The evolution of spinal/epidural neostigmine in clinical application: Thoughts after two decades

Gabriela Rocha Lauretti

Department of Biomechanics, Medicine and Rehabilitation of Locomotor Members, Teaching Hospital, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Address for correspondence:
Prof. Gabriela Rocha Lauretti,
Rua Maestro Joaquim Rangel,
644, CEP 14025-610 Ribeirão Preto,
São Paulo, Brazil.
E-mail: grlauret@fmrp.usp.br

ABSTRACT

Since the first clinical application of analgesia following spinal anticholinesterase by 1940's, several clinical double-blind studies have been conducted to date, where intrathecal doses of neostigmine in humans ranged from 750 to 1 μg, due to side-effects. Conversely, epidural neostigmine has been evaluated in proportionally higher doses and represents an alternative, but still deserves more investigation concerning both acute and chronic pain, as it seems devoid of important side-effects.

Key words: *Epidural neostigmine, pain, review, spinal neostigmine*

INTRODUCTION

The text focus on the natural evolution of neostigmine's applicability in pain relief. The story starts by anecdotal case reports of analgesia following spinal anticholinesterase by 1940's. 30 years late the interest in anti-nociception by anticholinesterase agents were restarted by Pleuvry and Tobias, in England, culminating with its demonstration of spinal analgesia in animals by 1980's. The search carried on in volunteers and finally with different sorts of clinical randomized double-blind studies, which started by 1990's. Firstly, the differences between patients and volunteers, subsequently the dose-dependent analgesia and side-effects of spinal neostigmine; and finally the surprise of analgesia after its epidural administration were described. When one analyze the past two decades, intrathecal (IT) doses of neostigmine in humans ranged from 750 to 1 μg. Due to side-effects the dose was substantially decreased. As a consequence of the small dose, neostigmine should be applied only as part of multimodal spinal analgesia and further clinical trials are still needed. Conversely, epidural neostigmine may be evaluated in proportionally higher doses and represents an alternative, but still deserves more investigation concerning both acute and chronic pain, as it seems devoid of important side-effects.

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HISTORY OF THE CLINICAL APPLICATION OF ANTICHOLINESTERASE AGENTS AS ANALGESICS: FROM ANECDOTAL REPORTS OF PATIENTS, THROUGH ANIMAL DATA, TO A PROPER STUDY IN VOLUNTEERS (1933-1985)

Eighty years have elapsed since the first citation of the analgesic effects of anticholinesterase agents, when Pellandra[1] observed that intravenous administration of the anticholinesterase drug physostigmine produced analgesia in human beings. In 1942, Kremer described the use of cholinergic and anticholinesterase agents by the IT route to induce analgesia in hemiplegic patients.[2] By 1945, the systemic analgesic action of physostigmine and neostigmine and of the opioid morphine was evaluated in patients by Flodmark and Wrammer.[3]

In the seventies, the antinociceptive effect of cholinergic drugs and a link with opioid analgesia was emphasized.[4,5] Pleuvry and Tobias, in England, were the ones to restart the interest in the cholinergic mechanism of pain.[4] In 1981, autoradiography studies demonstrated the existence of muscarinic binding sites in the substantia gelatinosa, in laminae III and V of the dorsal gray matter of the medulla six, coinciding with the binding sites for opioids. By 1985, Yaksh *et al.* described the antinociception in rat and cat

following spinal cholinomimetic drugs.[7] Petersson *et al.*, impressed by the potential analgesic characteristics of anticholinesterase agents, confirmed that intravenous administration of physostigmine induced immediate, although short-lasting, post-operative analgesia in patients submitted to various types of surgical procedures.[8] In the nineties, a systematic approach to determine potential neurotoxicity of IT methyl sulfate neostigmine revealed safety after histological, physiologic and behavioral testing in rat, dog and sheep,[9,10] and neostigmine also did not influence the neurotoxicity of lidocaine *in vitro*.[11] Spinal cord histological examination in sheep and rat also revealed the safety of paraben-and glucose-containing IT neostigmine.[12] Subsequent clinical testing in human volunteers[13,14] and patients with terminal cancer refractory to conventional therapy[15,16] motivated further clinical trials, that will be detailed in succeeding sections.

SPINAL/EPIDURAL ANALGESIC ACTION OF NEOSTIGMINE

Pharmacokinetics

Neostigmine was introduced in 1931. It is a reversible inhibitor of the enzyme cholinesterase, which results in an increased concentration of the acetylcholine (Ach) neurotransmitter. However, due to its hydrophilic nature (presence of a functional quaternary ammonia), it does not cross the duramater, what justified the interest of its applicability as IT analgesic until early 1990's. After spinal administration of neostigmine, Ach concentration increased from <20 pmol/ml at baseline to >100 pmol/ml within 15 min, while plasma concentration was approximately 5 ng/ml. Concentration in cerebrospinal fluid could be measured for 24 h.[13] The pharmacokinetic of IT neostigmine was best described by a triexponential function with an absorption phase. Individual predicted concentrations varied 100-fold.[17] It was characterized by prolonged distribution ($t1/2\alpha$ = 23 min) and elimination ($t1/2\beta$ = 260 min).[13] No study to date has evaluated the pharmacokinetics of epidural neostigmine.

Mechanisms of IT neostigmine analgesia

The analgesia resulting from spinal administration of neostigmine may be due to the increased concentration of Ach and the consequent binding to M1, M3, M2 and M4[18] muscarinic and to nicotinic receptors [Figure 1].[19-23]

Muscarinic receptors are located in cholinergic interneurons of the dorsal horn of the spinal cord, in the substantia gelatinosa, in laminae III and V of the spinal cord;[6] while α3, α4, α5, α7, β2, β3 and β4 nicotinic subunits are expressed on primary afferent terminals, inhibitory interneurons, descending noradrenergic fibers[21] in the dorsal root ganglion[22] and in microglias.[23]

It was demonstrated that activation of spinal muscarinic type-2 receptors suppressed spinal gamma-amino butyric acid-B (GABA-B) receptor input[24] and that this disinhibiting mechanism ultimately lead to the release of adrenal catecholamines[25] and subsequent reduction in peripheral inflammation.[26] Spinal cord stimulation was also associated with the activation of the cholinergic system in the dorsal horn and mediated via muscarinic receptors, particularly M4, while nicotinic receptors appeared not to be involved.[27]

The existence of a difference in the predominance of different types of cholinergic receptors between males and females has been suggested,[28-30] although controversial.[31] While in males muscarinic receptors may be responsible for the antinociceptive effect, the participation of muscarinic and nicotinic receptors was demonstrated in females.[28]

The spinal cholinergic interneurons may be activated by serotoninergic and noradrenergic descending pathways that inhibit pain.[32] Gabaergic interneurons have muscarinic receptors in the terminal axons and in somatodendritic sites and activation of these receptors increase the excitability of inhibitory interneurons, enhancing the release of GABA in the substantia gelatinosa.[33] This inhibitory gabaergic system is also controlled by cholinergic neurons located deeply in the posterior horn of the spinal medulla.[34] The activation of muscarinic receptors inhibits spinal dorsal horn projection neurons, suggesting a partial

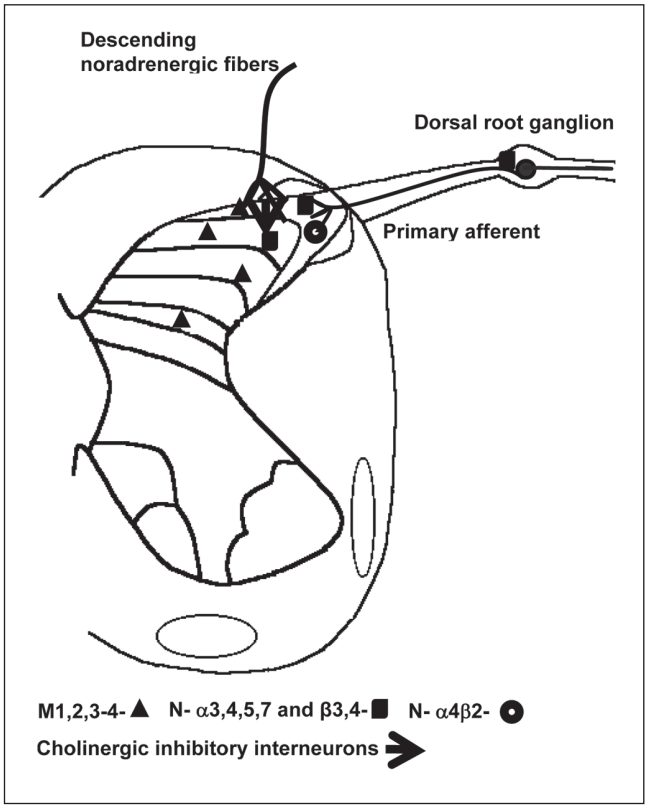

Figure 1: Cholinergic pathways at the dorsal horn

role of GABA-B receptors in normal or in diabetic rats.[35] In addition spinal neostigmine administration resulted in reduced substance P,[36] and there appears to be unidirectional cross-tolerance between morphine and neostigmine.[37] In cats, spinal neostigmine showed antinociceptive effect and this inhibition was only partially mediated by cholinergic mechanism.[38]

Similarly, IT neostigmine may act in different ways on phase and tonic pain,[39] may interact synergistically with α2-agonists,[40,41] nitric oxide and muscimol,[42] may have an additive or synergistic analgesic effect when administered in combination with m agonists,[43] IT gabapentin[44] and nonsteroidal anti-inflammatory drugs.[45] Spinal administration of neostigmine to mice resulted in synergistic or supra-additive effects when the drug was used in combination with ketoprofen, paracetamol or diclofenac. However, only an additive analgesic effect occurred when neostigmine was combined with meloxicam and pyroxicam.[45]

Ach is a major neurotransmitter but also an important signaling molecule in neuron-glia interactions. Expression of Ach receptors has been reported in several glial cell populations, including oligodendrocytes,[46] which may be activated in chronic pan states. Recently, an electron microscopy analysis demonstrated that cholinergic boutons are presynaptic to the dorsal horn neurons as well as to the terminals of sensory primary afferents, suggesting that they are likely to modulate incoming somatosensory information.[47] The authors are suggested that this newly identified dorsal horn cholinergic system in monkeys was the source of the Ach involved in the analgesic effects of epidural neostigmine.[47]

Related to chronic pain, an increased expression of the α3 and α5 nicotinic subunits may contribute to the mechanical hypersensitivity observed following spinal nerve ligation,[21] and IT neostigmine reduced allodynia secondary to rib-retraction in rats, alleviating post-thoracotomy pain.[48] Neostigmine also stimulated the expression of HLA-DR (human leukocyte antigen-DR-microglial marker) and the production of tumor necrosis factor alpha (TNF-α) at dendritic cells while inhibiting the production of TNF-α and interleukin (IL)[13] triggered by long potential stimulation, supporting the existence of the loop through which Ach modulates the function of dendritic cells.[49]

Mechanisms of epidural neostigmine analgesia

Epidural neostigmine analgesia seems to be a result of central rather than peripheral action. In patients undergoing surgery, epidural neostigmine resulted in analgesia after the administration of a ten-fold lower dose (1 μg/kg), when compared to knee intraarticular administration, suggesting a central effect.[50] Epidural neostigmine acts on the enzymes acetylcholinesterase and butylcholinesterase expressed in the meninges that cover the spinal cord.[51,52] Another aspect to be considered is the possible direct action of neostigmine as a muscarinic agonist,[53] in addition to the indirect stimulation of the release of the second intracellular messenger, nitric oxide[54] and suppression of cFos expression.[55]

DOSE-RELATED EFFECTS OF NEOSTIGMINE

In 1995, Hood and Eisenach published the phase I safety assessment of IT neostigmine methylsulfate in humans, when 28 healthy volunteers received IT neostigmine (50-750 μg). The authors demonstrated a dose-dependent incidence of analgesia and adverse effects. Neostigmine (150 μg) caused mild nausea and 500-750 μg caused severe nausea and vomiting. Neostigmine (150-750 μg) produced subjective leg weakness, decreased deep tendon reflexes and sedation. The 750 μg dose was associated with anxiety, increased blood pressure and heart rate and decreased end-tidal carbon dioxide.[13]

At the time, it seemed reasonable to test spinal neostigmine doses ranging from 50 to 200 μg, based on volunteers data. In mid-1996, the first prospective double-blind scientific study evaluated 50, 100, and 200 μg IT neostigmine to patients submitted to standardized general anesthesia for gynecological procedures by the vaginal route.[54] This study confirmed data obtained with volunteers[13] demonstrating dose-dependent analgesia, with peculiar adverse effects such as nystagmus, salivation, mydriasis and bradycardia not responding to intravenous atropine.[56] In contrast, in volunteers who received only the administration of neostigmine by the IT route, the most prominent adverse effect was the occurrence of nausea and vomiting,[13] which was later seen as anguish-producing and stressful for patients submitted to anesthesia by the regional route.[57,58] The nausea and vomiting observed in volunteers depended on the dose used, on the baricity of the solution and on the method of administration. The cephalic ascension of the drug was apparently responsible for emesis.[13] However, since the doses tested were high (50-750 μg), the initial false impression was that emesis resulted from the high doses, whereas doses in the 100-200 μg range administered to volunteers resulted in analgesia devoid of adverse effects.[13] However, the differences observed at the time between volunteers and patients were intriguing. Specialists were aware of the fact that neostigmine caused analgesia and adverse effects, both of them dose dependent,[13] but the potencies differed between these two populations. Studies on volunteers did not demonstrate analgesia with the administration of doses lower than 100 μ,g,[13] whereas studies on patients demonstrated post-operative analgesia

at lower doses.[56,59] A multicenter study demonstrated dose-dependent analgesia and adverse effects when 25, 50, and 100 μg neostigmine were administered intrathecally to patients submitted to hysterectomy by the vaginal route.[59] Similarly, 25, 50, and 75 μg IT neostigmine resulted in dose-dependent analgesia in patients submitted to orthopedic procedures under regional anesthesia.[60]

This difference agreed with results observed in animals that demonstrated greater potency of IT neostigmine when the drug was administered in the presence of a surgical stimulus compared with the absence of pain.[32] It was assumed that in the presence of a painful stimulus, the patients would have exacerbation of a cholinergic medullary pathway and therefore would not tolerate such high doses of neostigmine as volunteers not stimulated by a surgical act. Complementing this hypothesis, it was speculated that the ratio of the dose of IT neostigmine between patients and volunteers would be approximately 6 (ranging from 4 to 8) and it was inferred that 25-100 μg in patients would correspond to 150-750 μg in volunteers, being related to analgesia and adverse effects.[32] As an example of this theory, if only 750 μg caused analgesia in the hands of volunteers,[13] we may assume that 125 μg neostigmine by the IT route would result in the same benefit in patients submitted to surgery of the upper limb.[61]

CLINICAL TRIALS

Spinal neostigmine as part of multimodal analgesia

This section is divided in the clinical reports where neostigmine was administered alone or in combination with other drugs through the spinal or epidural space [Table 1].

Spinal neostigmine alone

IT neostigmine (200, 100, and 50 μg) was initially evaluated in patients undergoing gynecologic surgeries under general anesthesia and demonstrated dose-dependent analgesia and adverse effects.[59] Afterward, a prospective double-blind study demonstrated that the analgesic effect of spinal neostigmine diluted in saline was not equally effective for the different types of pain or for the different intensities of surgical stimuli. An investigation involving the qualitative evaluation of the analgesic actions of neostigmine administered by the IT route demonstrated that the drug was more effective for pain of the somatic type compared with pain of the visceral type and that intravenous administration of the anticholinergic agent N-butyl scopolamine acted peripherally as an effective complement for visceral pain, suggesting an association between the central cholinergic system and the peripheral anticholinergic system.[61] The analgesic effect resulting from the peripheral anticholinergic drug was effective for visceral pain and might have reflected blockade of sympathetic ganglia through binding to nicotinic receptors, or a direct antispasmodic action on the viscera through an action on muscarinic receptors.[62]

Spinal neostigmine and local anesthetics

A double-blinded study reported 6-9 h analgesia after 100 and 50 μg IT neostigmine in inguinal herniorrhaphy, with a high incidence of nausea and vomiting.[63] In accordance, 50 and 25 μg neostigmine plus 10 mg hyperbaric bupivacaine for perianal surgery also demonstrate analgesia, emesis and prolonged motor blockade.[64] Another study described 7 h of analgesia after the IV low dose ketamine combined with 50 μg IT neostigmine and bupivacaine in gynecologic surgeries, associated with a high incidence of emesis.[65] In conformity, a study conducted on volunteers submitted to IT anesthesia with 7.5 mg bupivacaine in combination with 50, 12.5 or 6.25 μg neostigmine diluted in 5% glucose demonstrated that the incidence of nausea and vomiting was dose dependent and the duration of motor blockade was increased, limiting the use of this combination in ambulatory patients.[66]

Table 1: Analgesic effects of neostigmine

Groups	IT neostigmine in patients	IT neostigmine in volunteers	Epidural neostigmine in patients
Dose	Dose-dependent-1-300 μg[64-70]	Dose-dependent, 100-200 μg with no adverse effects;[13] dose ratio patients/volunteers=6[61]	Dose dependent after doses >1 μg/kg
Potency	Greater potency in the presence of surgical stimuli[61]	Lesser potency in the absence of surgical stimuli[61]	—
Type of pain	More effective for somatic rather visceral type of pain[62]	Not evaluated	Not evaluated
Local anesthetics analgesia	Enhanced[64,65,67,68,71]	Not evaluated	Enhanced[87,89,91,94]
Opioid analgesia	Enhanced[58,72,73-75,82]	Not evaluated	Enhanced[16,95,96,98]
Clonidine analgesia	Enhanced;[76] divergent[79]	Not evaluated	Enhanced combined with sufentanil and ropivacaine[101]
Peripheral anticholinergic analgesia	Enhanced[62]	Not evaluated	Not evaluated

IT: Intrathecal

Tan *et al.* evaluated IT 50 μg neostigmine compared to 300 μg morphine in patients submitted to knee arthrodesis. The study revealed the occurrence of 7 h of post-operative analgesia with the use of neostigmine, with greater patient satisfaction and a lower incidence of adverse effects.[67] Using an open-label, dose-ranging design, patients undergoing cesarean section received either IT placebo or neostigmine 100, 30 and 10 μg solution of 5% glucose in normal saline followed by 2% epidural lidocaine for cesarean section. Compared with the glucose control, neostigmine produced a dose-independent reduction in post-operative morphine use and hourly morphine use was significantly reduced in the neostigmine groups for 10 h post-operatively, without adverse fetal or maternal effects.[68] 5 μg IT neostigmine combined with bupivacaine resulted in a lower consumption of analgesics during the post-operative period and in 14 h of post-operative analgesia when combined with a skin patch with 5 mg nitroglycerin. No adverse effect was observed.[69]

In children, it was assessed analgesia of spinal 0.25, 0.5, 0.75, and 1 μ/kg neostigmine added to bupivacaine for lower abdominal and urogenital procedures. Neostigmine at a dose of 0.75 μ/kg added to bupivacaine significantly prolonged spinal anesthesia duration with reduced post-operative pain scores and rescue analgesic requirements in infants undergoing lower abdominal and urogenital procedures and no additional benefits were provided on increasing it to 1 μ/kg.[70]

Spinal neostigmine and opioids

A double-blinded study demonstrated that combined administration of 50 mg neostigmine and 50 μg morphine resulted in 23 h of effective analgesia in the study population.[58] In patients submitted to abdominal hysterectomy, the combination of 25 μg neostigmine with 25 μg fentanyl given intrathecally with 15 mg of hyperbaric bupivacaine delayed post-operative pain and lowered the number of rescue analgesics,[71] in accordance to others who recently evaluated 25 μg neostigmine with 25 μg fentanyl in the lower abdominal surgery.[72] A subsequent study assessed patients submitted to gynecologic surgeries by the abdominal route under spinal anesthesia with bupivacaine.[73] The patients received combined administration of morphine and low doses of neostigmine for pain of the visceral type. The results revealed that the control patients obtained 3 h of post-operative analgesia, with a higher consumption of analgesics over a period of 24 h. The group that received only bupivacaine and morphine had 4 h of post-operative analgesia. However, the combination of 1, 2.5 or 5 μg neostigmine and morphine resulted in 8 h of analgesia, demonstrating the enhancement of the analgesic effect of morphine, with no increase in the incidence of adverse effects.[72] In accordance, Jain *et al.* described enhanced analgesia after 1 μg IT neostigmine combined to 20 μg fentanyl in total knee replacement surgery.[74] The final analgesic effect may clinically reflect the importance of central cholinergic participation in the mediation of morphine nociception.[22]

Spinal neostigmine and clonidine

A prospective study in cesarean section demonstrated that the combination of 50 μg neostigmine and 150 μg clonidine resulted in a prolongation of post-operative analgesia, although with a higher incidence of nausea and vomiting and motor blockade.[75] The lower consumption of opioids would be explained by the exacerbation of the cholinergic tonus present during the painful stimulus in addition to the IT administration of neostigmine, with both events possibly resulting in increased concentrations of the neurotransmitter Ach in cerebrospinal fluid, present in medullary cholinergic interneurons, thus enhancing the antinociceptive effect of morphine.[76,77] However, another research group did not demonstrate a benefit of the addition of 10 μg IT neostigmine to the combination of IT bupivacaine, clonidine and sufentanil in spinal labor analgesia.[78]

Spinal neostigmine in obstetrics

Multimodal analgesia for the control of labor pain was also evaluated. One group of patients received 2.5 mg bupivacaine in combination with 25 μg IT fentanyl, while a second group additionally received 30 μg clonidine as a third drug and a third group received 10 μg neostigmine as the fourth drug. The addition of clonidine and neostigmine potentiated the analgesia of the first group, which however experienced a higher incidence of nausea.[79] An experimental study demonstrated that IT neostigmine resulted in a greater potentiation of the α2-agonist clonidine compared with dexmedetomidine.[41] The explanations proposed included the lower intrinsic potency of clonidine, which may be clinically enhanced by neostigmine, or the fact that the mechanism of action of dexmedetomidine may be less dependent on nitric oxide production.[41] Another study conducted on patients revealed that the addition of 10 μg IT neostigmine reduced the affective analgesic dose by 25% in 50% (ED 50%) of the patients, shifting the curve of the response to IT sufentanil to the left.[80]

Epidural neostigmine as part of multimodal analgesia

Selection of doses to be evaluated by the epidural route

Neostigmine is a hydrophilic molecule similar to morphine. It is known that only 10-20% of the morphine dose administered epidurally crosses the dura mater to reach the IT space, so that a 10 mg morphine dose administered epidurally is equivalent to 1 mg morphine administered

intrathecally.[81] The extrapolation of these data to the definition of the neostigmine dose to be evaluated by the epidural route followed logical reasoning: As demonstrated in reports published up to that time, the literature suggested that IT doses of 5 μg or 10 μg[73] might be effective as part of multimodal analgesia and the administration of ten times the dose of IT neostigmine might result in post-operative analgesia.[80] Consequently, the IT dose of 10 mg neostigmine would be equivalent to 100 μg neostigmine by the epidural route (or 2 μg/kg in a patient weighing 50 kg) and the IT dose of 5 μg neostigmine would be equivalent to the epidural dose of 1 μg/kg.[82]

Epidural neostigmine alone

Two studies published on this subject are concerned to children[83] and adults.[84] The double-blinded study evaluated 120 children scheduled for surgical repair of hypospadias under general anesthesia. Children were divided into groups and received either no caudal block or neostigmine in doses of 10, 20, 30, 40 and 50 μg/kg respectively at the end of the surgery. Caudal neostigmine alone in the dose range of 20-50 μg/kg provided dose-dependent analgesia. However, dose exceeding 30 μg/kg was associated with a higher incidence of nausea and vomiting.[83] Never in the literature, a patient received such a high dose of epidural neostigmine. Such a dose would be equivalent to 700-3500 μg in a median 70-kg adult patient, more than ten-fold the safe tested dose used in adults, described by others.[85]

In the second study, epidural 4 or 8 μg/kg were infused epidurally diluted with saline under combined spinal anesthesia with lidocaine. The authors described that analgesia after the preemptive administration of epidural 8 μg/kg at 12 and 24 h compared with the other groups with no side-effects.[84]

Epidural neostigmine and local anesthetics

Studies on acute pain assessing the administration of neostigmine by the epidural route started in orthopedic surgery. Patients submitted to knee surgeries received saline or 1, 2 or 4 μg/kg neostigmine, diluted in 1% lidocaine, by the epidural route in a combined anesthetic technique involving spinal anesthesia/epidural analgesia.[82] The results demonstrated 8 h of post-operative analgesia regardless of the dose, with no adverse effects.[81] The local anesthetic lidocaine has been demonstrated to suppress different pain conditions when administered systemically, and part of the antinociceptive effect of systemic lidocaine appears to be mediated via muscarinic and nicotinic receptors.[86] Consequently, epidural lidocaine could also be partially systemically absorbed and enhance epidural neostigmine analgesia.

A different study evaluated epidural lidocaine alone or combined with epidural neostigmine (100 and 200 μg). The addition of neostigmine resulted in significant longer duration of analgesia (dose independent) and sedation (dose dependent). Sensory and motor blockade were identical in all three groups. The authors considered useful analgesia and desirable sedation.[87]

Genitourinary procedures in children demonstrated no efficacy of 1 μg/kg caudal neostigmine mixed with bupivacaine.[88] However, a single caudal injection of 2 μg/kg neostigmine added to ropivacaine offered an advantage over ropivacaine alone for pain relief in children undergoing genitourinary surgery.[89] Another study demonstrated that caudal neostigmine (2, 3 and 4 μg/kg) with bupivacaine produced a dose-independent analgesic effect (16-17 h) and a reduction in post-operative rescue analgesic consumption without increasing the incidence of adverse effects.[90] Another research group evaluated the post-operative analgesic action of high doses of epidural neostigmine and reported that 10 μg/kg, but not 5 μg/kg, resulted in 6 h of analgesia in patients submitted to hysterectomy. The patients did not experience emesis and were submitted to general anesthesia in combination with epidural blockade,[91] nevertheless, sedation was not evaluated.

A total of 80 patients undergoing elective cesarean were given combined spinal-epidural anesthesia with 8 mg hyperbaric bupivacaine plus 10 μg fentanyl. Patients were randomized to receive either saline or 75, 150, or 300 μg neostigmine in 10 ml saline after cord clamping. Global pain assessment for the first 24 h was reduced from 5.4 in the saline group to 3.5 in the neostigmine groups. Nausea and morphine consumption were similar among groups. Intraoperative shivering and sedation were increased in the 300 μg neostigmine group only and post-operative sedation was increased by neostigmine in a dose-independent fashion suggesting a limited role for single bolus-administration epidural neostigmine for analgesia after cesarean delivery.[85] Finally, 60 patients undergoing below umbilical surgeries under epidural anesthesia received 20 ml of 0.5% bupivacaine with either 1 ml of normal saline, 100 μg of neostigmine or 50 mg of ketamine. Both neostigmine and ketamine demonstrated better hemodynamic stability with lesser incidence of hypotension and better analgesia.[92]

Epidural neostigmine and opioids

The combined administration of low doses of morphine and neostigmine by the epidural route was subsequently evaluated.[93] 60 μg neostigmine and 0.6 mg morphine, both administered epidurally, resulted in 11 h of post-operative analgesia in orthopedic surgeries, with no adverse effects.[93] In accordance, a prospective double-blind study concerning

the administration of epidural neostigmine in cancer pain described enhancement of epidural morphine analgesia, devoid of adverse effects.[16] Similarly, caudal 2 μg/kg neostigmine was demonstrated to enhance caudal sufentanil perioperative analgesia.[94]

Epidural neostigmine in obstetrics

Labor, a model of acute pain involving both somatic and visceral pain types revealed no benefit (but no side-effects) off adding 4 μg/kg epidural neostigmine to the mixture 100 mg ropivacaine/10 μg sufentanil,[95] however similar duration of analgesia following 6-7 μg/kg epidural neostigmine combined with 10 mg sufentanil compared to epidural 20 μg sufentanil[96] and further demonstrated that the inclusion of 60 mg lidocaine with epinephrine epidural test dose would affect ambulation in earlier labor.[97]

Prior to 2009, studies examined only single epidural neostigmine bolus administration and did not assess the efficacy of continuous epidural infusion or several aspects of maternal and fetal safety. After then, new data was available concerning epidural neostigmine efficacy and safety for both fetus and mother. A total of 12 healthy women scheduled for elective cesarean delivery were assigned to receive epidural neostigmine 40 or 80 μg as a single bolus, with fetal heart rate and uterine contractions monitored for 20 min. In a subsequent experiment, 40 healthy laboring women were randomized to receive bupivacaine 1.25 mg/mL alone or with neostigmine 4 μg/mL by patient-controlled epidural analgesia. The results revealed that epidural neostigmine bolus did not alter fetal heart rate, nor induce contractions, neither produce nausea. Epidural neostigmine infusion reduced bupivacaine requirement by 19% in all patients and 25% in those with >4 h of treatment but might have contributed to the incidence of mild sedation. Mode of delivery, incidence of maternal nausea, and fetal heart rate abnormality were similar between groups.[98]

In a different study, 70 laboring patients received spinal analgesia with ropivacaine and sufentanil. At 15 min after spinal injection, 10 mL of plain saline or neostigmine 500 μg combined with clonidine 75 μg. Epidural clonidine and neostigmine significantly prolonged initial analgesia and reduced hourly ropivacaine consumption. More patients in the experimental group delivered before the first request for additional analgesia (9 vs. 2). As a conclusion, administration of neostigmine 500 μg and clonidine 75 μg, following the IT injection of ropivacaine and sufentanil, prolongs analgesia, reduced hourly ropivacaine consumption[99] and apparently improved time of delivery.

Prophylactic analgesic action of epidural neostigmine

The authors reported that opioid consumption over a period of 48 h was lower in the group that received 500 μg neostigmine compared to the control group and to the group that received 25 mg of bupivacaine and 50 mg epidural ketamine.[100] The observation of such long-lasting prophylactic effect by neostigmine[100] may reflect the transiently suppression of the stress response demonstrated.[101] The preincisional epidural neostigmine resulted in lower plasma levels of cortisol, while IL-6 was not affected during lower open abdominal.[85] Continuous thoracic epidural neostigmine was evaluated in thoracotomy. The epidural dose of 500 μg bolus followed by 125 μg/h provided preemptive analgesia and an analgesic-sparing effect that improved post-operative analgesia for these patients without increasing the incidence of adverse effects.[102]

ADVERSE EFFECTS

Adverse effects are summarized in Table 2.

Spinal neostigmine

IT neostigmine increased incidence of nausea and vomiting, bradycardia requiring intravenous atropine, anxiety, agitation, or restlessness. It did not affect the duration of motor blockade

Table 2: Adverse effects of IT and epidural neostigmine

Groups	IT neostigmine in patients	IT neostigmine in volunteers	Epidural neostigmine in patients
Nausea/vomiting	Dose-dependent, severe, minimum at doses <5 μg, enhanced by IV opioids[72]	Mild nausea after 150 μg, severe nausea after 500 and 750 μg, dependent on the baricity[13]	Not significant at doses <30 μg/kg[85]
Motor block	Prolonged bupivacaine motor block[65,67,71] divergence in other studies[59,60,69,70]	Subjective leg weakness, decreased deep tendon reflexes after 150-750 μg[13]	None
Bradycardia	After 200 μg, not reversed by atropine[56]	None	None
Tachycardia	None	After 750 μg[13]	None
Hypertension	None at doses up to 100 μg[111]	After 750 μg[13]	100 mg-better haemodynamic stabilitiy, lesser hyptension[94]
Sedation	None described (doses ranging 1-200 μg)	None	Increased at doses 100-200 μg[89] or 300 μg,[87] or >300 μg[76]
Anxiety	None	After 750 μg[13]	None

IT: Intrathecal

or the total amount of ephedrine required.[103] The nausea and vomiting observed in volunteers after spinal neostigmine were depended on the dose used, on the baricity of the solution and on the method of administration and the cephalic ascension of the drug was apparently responsible for emesis.[13] Emesis secondary to IT neostigmine used to be difficult to treat in awake or lightly sedated patients and exacerbated by the combination of opioids injected intravenously, but not when they were injected intrathecally.[71]

Other studies that were conducted to assess the efficacy of different antiemetic drugs in the control of nausea and vomiting characterized emesis as being more intense after manipulation of intra-abdominal viscera[57] compared to orthopedic procedures (somatic type of pain),[58] but not responsive to intravenous droperidol (500 mg), metoclopramide (10 mg),[57,58] ondansetron (4 mg),[65] or dexamethasone (10 mg).[106] The only effective drug seems to be intravenous propofol (2-4 mg/kg/h), but only during the period of infusion,[57,58] secondary to the intrinsic antiemetic property of propofol at sub-hypnotic doses.[105] A possible sedative effect may have reduced the sensation of nausea.[106]

Epidural neostigmine

Administration of neostigmine by the epidural route would be mainly characterized by the action of enzymes located in the meninges,[51,52] with low participation at spinal sites.[13] Until date, epidural doses exceeding 30 μg/kg were associated with a higher incidence of nausea and vomiting[84] and post-operative sedation was increased after 300 μg epidural neostigmine following cesarean delivery.[75]

Anti-hypotensive action of spinal neostigmine

Continued efforts were made in order to assess another possible property of spinal neostigmine, i.e., the ability of the drug to antagonize the hypotensive action secondary to IT anesthesia. In 1994, a study on sheep suggested that hypotension secondary to the administration of a α2-agonist may be prevented by the stimulation of M2 spinal muscarinic cholinergic receptors and by nitric oxide synthesis.[107] It would be extremely interesting and clinically applicable if the drug could minimize the hypotension resulting from regional blockade with a local anesthetic, as demonstrated in rats,[108] in addition to providing post-operative analgesia.

Unfortunately, because of emesis, the doses that could be used in patients were limited and did not reduce the occurrence of hypotension in patients submitted to regional anesthesia with bupivacaine.[109] Studies on sheep[110] clarified that the difference observed between the results obtained with rats and with patients were probably due to the larger size and consequent lower exposure of the spinal cord of the patients proportionally compared with the size of the spinal cord of small animals.[108,110]

CONCLUSIONS

When one analyze the past two decades, IT doses of neostigmine in humans ranged from 750 to 1 μg. Due to side-effects the dose was substantially decreased. Because of the small doses, neostigmine should be applied only as part of multimodal spinal analgesia, and further clinical trials are still needed. Conversely, epidural neostigmine may be evaluated in proportionally higher doses and represents an alternative, but still deserves more investigation concerning both acute and chronic pain, as it seems devoid of important side-effects. Future studies may also include formulations containing liposomes using technology of gradual neostigmine release.[111]

Based on the present data, IT neostigmine dose related efficacy and safety is better approached in patients with spinal doses less than 10 μg, while epidural neostigmine can afford to trials with different doses due to the apparent lack of side effects.

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