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Analgesic effect of intrathecal neostigmine combined with bupivacaine and fentanyl

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Abstract

Background: The spinal route of analgesia has consolidated its place as a major modality in the management of both acute and chronic pain. The search for ideal additives to local anaesthetic agents to prolong the analgesic effects poses a challenge to the anaesthetists. Neostigmine, an anticholinesterase, presents a novel approach to providing analgesia. Neostigmine, when given intrathecally, inhibits breakdown of an endogenous spinal neurotransmitter, acetylcholine, thereby inducing analgesia. We aimed to determine the analgesic and adverse effects of intrathecal neostigmine combined with hyperbaric bupivacaine and fentanyl.

Method: Sixty male adults, ASA I-II requiring lower abdominal surgical procedures under spinal anaesthesia were randomly allocated to 2 groups: Neostigmine group, received intrathecal (IT) 0.5% hyperbaric bupivacaine 15mg, fentanyl 25μg and preservative-free neostigmine 25μg while saline group, received same dose of bupivacaine and fentanyl plus 0.5ml saline. The duration of analgesia, time to use first rescue analgesics and the incidence of adverse effects were recorded.

Results: The mean duration of effective analgesia was 485.6±37.6 minutes in neostigmine group compared with saline group, 316.0±49.15 minutes, p <0.001. Total analgesic consumption 12 hours post-intrathecal injection was also less in the neostigmine group. The incidence of adverse effects such as hypotension, bradycardia, nausea and vomiting were not statistically significant in both groups, p > 0.05.

Conclusion: This study showed that spinal neostigmine 25μg added to hyperbaric bupivacaine and fentanyl provided a significantly longer surgical analgesia and insignificant adverse effects in male adults who had lower abdominal surgery under spinal anaesthesia.

Keywords: *Anticholinesterase, neostimine, bupivacaine, fentanyl, intrathecal*

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Résumé

Contexte: L'analgésie de la colonne vertébrale a consolidé sa place en tant que modalité majeure dans le traitement de la douleur aiguë et chronique. La recherche pour les additifs idéaux des agents analgésiques représente un défi pour les anesthésistes. La néostigmine, un anticholinestérasique, présente une nouvelle approche pour fournir une analgésie. La néostigmine, lorsqu'elle est administrée par voie intrathécale, inhibe la dégradation d'un neurotransmetteur endogène, l'acétylcholine épinière, induisant ainsi une analgésie. Nous avons cherché à déterminer les effets analgésiques et indésirables de la néostigmine intrathécale combinée avec de la bupivacaïne hyperbare et du fentanyl.

Méthode: Soixante adultes de sexe masculin, ASA I-II dont les interventions chirurgicales au niveau de l'abdomen sous anesthésie rachidienne urgeaient ont été répartis au hasard en 2 groupes: la néostigmine, a reçu par voie intrathécale (IT) 0,5% de bupivacaïne hyperbare 15 mg, fentanyl 25ìg et 25ìg sans conservateurs alors que le groupe néostigmine solution saline, a reçu la même dose de bupivacaïne et de fentanyl, plus une solution saline 0,5 ml. La durée de l'analgésie, le temps à mettre pour les premiers secours analgésiques et l'incidence des effets indésirables ont été enregistrés.

Résultats: La durée moyenne de l'analgésie efficace a été de 485,6 ± 37,6 minutes pour le groupe néostigmine par rapport au groupe de la solution saline, qui a été de 316,0 ± 49,15 minutes, p <0,001. Un total de 12 heures de consommations analgésiques après l'injection intrathécale était également moindre dans le groupe néostigmine. L'incidence des effets indésirables comme l'hypotension, la bradycardie, les nausées et les vomissements n'était pas statistiquement significatif dans les deux groupes, p> 0,05.

Conclusion: Cette étude a montré que la néostigmine de la colonne vertébrale 25ìg ajoutée à la bupivacaïne hyperbare et au fentanyl a produit une analgésie chirurgicale significative et des effets indésirables insignifiants chez des adultes de sexe masculin ayant subi une chirurgie abdominale sous anesthésie rachidienne.

Introduction

The management of acute intraoperative and postoperative pain using spinal anaesthesia involves combination of local anaesthetics(LA) with neuraxial adjuvant drugs.The aims are to prolong anaesthesia

Table 2: Diagnosis & type of surgery performed

Group	Diagnosis & type of Surgery performed	Saline Group	Neostigmine Group
Orthopaedic	Fractured lower limbs - ORIF	8	7
	Gangrene Lower limbs - Amputation	2 (34.5%)	3 (33.3%)
Urology	Prostate hypertrophy -Open Prostatectomy	6	5
	Urethral stricture - Urethroplasty	4 (34.5%)	5 (33.3%)
General Surgery	Ingunal hernia -Inguinal herniorraphy	7	9
	Fistula-in-ano -Fistulectomy	2 (31%)	1 (33.3%)
Total		29	30

Table 3: Clinical characteristics

Group	Saline group	Neostigmine Group	Student t-test	P – value
Number of patients	29	30	-	-
Mean time from spinal injection to highest level(T_6) – mins	11.5 ± 2.3	12.5 ± 3.4	1.398	0.167
Time of motor block regression to Bromage scale 0 – mins	238.14 ± 4.97	292.0 ± 18.93	0.772	0.05
Duration of Surgery (mins)	108.3 ± 83.5	91.4 ± 39.5	1.002	0.321
Duration of effective analgesia, mins	316.8 ± 49.15	485.6 ± 37.5		<0.001
Total analgesic consumption 12hrs post-IT injection, mins				
Ketorolac (mg)	66.2 ± 14.7	30.3 ± 10.2		
Paracetamol	1137.93 ±185.96	680.1 ±207.44	-	<0.001

Table 4: Intraoperative side effects and interventions

le Effect	Treatment	Saline group n = 29	Neostigmine group n=30	P-Value
potension	IV 0.9% Saline Infusion and I.V Epinephrine 0.2mg	4(13.8%)	2(6.7%)	0.424*
adycardia	I.V Atropine 0.6mg	3(10.35)	3(10%)	1.000*
usea	-	1(3.5%)	-	0.35*
miting	IV Metoclopromide 10mg	2(6.9%)	1(3.3%)	0.35*
ivering (mild)	Oxygen, warmth, and reassurance	6(20.7%)	2(6.7%)	0.145*
ritus	None	-	1(3.3%)	1.000*
dation	-	2(6.95)	-	0.237*

*Fisher exact test

Adverse effects such as hypotension, bradycardia, nausea, vomiting, restlessness, pruritus and respiratory depression (respiratory rate < 10 breaths/min) were recorded. Episodes of hypotension (SBP < 90mm Hg or lower than 30% of baseline SBP)) were treated with rapid infusion of crystalloids with or without incremental dose of adrenaline 1:10,000. Bradycardia (Heart rate < 55 beats/min) was treated with IV atropine 0.6mg. Vomiting was treated with IV metoclopromide 10mg.

All evaluations were performed and recorded at 1 hour intervals for 12 hours post-intrathecal injection.

Data were analyzed using SPSS 16(SPSS Inc, Chicago,IL). Demographic variables were represented using tables and charts, percentages and graphs while summary statistics were done using means, range, standard deviation and proportions. Test of independence for numerical variables were determined using Chi square and qualitative variables were determined using t-test and ANOVA. Level of statistical significance was set at p value of <0.05.

Results

A total of 59 patients were studied out of 60 recruited for this study. One of the patients in the saline group had his subarachnoid block (SAB) converted to general anaesthesia on account of unanticipated prolongation of surgical procedure and was subsequently excluded from the analysis. The demographic data were comparable in the 2 groups as shown in Table 1.The diagnosis and type of surgery performed are shown in Table 2.

All patients had adequate analgesia before surgical incision was made with sensory block $\geq T_{10}$. The onset of anaesthesia (time to reach T_6 sensory block) was similar in both groups: saline group (11.5 ± 2.3min) and neostigmine group (12.5 ± 3.4 mins), p = 0.167. Neurologically, Neostigmine group showed prolonged motor block as evidenced by the time to fully flex the knee and foot (Bromage 0) of 292.4 ± 18.93 mins compared to saline group 238.14 ± 4.9mins, p = 0.05. (Table 3)

The duration of effective anaesthesia or analgesia (i.e the time from injection of intrathecal drugs to the time the pain score was ≥ 5) was significantly longer, 485.6±37.6 minutes in the neostigmine group compared to saline group, 316.8 ±49.2 minutes, p < 0.001. The total dose of analgesic consumption 12 hours post-intrathecal injection of study drugs was also significantly more in the saline group, 66.2 ±14.7mg ketorolac and 1137 ±186.0mg paracetamol compared to neostigmine group, 31.3 ±10.2 mg ketorolac and 680.1 ± 207.4mg paracetamol, p < 0.001 (Table 3)

Haemodynamically, the 2 groups showed insignificant incidence of hypotension and bradycardia (Table 4). However, a critical look at the cardiovascular changes showed a relatively stable mean systolic and mean arterial pressure (MAP) in the first 15-45 mins postspinal injection in neostigmine group (Fig. 1, 2). Mean heart rate (HR) changes in both groups is similar (Fig 3).

Other incidences of adverse effects (Table 4) showed a statistically insignificant (p value > 0.05) incidence of shivering, nausea, vomiting, pruritus and sedation. No patient had respiratory depression.

Discussion

The use of neostigmine as neuraxial adjuvants to local anaesthetics has undergone series of toxicologic assessments in animals and humans and has been found to be safe [1,6]. Various studies by Yaksh *et al* [6,7], Hood et al [1,8] and Eisenach *et al* [9] showed no evidence of adverse effects on spinal cord blood flow and neural tissue function except dose-dependent

Table 1: Demographic characteristic of patients

	Saline Group	Neostigmine Group	P-Value
Number of Patients	29	30	-
Age of Patients (yrs) Mean SD	43.9 (±16.8)	38.6(±15.5.)	0.207
Weight of Patients (kg)	68.7 (± 12.6)	66.7 (±10.0)	0.499
Height of Patient (cm)	174.6 (±6.08)	174.9(±86)	0.850
ASA grade I/II	15/14	20/10	-

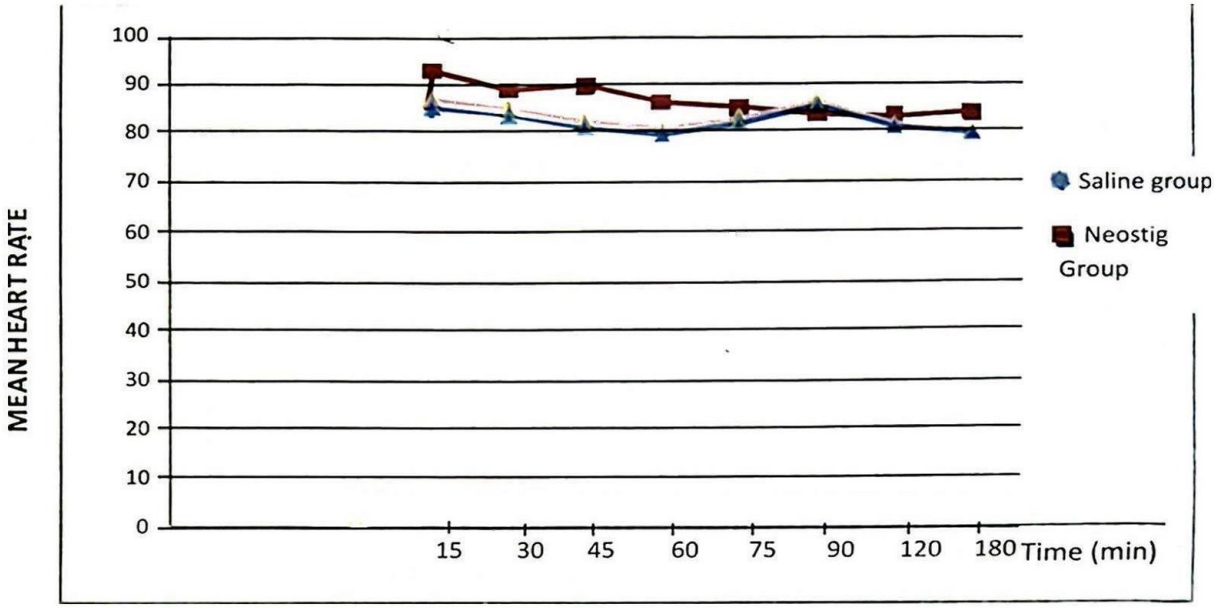

Fig 3: Mean heart rate changes

nausea and vomiting. A meta-analysis by Ho and colleagues analyzed 19 studies in a surgical population, and they did not find any neurological complication with the use of intrathecal neostigmine [10].

The fact that intrathecal neostigmine would enhance the analgesic action of an opioid has been demonstrated by different group of researchers [4,11,12]. The analgesic effect from intrathecal neostigmine results from increase and accumulation in the concentration of the neurotransmitter, acetylcholine (ach) and consequent action at the muscarinic M_1 and M_3 and presynaptic nicotinic receptors present in the cholinergic interneurons at the laminae II and V of the dorsal horn [13]. This study showed that neostigmine 25µg added to intrathecal bupivacaine 15mg and fentanyl 25µg could provide 486 mins (8.1 hrs) of effective analgesia. This combinations also caused a prolonged motor block but serious adverse effects such as hypotension, nausea and vomiting were insignificant.

The additive analgesic effect of opioids and cholinesterase inhibitor has been previously reported. Intrathecal neostigmine 25-75µg does have a sparing effect on morphine consumption after major gynaecological surgery [14]. Intrathecal neostigmine, 1-5µg added to bupivacaine and morphine doubled the time to rescue analgesia and reduced consumption in the first 24 hours after gynaecolgical procedures without raising the incidence of postoperative nausea and vomiting [15]. Lauretti *et al* demonstrated that vaginoplasty surgery similar in duration to spinal morphine [4]. They also concluded that the combination of morphine and neostigmine may allow a reduction in the dose of each component for postoperative analgesia.

In patients undergoing knee replacement surgery, intrathecal neostigmine prolonged motor blockade compared with morphine, which was associated with more pruritus, a late onset of postoperative pain and longer time to rescue analgesia [16]. Overall satisfaction was better in the neostigmine group than in the morphine or placebo. Chung *et al* showed that the combinations of intrathecal neostigmine 12.5µg and intrathecal morphine 50µg for Caesarian section produced better postoperative analgesia with significantly reduced side effects than intrathecal neostigmine 25µg or morphine 100µg alone [11].

Intrathecal neostigmine has been shown by various studies to produce a dose-dependent nausea and vomiting [9,14,15,17]. Liu and co-researchers showed that the addition of neostigmine (6.25µg- 50µg) to 0.5% hyperbaric bupivacaine produced a dose-dependent nausea (33-67%) and vomiting (17-50%) [18]. Spencer *et al* suggested that nausea and vomiting caused by intrathecal neostigmine can be reduced by adding neostigmine to hyperbaric solutions such as hyperbaric bupivacaine, elevating the head of the operating table and using a low-dose [18]. These suggestions were strictly adhered to in this study and this may account for the absence of nausea and very low incidence of

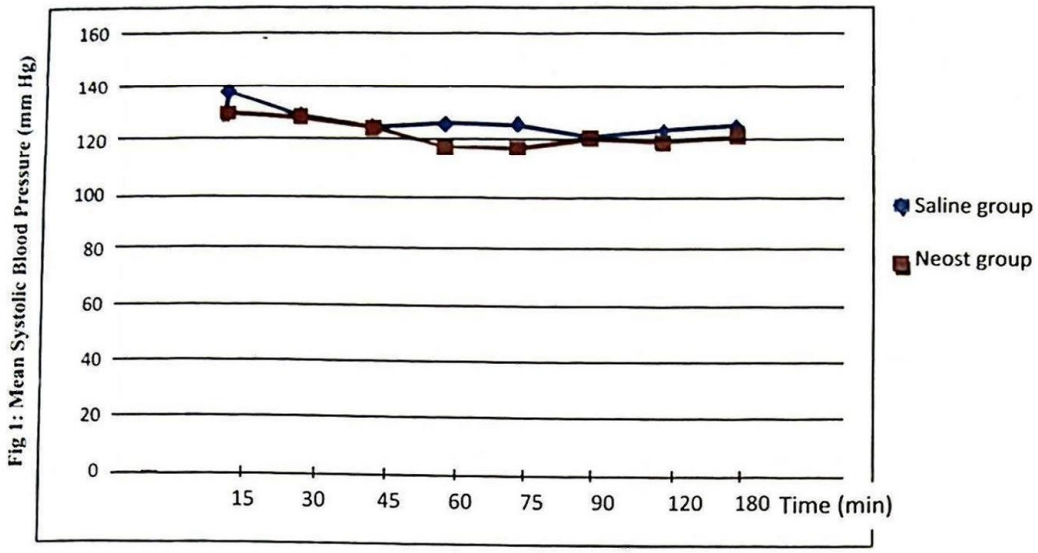

Fig 1: Mean systolic blood pressure changes post injection of study drugs

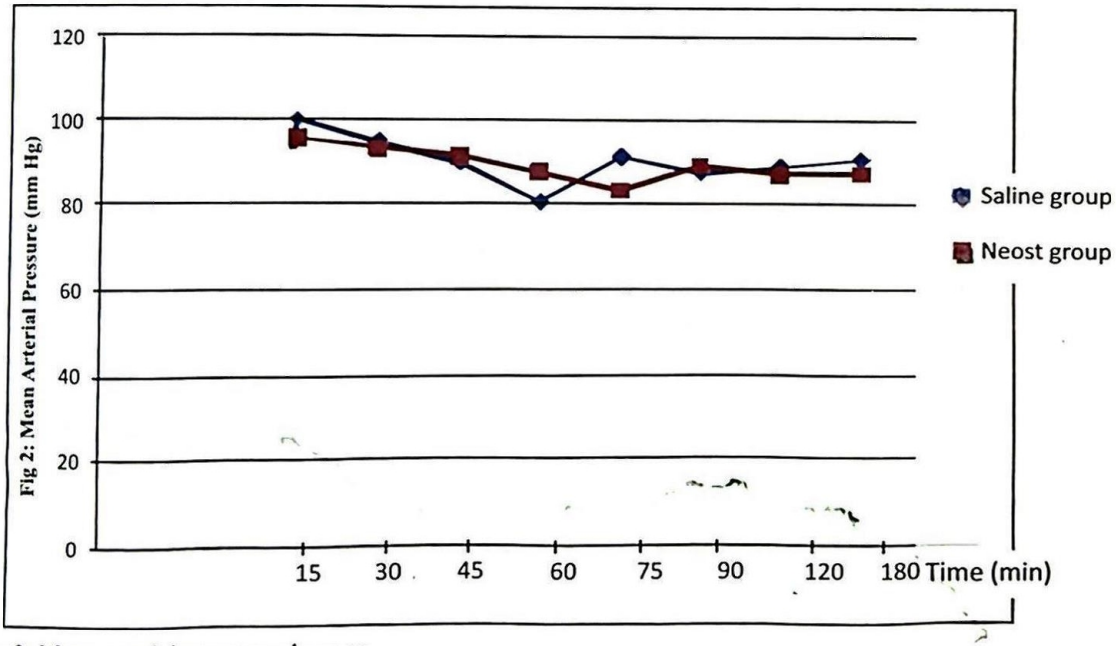

Fig 2: Mean arterial pressure changes

In conclusion, this study showed that the addition of neostigmine 25μg to intrathecal bupivacaine and fentanyl enhanced spinal anaesthesia and produced prolonged postoperative analgesia compared with bupivacaine-fentanyl alone. It also offered low adverse effects. A prolonged motor block caused by intrathecal neostigmine is beneficial in some types of surgery (e g orthopaedic) where profound muscle relaxation is required. However, in a day-case spinal anaesthesia its clinical use may be limited as a prolonged motor block will cause delay in discharging patient home.

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