COMPARATIVE STUDY OF INTRATHECAL BUPIVACAINE WITH OR WITHOUT NEOSTIGMINE FOR INFRAUMBILICAL SURGERIES

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ABSTRACT

BACKGROUND

Spinal anaesthesia requires a small volume of drug to produce profound sensory analgesia and motor blockade, but has limited duration of action. An adjuvant to local anaesthetic agent produces a better quality regional block. Intrathecal (IT) neostigmine has been used as an adjunct to Spinal Anaesthesia (SA) for the prevention of acute perioperative pain. It has been shown to potentiate opioid analgesia.[1] According to recent literature, the inhibition of acetylcholine degradation by neostigmine enhances the descending control of afferent nociceptive stimuli and provides new approach for enhancement of desirable analgesia with few dose-related side effects.[2] The use of neostigmine intrathecally does not cause any hypotension, sedation, respiratory depression or neurological dysfunction.[2] Hence, we studied to compare the effect of intrathecal neostigmine 50 µg added to intrathecal hyperbaric bupivacaine with regard to sensory characteristics, motor characteristics and side effects.

MATERIALS AND METHODS

This was a prospective, randomised controlled double blinded study in 60 patients posted for infraumbilical surgeries belonging to ASA I and II status and aged between 18 to 60 years. One group received intrathecal 0.5% hyperbaric bupivacaine 3 mL (15 mg) group A and second group received preservative-free neostigmine 50 µg with 3 mL (15 mg) of intrathecal 0.5% hyperbaric bupivacaine group B and they were compared with regard to sensory characteristics, motor characteristics and side effects.

RESULTS

The addition of neostigmine 50 ug to hyperbaric bupivacaine prolonged mean duration of analgesia from the time of onset of complete sensory blockade to the time at which rescue analgesic was given using VAS score. It was 322.2 + 25.76 (SD) min. in the neostigmine group suggesting a statistically significant delay in onset of breakthrough pain between group A and group B.

CONCLUSION

Intrathecal neostigmine 50 ug with bupivacaine produces a good sensory and motor block for the surgical procedure with safe, durable and predictable postoperative analgesia. Administration of intrathecal neostigmine as an adjuvant to bupivacaine produces effective, prolonged and haemodynamically stable postoperative analgesia as compared to administration of intrathecal bupivacaine alone.[2]

KEYWORDS

Hyperbaric Bupivacaine, Intrathecal Neostigmine, Infraumbilical Surgery, Postoperative Pain, Spinal Anaesthesia, Analgesia, Bromage Scale.

HOW TO CITE THIS ARTICLE: Sankararao DVG, Bhairavabhatla KV. Comparative study of intrathecal bupivacaine with or without neostigmine for infraumbilical surgeries. J. Evid. Based Med. Healthc. 2017; 4(49), 2992-2996. DOI: 10.18410/jebmh/2017/592

BACKGROUND

Pain is associated with actual or impending tissue damage. Surgical pain or postoperative pain is a universal phenomenon experienced by millions of patients throughout the world. A pain-free and stress-free postoperative period definitely reduces morbidity and mortality of any surgical operation. Recent surveys have revealed that the incidence of moderate or even severe postoperative pain maybe as high as 30-70%.[3,4]

Various methods of postoperative pain relief are available.[5]

1. Systemic analgesic techniques - opioids, non-opioids.
2. Regional analgesic techniques - intrathecal analgesia, epidural analgesia.
3. Other techniques- TENS, acupuncture and psychological approaches.

Neuraxial block is used to control postoperative analgesia. Several adjuvant drugs had been used to produce postoperative analgesia. Neostigmine, an acetylcholinesterase inhibitor is one of those adjuvant drugs,

Financial or Other, Competing Interest: None.
Submission 06-06-2017, Peer Review 10-06-2017,
Acceptance 14-06-2017, Published 17-06-2017.
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DOI: 10.18410/jebmh/2017/592

which inhibits breakdown of endogenous spinal neuromodulator acetylcholine, which has been shown to have antinociceptive effects.

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 dura mater, what justified the interest of its applicability as IT analgesic until early 1990s. After spinal administration of neostigmine, Ach concentration increased from <20 pmol/mL at baseline to >100 pmol/mL within 15 mins., while plasma concentration was approximately 5 ng/mL. Concentration in cerebrospinal fluid could be measured for 24 hrs. The pharmacokinetic of IT neostigmine was best described by a triexponential function with an absorption phase. Individual predicted concentrations varied 100-fold. It was characterised by prolonged distribution ($t1/2\alpha$ = 23 mins.) and elimination ($t1/2\beta$ = 260 mins.). No study to date has evaluated the pharmacokinetics of epidural neostigmine.

Spinal Neostigmine

IT neostigmine increased incidence of nausea and vomiting, bradycardia requiring intravenous atropine, anxiety, agitation or restlessness. 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. 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.

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 antagonise the hypotensive action secondary to IT anaesthesia. In 1994, a study on sheep suggested that hypotension secondary to the administration of a α2-agonist maybe prevented by the stimulation of M2 spinal muscarinic cholinergic receptors and by nitric oxide synthesis. It would be extremely interesting and clinically applicable if the drug could minimise the hypotension resulting from regional blockade with a local anaesthetic as demonstrated in rats in addition to providing postoperative analgesia.

Aims and Objectives

1. To study any change in the onset of sensory blockade by the addition of neostigmine to bupivacaine intrathecally.
2. To determine the duration and quality of analgesia.
3. To study any side effects during intra and postoperative periods.

MATERIALS AND METHODS

After obtaining institutional ethical committee approval, 60 patients were considered for study. They were randomly divided into 2 groups 30 each by a computer-based program. The study was conducted in Maharajah's Institute of Medical Sciences, Vizianagaram, from November 2014 - November 2016. Patients' consent was taken after explaining the methodology. The patients were of ASA grade 1 and 2 of either sex in age groups 18-60 yrs. undergoing elective lower abdominal, gynaecological and perineal surgeries under spinal anaesthesia.

The exclusion criteria were patients with systemic cardiovascular, respiratory, hepatic, renal, CNS disorders, disease and deformity of spine, patients with haemorrhagic disorders and patients having skin disease or local sepsis at the site of lumbar puncture.

Preoperative assessment was done on the day prior to the surgery and routine investigations were completed. After shifting the patient to operation theatre, baseline BP, PR and SPO_2 were recorded. After performing lumbar puncture, free flow of CSF, 3 cc of 0.5% bupivacaine for group A patients and 3 cc of 0.5% bupivacaine with 50 ug of neostigmine for group B patients were injected into subarachnoid space.

The onset of analgesia was assessed on time taken from drug injected to the onset of sensory blockade (absence of pinprick sensation). The two segment dermatomal regression of sensory block was also recorded at various intervals. The duration of analgesia was assessed using VAS 0-10 cm score from no pain to worst pain on marked paper strip at 15, 30, 60 minutes and thereafter at 1 hour interval for 6 hours postoperative period. Patients above score 4 received rescue analgesia in the form of injection diclofenac sodium 75 mg intramuscular in the postoperative period. Time of first rescue analgesic required and VAS score at that time was noted.

The parameters used for comparison between 2 groups are-

1. Onset of blockade.
2. Duration and quality of analgesia using VAS.
3. Side effects such as nausea, vomiting, hypotension, bradycardia, diaphoresis and others were noted.

Statistical Analysis

Continuous data was analysed by Student's T-test and categorical data by Chi-square test. Any possible significance has been determined considering it statistically significant if it's P <5% (i.e. <0.05) level of significance.

RESULTS

The study population consists of 60 patients posted for elective lower abdominal, gynaecological and perineal surgeries. They were divided into 2 groups of 30 each.

Group A - Patients who were given only local anaesthetic injection bupivacaine 0.5% 3 cc.

Group B - Patients who were given 50 ug of preservative-free intrathecal neostigmine methyl sulfate with local anaesthetic bupivacaine 0.5% 3 cc.

There was no difference in demographic pattern between the two groups.

Age in Years	Group A Male	Group A Female	Group B Male	Group B Female
20-30	4	0	5	0
31-40	8	3	2	3
41-50	8	1	7	2
51-60	5	1	6	5
Total	**25**	**5**	**20**	**10**

Table 1. Age and Sex Distribution

Height in cms	Group A	Group B
<150	5	11
151-160	5	17
161-170	12	2
171-180	8	0
Total	**30**	**30**

Table 2. Distribution of Height

Weight in kgs	Group A Male	Group A Female	Group B Male	Group B Female
45-50	1	2	6	1
51-60	5	2	13	8
61-70	16	1	1	1
71-80	3	0	0	0
Total	**25**	**5**	**20**	**10**

Table 3. Distribution of Weight

Group A Mean ± SD	Group B Mean ± SD	P value
2.41 ± 0.14	2.45 ± 0.05	0.837

Table 4. Onset of Sensory Blockade (Minutes)

P >0.05 and is insignificant.

Group A Mean ± SD	Group B Mean ± SD	P value
93.67 ± 16.13	124.8 ± 5.05	0.000

Table 5. Two Dermatomal Segments Regression of The Sensory Level (in Minutes)

P <0.0001 = Extremely Significant.

Duration of Surgery in Minutes	Group A	Group B
40-80	7	6
80-120	16	19
121-160	7	5

Table 6. Duration of Surgery (in Minutes)

Mean duration of surgery in Group A is 107.37 ± 25.557 SD and Group B is 103.43 and the P value is 0.544 (>0.05 = insignificant).

Duration in Minutes	Group A	Group B
100-200	24	0
201-300	6	8
301-400	0	22
Total	**30**	**30**

Table 7. Duration of Analgesia (in Minutes)

Group A Mean ± SD	Group B Mean ± SD	P Value
128.83 ± 33.002	324.33 ± 27.378	0.000

Table 8. Duration of Analgesia (Summary)

P <0.0001 = Extremely Significant.

Pain Score	Quality of Analgesia	Group A	Group B
0	No pain relief	0	0
1	Poor pain relief	20	0
2	Fair pain relief	10	1
3	Good pain relief	0	18
4	Excellent pain relief	0	11

Table 9. Quality of Analgesia

P <0.0001 = Extremely Significant.

Adverse Effects	Group A	Group B
Nausea and vomiting	0	5
Hypotension	2	0
Bradycardia	1	0
Diaphoresis	0	0
Others	0	0

Table 10. Adverse Effects

DISCUSSION

Surgical stress causes release of cytokines (e.g. interleukin-1, interlukin-6 and tumour necrosis factor- alpha) and precipitates adverse neuroendocrine and sympathoadrenal responses resulting in detrimental physiological responses particularly in high-risk patients.[6] The increased secretion of the catabolic hormones cortisol, glucagon, growth hormone and catecholamines and the decreased secretion of the anabolic hormones insulin and testosterone characterise the neuroendocrine response. The end result of this is hyperglycaemia and a negative nitrogen balance, the consequences of which include poor wound healing, muscle wasting, fatigue and impaired immune competency. Various drugs have been tried in the subarachnoid space along with local anaesthetics with the aim of improving the quality of postoperative pain relief. The cholinesterase-inhibitor neostigmine is one among such adjuvant. Analgesic effects of anticholinesterase agents were first noticed when Pellendra observed that intravenous administration of the anticholinesterase drug physostigmine produced analgesia in human beings. Neostigmine inhibits breakdown of endogenous spinal neuromodulator acetylcholine, which has been shown to have antinociceptive effects. The inhibition of spinal cholinesterase by neostigmine results in an increase of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord.[1] The enhanced analgesic efficacy of IT neostigmine results from greater release of spinal acetylcholine from the more intense and prolonged discomfort of postoperative pain and consequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors present in the cholinergic interneurons at the lamina III and V of the dorsal horn.[1] It is reported that the inhibition of

spinal cholinesterase by neostigmine produces great enhancement of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord.[7] The analgesic effect of spinal neostigmine was suggested to result from an increase in the concentration of the neurotransmitter acetylcholine and its consequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors present in the cholinergic interneurons at the laminae II and V of the dorsal horn.[8] Neuraxial neostigmine increases sympathetic outflow, thus counteracts the hypotension caused by bupivacaine and bradycardia caused by alpha-2 agonists.[9]

Onset of Sensory Blockade

The mean onset time of sensory block was comparable in both the groups with 2.41 ± 0.14 SD minutes for patients belonging to group A and 2.45 ± 0.05 SD minutes for patients belonging to group B. However, 2 segment regression of sensory block was statistically prolonged with addition of 50 ug neostigmine. These results correlated with Seyed Hamid et al.[10]

In our study, addition of 50 ug of neostigmine intrathecally in group B patient did not enhance the onset of sensory block and this result correlates with that of Saini's et al 2006.[11]

The 2 segment regression of block was prolonged in 50 ug neostigmine group as compared to bupivacaine group and this correlates with that of Chung et al, 1998; Saini's et al, 2006; and Hye MA, 2010.

Analgesia- Duration and Quality

Intrathecal neostigmine alone at higher doses causes a dose-dependent analgesia accompanied by nausea, vomiting and evacuation of bowel and bladder as shown in the studies done by Lauretti GR et al, Habib AS et al and Kalme JG et al. This has precluded the use of neostigmine as a sole analgesic agent. When used in lower doses along with local anaesthetic like lignocaine or bupivacaine, it provides prolonged and effective postoperative analgesia as shown in studies done by Chung et al and J.G. Klamt.

In our study, the duration of analgesia was analysed as period between complete onset of sensory blockade to the time at which patient started complaining of pain or first rescue analgesic was given using VAS score. Our statistical analysis showed that group A (128.83 ± 33.002) complained of pain earlier than that of group B (324.33 ± 27.378). From the above results, we can say that 50 ug of intrathecal neostigmine as an adjuvant with hyperbaric bupivacaine prolong the duration of postoperative analgesia when compared to hyperbaric bupivacaine alone analgesia and this correlates with the findings of PM Pan et al, 1995; Lauretti et al, 1996; Klamt et al, 1997; Krukowski et al, 1997; Lauretti et al, 1998; and Tan PH et al 2001. Pan PM showed that the combination of 150 ug intrathecal clonidine and 50 ug intrathecal neostigmine provided longer postsurgical analgesia than with either drug used alone.[12]

Lauretti et al stated that intrathecal neostigmine produced a dose-independent analgesia and a dose-dependent incidence of adverse effects.

Klamt et al, 1997, studied postoperative analgesic effect of intrathecal neostigmine and its effects on spinal anaesthesia.[13] They said that in patients undergoing anterior and posterior vaginoplasty under spinal anaesthesia with neostigmine as adjuvant analgesia lasted for about 12 hrs.

Krukowski[14] et al indicated that intrathecal neostigmine can produce 10 hrs. of post caesarean section analgesia without adverse foetal effects in 24 healthy pregnant patients who underwent elective caesarean section under combined spinal epidural techniques with doses of neostigmine ranging from 10-100 ug.

Tan PH et al studied that intrathecal neostigmine 50 ug produced postoperative analgesia lasting about 7 hours with fewer side effects and better satisfaction ratings than intrathecal morphine 300 ug.

The present study correlates well with all the above studies. Our study showed a mean duration of 128.83 ± 33.002 SD mins. in patients belonging to group A and 324.33 ± 27.378 SD mins. in patients belonging to group B from the time of onset of complete sensory blockade to the time at which rescue analgesic was given using VAS score. Rescue medication used for postoperative analgesia is diclofenac injection.

Our present study showed that intrathecal neostigmine of 50 ug provided a good and efficacious pain relief, which correlates with the study of Klamt et al, 1997.[13]

Intrathecal neostigmine produces analgesia, but also nausea limiting its utility. In contrast, epidural administration of neostigmine has been suggested to produce postoperative analgesia without nausea. Nakayama et al, 2001 also concluded that duration of analgesia was significantly increased with epidural neostigmine 5 ug/kg or 10 ug/kg with bupivacaine and effects were dose-independent.[15]

Analyses of the past two decades, intrathecal doses of neostigmine in humans ranged from 75-100 ug. Due to its side effects, the dose was substantially decreased. Because of small doses, neostigmine should be applied only as part of multimodal spinal analgesia and further clinical trials are still needed.

Future studies may also include formulations containing liposomes using technology of gradual neostigmine release.[16]

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 hrs. of postoperative analgesia with the use of neostigmine with greater patient satisfaction and a lower incidence of adverse effects.[17]

CONCLUSION

The duration and quality of postoperative analgesia following intrathecal administration of neostigmine was found to be statistically significant thereby suggesting that 50 ug of intrathecal neostigmine along with bupivacaine provided good postoperative analgesia with duration of 324.33 ± 27.378 (SD) minutes in our study.

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