*Tripolitana Medical Journal* (2013) Vol. 2, No. 2, pp. 67-69

tmj

**Short Communication**

ISSN 2077-5628

# Intrathecal Neostigmine and Postoperative Analgesia in Cesarean Section

Abdulmutaleb Issa[1@] and Wafa Akra[1]

[1]Department of Anaesthesiology, Tripoli Medical Centre, Tripoli-Libya.

*Received 20 August 2013/Accepted 27 December 2013*

## ABSTRACT

Spinal anesthesia has become so commonly used in cesarean section (SC) that if there was no medical contraindication or patients refusal, it will be the anesthetist's first choice.

In an attempt to improve and prolong the spinal block and pain free time after cesarean section which is usually 1.5-2 hr, with the use of Bupivacaine intrathecally led scientists to think of adding other drugs to Bupivacaine.

By adding drugs to Bupivacaine before injecting it intrathecally prolongs the pain free time after SC which decreases the need for intravenous and intramuscular analgesics which in return decreases its side effects, toxicity, and expenses.

This study is aimed to compare between the intrathecal injection of Neostigmine and Bupivacaine and Bupivacaine alone in cesarean section and time of onset of pain after and duration of spinal block.

A randomized controlled study of 40 pregnant women of ASA 1 physical status undergoing cesarean section in the Maternity department of Tripoli Medical Center.

After obtaining consent from patients they were divided into two groups; Group A: consisting of 20 patients where intrathecal Bupivacaine alone injected. Group B: consisting of 20 patients where Neostigmine 30 ug prepared immediately and under aseptic technique with the use of insulin syringe and mixed with Bupivacaine prior to injecting it intrathecally. Also this group is further subdivided into 2 groups each of ten patients and given Dexamethasone intravenously while performing spinal block one subgroup given 4 mg and the other 8 mg as an attempt to minimize the nausea and vomiting caused by Neostigmine.

In both groups aseptic technique used to perform the spinal anesthesia with the use of 27 G spinal needle and 12 mg (2.2 ml) of heavy 0.5% Bupivacaine at L3-L4 level of spinal cord. Blood pressure before and after spinal anesthesia obtained. Bromage Scale and, Visual Analogue Pain Scale (VAS) of ten centimeters long starting with 0-no pain and ending with 10-most painful, are obtained from patients after operation and time recorded in each scale.

The study revealed that, Neostigmine as an adjunct to intrathecal anesthesia exhibits analgesic effects resulting in prolongation of sensory blockade of up to 10+ hr and motor blockade of up to 4.5 hr with no other side effects besides nausea and vomiting which still occurred in 40% of patients who received 8 mg I.V. Dexamethasone as an attempt to minimize these side effects.

**Keywords -** *Neostigmine; Bupivacaine; Spinal anesthesia; Cesarean section.*

## INTRODUCTION

The Intrathecal administrations of various agents have been described to provide postoperative analgesia for those women subjected to cesarean section (C/S). For pregnant women, pregnancy influences some physiological changes that alter the usual response to anesthesia and affect every organ. The use of the spinal anesthesia is believed to have a greater effect in pregnant as compared to non pregnant subjects.[1] Many of those pregnancy associated physiological changes appear to be useful in obstetrics for stress toleration and decrease maternal complications.[2]

In such instances, a number of studies have displayed that the use of different types of medications that are injected intrathecally or through epidural route, such as opioids and clonidine, to achieve better blocking of pain and good analgesia. In the research field, a number of local anesthetics (L.A) have been used in such situations.[3]

Local anesthetic is defined as a membrane stabilizing drug that causes reversible local anesthesia and influences the loss of nociception when deployed on specific pathways, i.e. nerve block.[4] An example of such local anesthetic medications is the Bupivacaine that is an amide type of LA used in the infiltration, nerve blocks, epidural and spinal anesthesia.[4] Such branded medications is produced by the AstraZeneca[@] Pharmaceutical company that is usually marketed under various trade names such as Marcaine™, Sensorcaine™, Vivacaine™.[5,6] The injection of these agents into surgical wounds has reported to reduce pain for a time of up to 20 hr, where on the other hand, its application as a neural blockade displays a duration of efficacy that varies from 1.5 to 8 hr.[7] Such reported variation was reported with respect to agent concentration, location of agent application, technique of injection and

*@ Author to whom correspondence should be addressed: Abdulmutaleb Issa; Tel. +218 91 3117837; E-mail abdulmutaleb@yahoo.com*

its combination with other agents.

Neostigmine local anesthetic was first synthesized by Aeschliman and Reinert in 1931.[8] The drug was added to local anesthetic solutions to increase degree efficacy or potency and duration of analgesia when injected into sub arachnoid space. It is of the class of cholinesterase inhibitor that inhibits the enzyme acetyl cholinesterase that is needed to break down the acetylcholine.[9,10]

This study was designed to compare the efficacy between the combined application of intrathecal injection of Neostigmine and Bupivacaine, and the Bupivacaine alone in cesarean section. This is to evaluate the onset of the pain during and after the spinal block.

## MATERIALS AND METHODS

A randomized controlled study containing 40 pregnant women of ASA category 1 (ASA: American Society of Anaesthesiologists that illustrates the Patients Risk Scoring System). Physical status undergoing this randomized sample had been undergone a cesarean section at the Maternity department of Tripoli Medical Center.

After obtaining the consent from all patients, they are divided into two equal groups with 20 individuals each. Group A consisting of 20 patients that were injected with intrathecal Bupivacaine alone. Group B consisting of 20 patients that were subjected to Neostigmine 30 µg and Bupivacaine. This was prepared immediately and under aseptic technique using to mix the Neostigmine 30 µg with the Bupivacaine and prior to injection intrathecally.

Group B was further divided into two groups of ten patients each. Such groups were subjected to various concentrations of intravenous Dexamethasone 4 and 8 mg. This was aimed to minimize the incidence of nausea and vomiting that are induced by the use of Neostigmine.

Spinal anesthesia was performed under strict aseptic technique using the 27G needle to inject a 12 mg of the heavy Bupivacaine 5% and the level of L3-L4 of the spinal cord. Blood pressure was monitored at specific intervals before and after the application of the spinal anesthesia.

Pain detection for patients under investigation was performed with respect to time. This was performed using the Bomage scale and the Visual Analogue Pain Scale that grades from 0 to 10. The level 0 denoted no pain whereas the scale 10 refers to the painful level.

*Statistical analysis:* After collection of data, coded and SPSS software used for analysis and calculation of mean, standard deviation, percentage used for descriptive statistics and Mann-Whitney test used for inferential statistics.

## RESULTS

Spinal anesthesia performed in 40 pregnant women of ASA1 physical status for cesarean section. Group A, 20 patients injected with Bupivacaine. Group B, 20 patients injected with Bupivacaine and Neostigmine, this group was further subdivided into 2 groups of 10 patients each. Group B1 received 4 mg I.V. Dexamethasone while group B2 received 8 mg I.V. Dexamethasone.

The Mann-Whitney test with $\alpha$ =0.05 used to compare between group A and group B. as follows;

1. Comparing the duration of spinal block between group A and group B. The mean of duration of block in group A =2.400 hr and the mean of group B =4.527 hr. *P.* value =0.000 which is less than $\alpha$=0.05 indicating a statistically significant difference between the two groups and that the duration of block in group B > group A.

2. Comparing the onset of pain after spinal block between group A and group B by studying the differences between the mean of onset of pain after S.A. in group A =3.332 hr and mean of group B =11.362 hr. *P.* value =0.000 which is less than $\alpha$=0.05 indicating a statistically significant differences between the two groups and that the pain free time in group B > group A.

In group B1 60% of patients vomited while in group B2 only 40% vomited which shows that using 8 mg I.V. Dexamethasone is superior in comparison to using 4 mg in minimizing nausea and vomiting.

## DISCUSSION

This study shows an evidence that intrathecal Neostigmine prolongs spinal block to 4.527 hr compared to the usual block of about 2 hr, furthermore it prolongs the pain free time to 11.362 hr which is the aim of this study compared to the usual pain free time of about 3 hr.

In a study of the dose response of analgesic effect of intrathecal Neostigmine for post-operative cesarean section analgesia, doses of 10, 30, 10 µg were used and showed that neostigmine produced a dose-independent reduction in post-operative use of analgesic and produced analgesia of up to 10 hr with no adverse fetal effects on heart nor on Apgar score but had a side effect of nausea and vomiting.[11,12]

In another study intrathecal Neostigmine 75,100 µg doses were used and produced a dose-dependent nausea and vomiting and had no significant effect on hemodynamics or respiratory parameters but extended the duration of post-operative analgesia.[12,13]

Implications of another study that intrathecal neostigmine dose of 25 µg produced post-operative analgesia for cesarean section similar to that of intrathecal morphine of 100 µg but with high incidence of nausea and vomiting however the combination of 12.5 µg Neostigmine and 50 µg Morphine produced better analgesia with fewer side effects.[14]

Neostigmine analgesic effects were also studied in pediatrics where it was used intrathecally as a dose of (specify the amount) µg/kg in lower abdominal and urosurgery for control of post-operative pain but with no decrease in nausea and vomiting.[15]

Studies of the analgesic efficacy of Neostigmine is not limited through the intrathecal route, as another study demonstrated the use of I.V. with Lidocaine in I.V.R.A. Biers block and compared to a group given the same drugs with a transdermal nitroglycerine. This showed that only Neostigmine in combination with Lidocaine has an

influencing role in lengthening surgical pain onset.[16]

Also in thoracic epidural where it was given for pre-induction and followed by infusion showed that it provided preemptive, preventive analgesia and an analgesic-sparing effect that improved postoperative analgesia for those patients without increasing incidence of nausea and vomiting better than if Neostigmine was started post operatively. [17]

It also decreases Bupivacaine use by patient controlled epidural analgesia during labor.[18]

Scientists proposed that any drug to be administered by neuraxial route should include safety information unique to the proposed route as supportive chemistry, nonclinical and clinical pharmacology information required for human studies may differ substantially between epidural and intrathecal routes for same drug.[18,19]

## CONCLUSION

It is evident that Neostigmine as an adjunct to intrathecal anesthesia exhibits analgesic effects resulting in prolongation of sensory blockade of up to +10 hr and motor blockade of up to 4.5 hr with no other side effects besides nausea and vomiting which still occurred in 40% of patients who received 8 mg I.V. Dexamethasone as an attempt to minimize these side effects.

It is proven from previous studies that Neostigmine produces a dose independent reduction in post-operative pain and a dose dependent nausea and vomiting when injected intrathecally, and as it is far less expensive (Table 1) compared to the other common I.V. and I.M. (Morphine, Pethidine, Tramadol, Ketoloc, Voltaren) analgesics used post operatively and the fact that, it is always available and does not need special storage I would recommend its use as an adjunct to spinal anesthesia provided that nausea and vomiting be controlled or minimized by a more potent antiemetic according to sensitivity of patient and need.

**Table 1**: Represents a group of selected drugs and their costs.

| **Drug** | **Approximate cost** (Euro, €) |
|---|---|
| Morphine sulphate 10 µg/5 ml | 0.1760 |
| Pethidine 50 mg /100 mg | 0.0906/ 0.10267 |
| Tramadol 50 mg | 0.1197 |
| Voltaren 50 mg | 0.578 |
| Tenoxicam 50 mg | 0.867 |
| Paracetamol 1gm infusion | 2.753 |
| Fentanyl 100 µg/AL fentanyl 1000µg | 0.1002 / 0.5800 |
| Neostigmine 0.5 mg | 0.0729 |
| Dexamethasone 4 mg | 0.433 |

## REFERENCES


[1] Govino BG, Scott DB, Lambert DH (1994) Pregnancy. Handbook of Spinal Anesthesia and Anelgesia, Mediglobe, SA, pp.94.

[2] Morgan E, Mikhail MS, Murray MJ (2006) Physiological changes and Maternal Mortality in obstetric Anesthesia, *Clinical Anaesthesiology*, 4th edn, pp. 892,893.

[3] Lenz VG, Kottler B, Schorer R (1985) Periduralanaesthesie-MEMO Anaesthesie, pp. 182-185.

[4] Govino BG, Scott DB, Lambert DH (1994) Local Anesthetic Agents. Handbook of Spinal Anesthesia and Analgesia, Mediglobe SA, pp. 77.

[5] Govino BG, Scott DB, Lambert DH (1994) Bupivacaine. Handbook of Spinal Anesthesia and Analgesia, Mediglobe SA, pp. 163.

[6] Morgan E, Mikhail MS, Murray MJ (2006) Bupivacaine, Clinical Anaesthesiology, 4th edn, pp.270.

[7] Thomas EJH, Davidsons A (1995) Central Neural Blockade, Practice of Anaesthesia, 6th edn, pp.715.

[8] Davidsons A (1995) Neostigmine, Practice of Anaesthesia, 6th edn, pp.161.

[9] Lenz VG (1985) Neostigmine-MEMO Anaesthesie, pp. 167.

[10] Aitkenhead AR (2007) Textbook of Anaesthesia, 5th edn, pp. 91, 129.

[11] Saini S, Sethi S, Malhotra N (2006) Analgesic effect of intrathecal neostigmine for postoperative cesarean section analgesia, *Journal of Anaesthesiology and Clinical Pharmacology Research* **22**(1), 35-40.

[12] Krukowski JA, Hood DD, Eisenach JC, Mallak KA., Parker RL (1997) Intrathecal neostigmine dose-dependent effects, *Anesth.Analg* **84**(6), 1269-1275.

[13] Hye MH, Masud KM, Banik D, Haque MF, Akhtaruzzaman KM (2010) Hemodynamic response to intrathecal neostigmine and duration of analgesia, *Mymensingh Medical Journal* (Bangladesh) **19**(4), 586-593.

[14] Chung CJ, Kim JS, Park HS, Chin YJ (1998) Intrathecal Morphine and neostigmine effects on nausea and Vomiting, *Anesth Analg* **87**(2), 341-346.

[15] Bakshi U, Chatterjee S, Sengupta S, Gupta D (2010) Neostigmine analgesic effect in pediatrics, Adjuvant drugs in central neural analgesia, *The Internet Journal of Anesthesiology*.

[16] Krukowski JA, Hood DD, Eisenach JC, Mallak KA and Parker RL (2008) Intravenous Lidocaine and Neostigmine, *International Journal of Pharmacology* **4**, 218-222.

[17] Morgan E, Mikhail MS, Murray MJ (2006) Thoracic Epidural Analgesia, Clinical Anaesthesiology, 4th edn, pp. 316.

[18] Davidsons A (1995) Epidural Analgesia during Labor, Practice of Anaesthesia, 6th edn, pp. 1287.

[19] Shafer SL (2007) Anesthesia and analgesia policy on off-label drug administration in clinical trials, *International Anesthesia Research Society* **105**(1), 13-15.