Neostigmine Counteracts Hypotension Following Intrathecal Lidocaine

İNTRATEKAL LİDOKAİN UYGULAMASINDAN SONRA GÖRÜLEN HİPOTANSİYONUN NEOSTİGMİN İLE ÖNLENMESİ

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Summary

The aim of this study is to investigate whether hypotension, u common side effect of spinal anaesthesia could be prevented by the simultaneous administration of lidocaine and neostigmine.

20 healthy, male mongrel dogs were premedicated with xylazine hydrochloride (2 mg kg″ intramuscularly) in this prospective study. Anaesthesia was induced with i.v. propofol (5 mg kg″) and fentanyl (7 pig kg″). Following intubation, anaesthesia was maintained with i.v. propofol infusion (40 mg kg″ hr″). Laminectomy was performed at Th 10-12 levels in the dorso-ventral position. Measurements were obtained following hemodynamic stabilization. Animals were allocated randomly into two groups to administer either lidocaine 30 mg (group I, n = 10) or lidocaine 30 mg + neostigmine 0.5 mg (group II, n=10) into subarachnoid space at Th 10 level. Mean arterial pressure (MAP) and heart rate (HR) were recorded in evety five minutes for one hour. Cardiac output (CO), pulmonaiy capillaiy wedge pressure (PCWP) and central venous pressure (CVP) were recorded at the I″, 30th and 60th minutes. Viscosity, as well as protein and glucose content and cell type of the cerebrospinal fluid (CSF) were determined before and one hour after neostigmine administration.

MAP and CO values of Group 11 showed a statistically significant increase, when compared with Group I and in Group II; glucose, protein content of CSF and viscosity after neostigmin administration showed a significant increase (p<.0.05).

The addition of neostigmine to lidocaine used in spinal anaesthesia showed that it could provide more stable hemodynamics.

Key Words: Animal, Dog, Anaesthesia, Spinal, Acetylcholinesterase inhibitor, Neostigmine

T Klin J Med Res 1999, 17:1-6

Geliş Tarihi: March 23, 1998

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Özet

Bu çalışmanın amacı spinal anestezinin sık görülen bir komplikasyonu olan hipotansiyonunun, lidokainle aynı anda uygulanan neostigminle önlenip önlenemeyeceğini araştırmaktır.

Bu prospektif çalışmada 20 sokak köpeğine ksilazin hidrokloridle (2 mg kg″ İM) premedikasyon yapıldı. Anestezi indüksiyonu i.v. propofol (5 mg kg″) ve fentanille (7 ng kg″) gerçekleştirildi. Entübasyondan sonra anestezi, i.v. propofol infüzyonuyla (40 mg kg″ saat″) idame ettirildi. Dorsoventral pozisyonda torakal 10-12 seviyesinden laminektomi yapıldı. Hemodinamik stabilizasyon sağlandıktan sonra ölçümler yapıldı. Hayvanlar rastgele torakal 10 seviyesinden stıbaraknoid aralığa 30 mg lidokain (grup I, n = 10) ve 30 mg lidokain + 0.5 mg neostigmin (grup II, H—JO) uygulanmak üzere 2 gruba ayrıldı. Bir saat süreyle her beş dakikada bir ortalama arter basıncı (OAB) ve kalp atım hızı (KAH) kaydedildi. Kardiyak debi (KD), pulmoner kapiller uç basıncı (PKUB) ve santral venöz basınç (SVB) 1., 30. ve 60. dakikalarda kaydedildi. Neostigmin uygulanmadan önece ve uygulandıktan bir saat sonra beyin omurilik sıvısının (BOS) viskozitesi, hücre tipi ve glukoz ile protein içeriği belirlendi.

II.grubun OAB ve KD değerleri I.gruba göre istatistiksel olarak anlamlı bir artış gösterdi ve II.grupta neostigmin uygulamasından sonraki BOS'un glukoz ile protein içeriği ve viskozitesi istatistiksel olarak anlamlı şekilde yüksek bulundu (p<0.05).

Spinal anestezide kullanılan lidokaine neostigmin eklenmesinin daha stabil hemodinami sağlayabileceği gösterildi.

Anahtar Kelimeler: Hayvan, Köpek, Anestezi, Spinal, Asetilkolin esteraz inhibitörü, Neostigmin

T Klin Araştırma 1999, 17:1-6

Spinal anaesthesia is a common anaesthetic technique and hypotension is an important side effect often develops as a result of sympathetic blockade (1). Intrathecal neostigmine represents a

novel approach to provide analgesia by inhibiting breakdown of an endogenous spinal neurotransmitter, acetylcholine. It prevents spinal-block hypotension, when administered intrathecally by activating spinal-cord sympathetic neurons via a muscarinic dependent pathway in many species including humans (2-5).

Therefore, we investigated whether hypotension could be prevented by adding neostigmine to intrathecal lidocainc and also evaluated the biochemical and microbiological alterations in cerebrospinal fluid (CSF) following administration of neostigmine plus lidocaine.

Methods

20 healthy, male mongrel dogs having mean weight 17.8±2.7 kg were studied. All of these animals were free of obvious disease and circulationg microfilaria and had normal biochemical tests.

This study was approved by the Ethical Committee of Veterinary Faculty, University of Ankara. The care for the animals complied with the principles of laboratory animals care and the guide for the care and use of laboratory animals.

The dogs were fasted for 12 hours. Following premedication with xylazine hydrochloride (2 mg kg^{-1} IM) for sedation, ECG electrodes were replaced on 4 limbs of the dogs in prone position. An 18 G intravenous cannula was inserted on vena cephalica antcbrachia and lactated Ringer's solution (10 ml kg^{-1} min^{-1}) was infused.

Anaesthesia was induced with i.v. bolus propofol (5 mg kg^{-1}) and fentanyl citrate (7 Ltg kg^{-1}). All of the animals were intubated with endotracheal tube (7.5 F) immediately after respiratory depression and their lungs were ventilated with 50 % oxygen in air, tidal volume being 15 ml kg^{-1} and frequency 16 breaths min^{-1} via a volume respirator (Engstrom 300, Sweden). Anaesthesia was maintained with continuous i.v. infusion of propofol 40 mg kg^{-1} hr^{-1}.

Femoral artery and vein cannulation were performed for the assessment of hemodynamic parameters by surgical dissection after shaving and scrubing of the surgical area with iodine. An 18 G catheter (Cavafix, Braun-Melsungen, Germany) was proceeded through femoral artery until descending aorta for continuous mean arterial pressure monitoring (MAP) and heart rate (HR). Femoral vein cannulation was performed with a pulmonary artery thermodilution catheter (American Edwards Laboratories, 7.5 F, Irvine, CA) for the measurement of central venous pressure (CVP), pulmonary cappillary wedge pressure (PCWP) and cardiac output (CO).

MAP, PCWP and CVP (Pressure transducer attached to a multi channel Petaş monitoring system, CO, Ankara, Türkiye) and CO were measured (Cardiac output computer-Desseret 1000 cardiac output company, France). MAP and HR were recorded in every five minutes begining from the 1st minute for one hour. CO, PCWP and CVP were recorded at 1st, 30th and 60th minutes.

Following laminectomy at Th 10-12 levels in the dorso-ventral position, dura mater was exposed. Hemodynamic stabilisation was provided in 10° upright position. Then baseline MAP, HR, CVP, PCWP and CO values were recorded. In the thermodilution method CO measurement was performed by obtaining triplicate outputs at frequent intervals using 5% dextorse in water as an indicator.

20 dogs were randomly allocated into two groups to administer either lidocaine hydrochloride 30 mg (Aritmal 2%, ampule = 5 ml, Dinçel A.Ş., Türkiye) in 2.5 ml saline (Group I, n=10) or lidocaine hydrochloride 30 mg in 1.5 ml saline + neostigmine hydrochloride 0.5 mg (Neostigmine 0.5 mg, ampule = 1 ml, Adeka, İst., Türkiye) (Group II, n=10) into subarachnoid space at Th 10 level with a 25 G syringe over 30 seconds.

The dose of local anesthetic was calculated approximately 0.22 ml/kg and injected into subarachnoid space as a standart for a dog 55-60 cm in occiput-tail rost measurement over one minute period (6,7). In regard to this, in each group, 4 ml was used as an average amount (30 mg lidocaine, which is 1.5 ml in 2.5 ml saline in the lidocaine group and lidocaine 30 mg (1.5 ml) in 1.5 ml saline + neostigmine 0.5 mg, which is 1 ml).

Viscosity (via Boehringer Manheim Sticks), protein (Prygallol Red method described by Fujita, Technicon RA-1000 autoanalyser by using DMA microprotein kit) and glucose (Technicon RA-1000

autoanalyser by using Mcnari Glicofix kit, glucose oxidase coupled reaction described by Trinder) content and cell type (white blood cells by using light microscope over Thoma glass) of CSF (1.5 ml) collected at Th 11 level before and 1 hour after neostigmine administration were assessed.

At the end of the study, the operative site was appropriately closed. No neurologic deficits were found during 12 hours of follow-up.

Statistical analysis was performed with non-parametric tests: Mann Whitney-U was used between the groups; Friedman and Multiple Comparison tests were used within the groups. Fischer's exact and Chi square tests were used in the comparison of 20% reduction in the MAP with respect to control values. Wilcoxon two rank was used when comparing physicochemical properties of the CSF between the groups. $p<0.05$ was considered as significant.

Results

Demographic properties were shown in Table 1.

MAP increased significantly in the lidocainc+neostigmine group when compared with lidocaine group at all times studied ($p<0.05$, Figures 1 and Table 2).

Increase in the HR in the lidocaine+neostigmine group was statistically significant, when compared with the lidocaine group at 40-60 minutes after the spinal injection ($p<0.05$, Figure 2).

CO values in the lidocaine+neostigmine group decreased significantly at all times studied ($p<0.05$, Figure 3).

PCWP and CVP values did not differ between the groups (Figure 4 and 5).

Table 1. Demographic properties (Mean ± Sd) (Min-Max)

n	20
Age (year)	1.6±0.5 (1-2)
Weight (kg)	17.8±2.7 (13-22)
Gender	Male

t

Table 2. Incidence of hypotension in the groups [n (%)]

	YES	NO
LIDOCAINE GROUP	10 (100)*	0(0)
LIDOCAINE+NEOSTIGMINE GROUP	1 (10)	9 (90)

**p<0.05 (between the groups)*

There was a statistically significant increase in the viscosity and content of protein and glucose of CSF following neostigmine administration in the study group, but they were within the normal range (Table 3).

Discussion

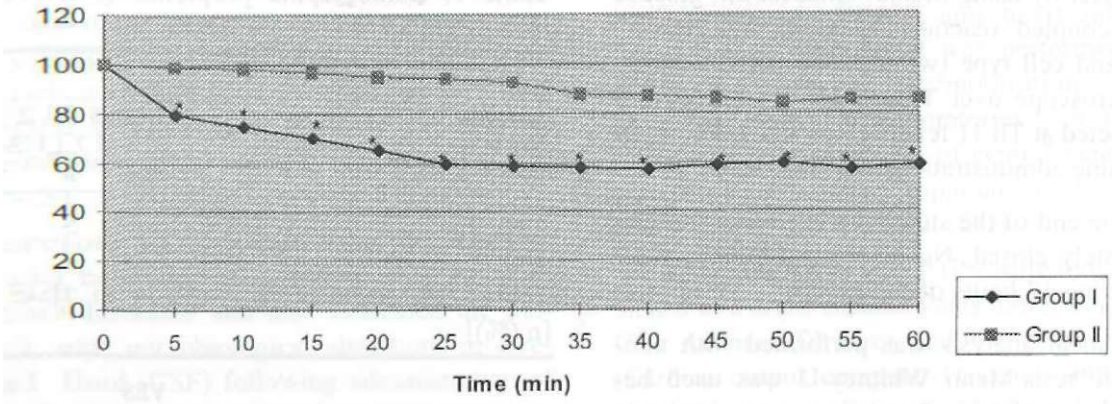
Lidocaine is a commonly used local anaesthetic in patients undergoing spinal anaesthesia and for experimental purpose in animals as well. The reasons for prefering lidocaine are its short half life and less toxic side effects than other local anaesthetics (6,8).

As hypotension is an important complication due to spinal anaesthesia, there are various precautions for preventing it such as; i.v. administration of crystalloid and colloid fluids, maneuvers for improving venous return and i.v. administration of ketamine (9-14). Additionally, it has been recently reported that intrathecal (IT) cholinergic agonists

Table 3. Changes in glucose, protein, viscosity and number of cells of the cerebrospinal fluid before and after neostigmine administration in the study group

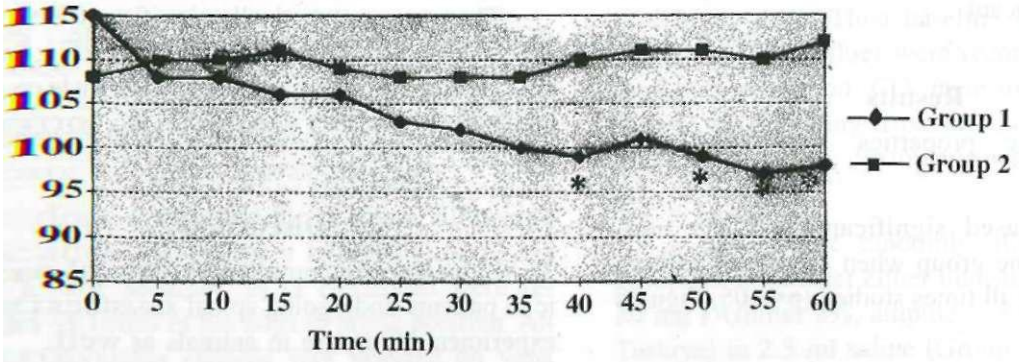
	Glucose (mg/dl)	Protein (mg/dl)	Viscosity	Number of cells in mm^3
Before	57.7	24.6	1.004	4.4
After	76.3*	38.3*	1.007*	4.5

**:p<0.05*



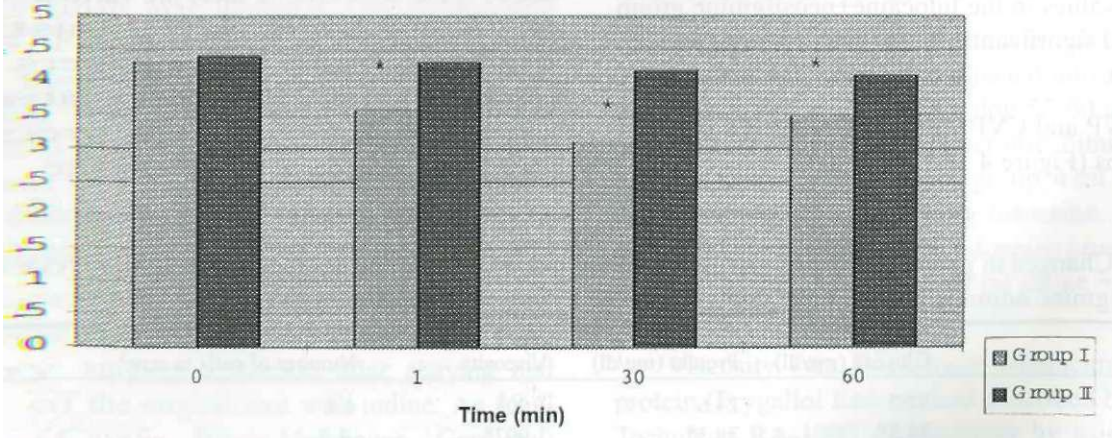
Between the groups)
Lidocaine
Lidocaine+Neostigmine

Mean Arteriel Pressure (MAP) versus time.



Between the groups)

Heart Rate (HR) versus time.



Between the groups)

Cardiac Output (CO) versus time.

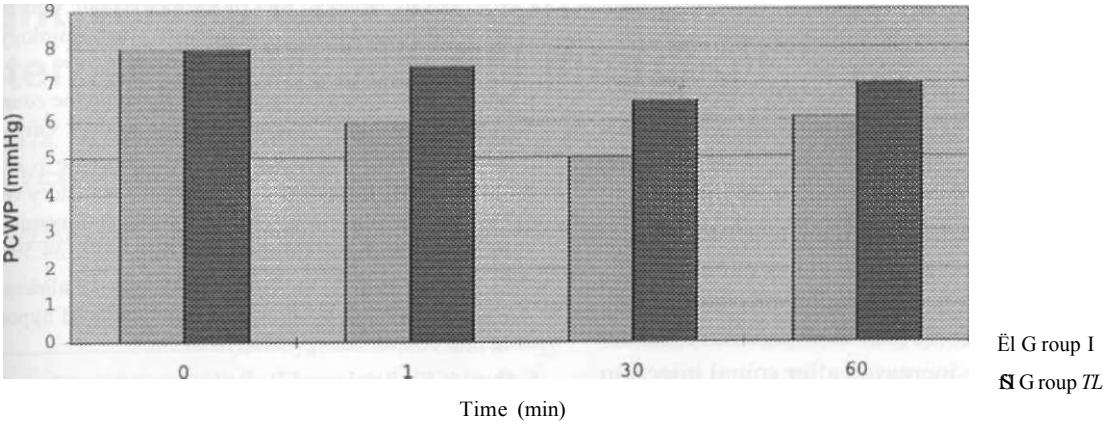


Figure 4. Pulmonary Capillary Wedge Pressure versus time.

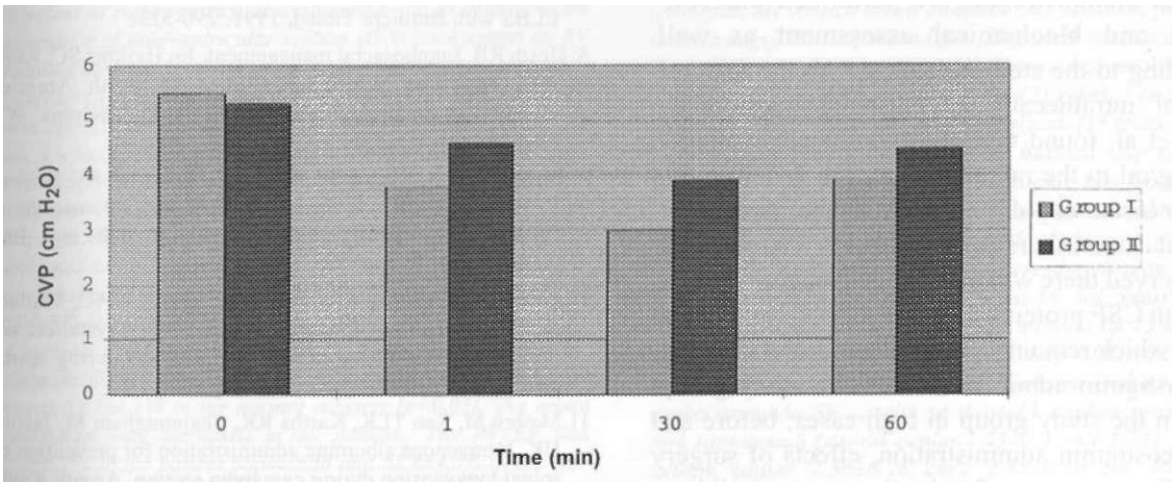


Figure 5. Santral Venous Pressure versus time.

could increase blood pressure due to spinal preganglionic sympathetic activity in contrast to its systemic administration (2-4).

As Carp et al. demonstrated that IT cholinergic agonists (neostigmine, physostigmine, edrophonium and ambenonium) lessenned bupivacaine spmal-block-induced hypotension in rats (5), we investigated whether hypotensive effect of IT lidocaine could be prevented by simultaneous administration of neostigmine in dogs with a spinal cord similar in size to that of humans. In our study we found that neostigmine lessenned spinal block induced hypotension because of its vasopressor effect like Carp et al (5).

Hood et al. reported that simultaneous administration of clonidine to neostigmine (2mg), minimally altered clonidine-induced hemodynamic depression in sheep (15). They reported that sympathetic stimulation by intrathecally administered neostigmine was mild in species with a larger spinal cord such as sheep. In contrast to this study, we found that IT neostigmine (0.5mg) addition to lidocaine counteracted hypotension due to lidocainc alone, although dogs were considered to have larger spinal cords like sheep. But in another study Hood et al. reported that the lack of cardiovascular stimulation could be due to dose, because in contrast to systemic administration relatively large doses of intrathecally administered cholinesterase inliibitors increased blood pressure and heart rate as it occurred in MAP values in our study (16). Therefore, the absence of cardiovascular stimula-

tion was explained by the low dose of neostigmine (< 500 ug). For that reason, we chose 0.5 mg.

In several studies it was reported that the degree of cardiovascular stimulation from intrathecally administered neostigmine was greater in rats than in sheep or humans as a result of diminished penetration of neostigmine into the intermediolateral cell column in species having larger spinal cords (3,4,15,16). However, our results are conflicting with these studies. Hood et al. demonstrated that arterial blood pressure increased after spinal injection of neostigmine in normal saline in healthy volunteers. Because of the necessity of toxicological investigation for a drug which is intended for intrathecal administration, we performed microbiological and biochemical assessment as well. According to the studies dealing with the toxic effects of intrathecally administered neostigmine, Yaksh et al. found that neostigmine concentration of 1 mg/ml in the rat and dog and in doses up to 4 mg/day in the dog did not cause spinal tissue toxicity that can attributed to the drug (17). In our study we observed there was a statistically siginificant increase in CSF protein and glucose levels and in viscosity, which remained within the normal range after neostigmin administration in the study group. Since in the study group in both cases; before and after neostigmin administration, effects of surgery on CSF were supposed to be the same, we did not need to evaluate CSF in the lidokain group.

We concluded that addition of cholinergic agonists such as; neostigmine to local anaesthetic agent; lidocaine counteracted cardiovascular depression due to spinal blockade and there was no evidence of spinal tissue toxicity that could be attributed to the drug according to these microbiological and biochemical assessments in the current experimental setting. However, we believe that further studies on receptor selectivity with neostigmine and different antagonists may illuminate different aspects of this subject.

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