. Prevention of hypotension and prolongation of postoperative analgesia in emergency cesarean sections: A randomized study with intrathecal clonidine. *Int J Crit Illn Inj Sci* 2012;2:63-9.
- [82] van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: a randomized controlled trial. *Br J Anaesth* 2006;97:365-70.
- [83] Bhure A, Kalita N, Ingle P, Gadkari CP. Comparison of different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia and postoperative an-

- algnesia in patients undergoing caesarian section. *People's Journal of Scientific Research* 2012;5:19-23.
- [84] Marzieh Beigom Khezri, Meisam Rezaei, Morteza Delkhosh Reihany, Ezzatalsadat Haji Seid Javadi. Comparison of postoperative analgesic effect of intrathecal clonidine and fentanyl added to bupivacaine in patients undergoing cesarean section: A prospective randomized double-blind study. *Pain Res Treat* 2014; Article ID 513628, 7 pages.
- [85] Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. *Saudi J Anaesth* 2013;7:283-90.
- [86] Paech MJ, Pavy TJ, Orlikowski CE, Yeo ST, Banks SL, Evans SF, Henderson J. Postcesarean analgesia with spinal morphine, clonidine, or their combination. *Anesth Analg* 2004;98:1460-6.
- [87] Shah BB, Joshi SS, Shidhaye RV, Lakhe JN. Comparison of different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing caesarian section. *Anaesth Pain & Intensive Care* 2012;16:266-72.
- [88] Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. *Anesthesiology* 1992;77:267-74.
- [89] Polati E, Finco G, Bartoloni A, et al. Treatment of postoperative pain by balanced spinal analgesia. *Chir Ital* 1995;47:30-6.
- [90] Kokki H. Spinal blocks. *Paediatr Anaesth*. 2012;22:56-64.
- [91] Gupta A, Saha U. Spinal anesthesia in children: A review. *J Anaesthesiol Clin Pharmacol* 2014;30:10-18.
- [92] Rochette A, Raux O, Troncin R, et al.. Clonidine prolongs spinal anesthesia in newborns: a prospective dose-ranging study. *Anesth Analg* 2004;98:56-9.
- [93] Kaabachi O, Ben Rajeb A, Mebazaa M, Safi H, Jelel C, Ben Ghachem M, Ben Ammar M. Spinal anesthesia in children: comparative study of hyperbaric bupivacaine with or without clonidine. *Ann Fr Anesth Reanim* 2002;21:617-21.
- [94] Cao JP, Miao XY, Liu J, Shi XY. An evaluation of intrathecal bupivacaine combined with intrathecal or intravenous clonidine in children undergoing orthopedic surgery: a randomized double-blinded study. *Paediatr Anaesth* 2011;21:399-405.
- [95] Batra YK, Rakesh SV, Panda NB, Lokesh VC, Subramanyam R. Intrathecal clonidine decreases propofol sedation requirements during spinal anesthesia in infants. *Paediatr Anaesth* 2010;20:625-32.

- [96] Dobrydnjov I, Axelsson K, Samarütel J, Holmström B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. *Acta Anaesthesiol Scand.* 2002;46:806-14.
- [97] Martínez GL, Alfonso R, León V AR, Orizondo PS. Clonidina intratecal para alivio del dolor posoperatorio en cirugía proctológica. Su combinación con otros agentes. *Rev Cubana Cir* 2001;40:297-304.
- [98] Singh YA, Dwivedib S, Yadav K. Comparative evaluation of effects of different doses of intrathecal clonidine with bupivacaine on post operative pain relief. *Int J Biol Med Res* 2013; 4:2703-06.
- [99] Engelman E, Marsala C. Efficacy of adding clonidine to intrathecal morphine in acute postoperative pain: meta-analysis. *Br J Anaesth* 2013;110:21-7.
- [100] Chopra P, Talwar V. Low dose intrathecal clonidine and fentanyl added to hyperbaric bupivacaine prolongs analgesia in gynecological surgery. *J Anaesthesiol Clin Pharmacol* 2014;30:233-7.
- [101] Nader ND, Li CM, Dosluoglu HH, Ignatowski TA, Spengler RN. Adjuvant therapy with intrathecal clonidine improves postoperative pain in patients undergoing coronary artery bypass graft. *Clin J Pain* 2009;25:101-6.
- [102] Lena P, Balarac N, Arnulf JJ, Teboul J, Bonnet F. Intrathecal morphine and clonidine for coronary artery bypass grafting. *Br J Anaesth* 2003;90:300-3.
- [103] Lena P, Balarac N, Arnulf JJ, et al.. Fast-track coronary artery bypass grafting surgery under general anesthesia with remifentanyl and spinal analgesia with morphine and clonidine. *J Cardiothorac Vasc Anesth.* 2005;19:49-53.
- [104] Baker A, Klimscha W, Eisenach JC, et al. Intrathecal clonidine for postoperative analgesia in elderly patients: the influence of baricity on hemodynamic and analgesic effects. *Anesth Analg* 2004;99:128-34.
- [105] Ginosar Y, Riley ET, Angst MS. Analgesic and sympatholytic effects of low-dose intrathecal clonidine compared with bupivacaine: a dose-response study in female volunteers. *Br J Anaesth* 2013;111:256-63.

