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Evaluation of Intrathecal Neostigmine in Different Doses Added to Xylocaine for Post Operative Analgesia

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ABSTRACT
Intrathecal (IT) neostigmine has been used as an adjunct to spinal anaesthesia. The purpose of this study was to determine whether a combination of low-dose neostigmine IT would enhance analgesia of xylocaine IT, in patients undergoing lower abdominal and lower limb surgeries under spinal anesthesia. Study was done on 45 patients, who were divided into 6 groups these groups were given neostigmine in various concentrations (.25mg,.5mg &.75mg) along with 5% xylocaine (heavy) IT with control group receiving only IT xylocaine.
Hence, Low dose neostigmine (0.25 mg) when added to xylocaine IT enhances duration of analgesia without affecting significantly cardiovascular status, duration of motor paralysis and adverse effects. Thus more and more use of low dose neostigmine as an adjunct to xylocaine (heavy) I.T. is being recommended.
Key words: *Xylocaine, Neostigmine, Spinal Anaesthesia.*

INTRODUTION

Pain in the post-operative period, although a well established entity and on which a lot of work has been done in the past, still remains an enigma. It is surprising that in spite of so much work and success achieved in the management of pain, postoperative pain is still being dealt by procedures adopted half a century ago. Drugs, mainly opiates and their derivatives are being extensively used to achieve post-operative analgesia. These drugs because of their side effects like sedation and respiratory depression have their Limitations.

It is still the cherished hope of anaesthetist and surgeon if they could find out a drug or a combination of drugs which would provide intra-operative anaesthesia and post-operative analgesia without jeopardizing the safety of the patient. Intrathecal neostigmine represents a novel approach to provide analgesia. It inhibits the breakdown of an endogenous spinal neurotransmitter acetylcholine which has been shown to have antinociceptive actions. Acetylcholine released from preganglionic sympathetic ganglia has been shown to have action at other spinal sites like inhibition of motor neuron activity, excitation of sympathetic outflow. Spinal neostigmine is advantageous over other currently used spinal drugs as it causes no hypotension (excitation of sympathetic outflow), no sedation, no respiratory depression or neurological dysfunction[4, 5].

The multimodal pain therapy approach including spinal neostigmine is efficacious, significant

systemic side effects of IT neostigmine, especially nausea and vomiting, have been reported with doses higher than 6.25 mcg, limiting it use in clinical practice[2]. The benefits of adding lower neostigmine dose to potentiate xylocaine analgesia, however, have not been evaluated to date.

We planned to determine prolongation of analgesic effect of intrathecal xylocaine (Heavy) by addition of neostigmine in surgeries done with SA.

MATERIAL & METHODS

The present study was conducted in the Jhalawar Medical College, Jhalawar during the period from January to December 2011. A total of 45 patients undergoing various elective lower abdominal, and lower limb surgical procedures, under spinal anaesthesia.

Patents with previous history of neurological disorders were excluded from the study. Informed consent was taken from all the patients included in study. The studied patients were divided in to 6 groups:-

Group A: Control group: 10 Patients received intrathecal injection of 5% Xylocaine (Heavy) solution.

Group B: 10 cases who received intrathecal injection of 5% Xylocaine (heavy) solution along with 0.25mg neostigmine, while 4mg Ondansetron was given intravenously.

Group C: 5 cases who received intrathecal injection of 5% Xylocaine (heavy)solution with 0.25mg Neostigmine, while stemetil (12.5 mg) and Ranitidine (50 mg) were given intravenously.

Group D: 5 cases who received intrathecal injection of 5% Xylocaine (heavy) solution with 0.25 mg Neostigmine, while Ranitidine (50mg) and Ondansetron (8mg) were given intravenously.

Group E: 10 cases who received intrathecal injection of 5% Xylocaine (Heavy) solution with 0.5 mg Neostigmine.

Group F: 5 cases who received intrathecal injection of 5% Xylocaine (Heavy) solution with 0.75mg Neostigmine.

All the patients were followed during operative procedure and Pulse rate and BP were measured every 15 minutes after intrathecal injection up to one hour, then every 30 minutes up to two hours and then at three hours, six hours and twelve hours interval. A constant watch was kept for any untoward effects like bradycardia, hypotension, perspiration, nausea and vomiting.

All the patients were transferred to the recovery room after completion of the surgical procedure and were kept there till the return of motor power and settling of the parameters. Constant watch was kept in the recovery room for any untoward effects like- anxiety, bradycardia, nausea, vomiting, urinary retention and hypertension.

After shifting the patient to the ward, again the motor power was assessed and return of movement in the great toe was taken as the recovery from the motor paralysis.

Duration of analgesia was measured from the time of onset of analgesia till the first analgesic demand from the patient.

OBSERVATIONS & RESULTS

In present study 24, 8,7and 5 patients were in 3^{rd,} 4th, 5th and 6th decade of life respectively. While one case was of 67years of age. Varieties of surgeries performed were lower limb surgeries 26, Herniorrhaphy 7, plication of piles 3, Fistulectomy 3, urosurgery 3, Haemorrhoidectomy, Lumbar Sympathectomy and Fissurectomy 1 each.

The duration of analgesia was maximum (11.8 hrs.) in group B where neostigmine .25 mg and Ondansetron 4 mg was used, while the duration of analgesia was minimum (7.6 hrs.) in group D where neostigmine .25 mg and Ranitidine 50 mg and Ondansetron 8 mg were used.

In group A there was a slight fall in pulse rate at 15 minutes then it increased to 89 per minute at 30 minutes, there after it was less than the pre spinal value till 120 minutes after the spinal anesthesia. In group B there was a significant fall in pulse rate at 30 minutes and there after it gradually increased to 92 per minute at 12 hours. When compared to pre spinal value these values were found to be

statistically insignificant except the fall at 30 minutes which was significant. In group C there was a fall in pulse rate at 15 minutes then it gradually increased to maximum of 94.4 per minute at 120 minutes. On statistical comparison with the pre spinal value only the fall at 15 minutes was found to be significant. In group D the values were less than the pre spinal value from 15 minutes to 180 minutes, In group E there was an a increase in the pulse rate over the period of time with maximum pulse rate at 6 hours. In group F there was a rise in the mean pulse rate at 6 hours (Max. 92.8/ min.) and remained at 91.2 per minute on comparison with the pre spinal value these were found to be statistically insignificant. Except at 6 hours where it was just significant. (Shown Table No. 1)

The mean value of BP in group A was found to be maximum at 45 minutes where it was 120.4 mmHg and minimum at 15 min. where it was 114.4 mmHg, while in group B there was a slight fall in BP at 15 min. then it increased to maximum of 129 mmHg at 120 minutes and similarly in group C there was a significant fall in BP at 15 min. then it increased to maximum of 123.6 mmHg at 120 minutes on comparison pre spinal value these were statistically in insignificant. In group D the BP was almost stable throughout, with maximum being 128.4 mmHg at 6 hours. In group E BP was maximum at 180 min. where it was 132.8 mmHg and minimum at 90 min. where it was 120 mmHg. Statistically, when compared with pre spinal value, these values were also insignificant. While in group F there was slight fall in BP at 30 min. and then it rose to maximum of 141.2 mmHg at 180 min. when statistically compared with the pre spinal value observations at 30 min, 45 min and 60 min were found to be significant, rest were insignificant.

Table No. -01

Changes in mean pulse rate at various intervals

GROUPS		0 min.	15 min.	30 min.	45 min.	60 min.	90 min.	120min.	180min.	6 Hrs	12 Hrs
A	Mean	88.1	83	89	88.6	87	86.8	86			
	S.D	10.36	17.53	18.51	16.05	16.86	16.59	12.59			
	P-Value		<.8	<.9	<.9	<.9	<.9	<.8			
B	Mean	88.6	82.9	75	86.3	89.1	88	89.7	91	91	92
	S.D	11.87	13.12	13.7	21.06	17.09	17.32	14.21	13.42	8.5	8.25
	P-Value		<.5	<0.02	<.9	<.9	<.9	<.9	<.6	<.6	<.6
C	Mean	81.8	68.8	82.8	84.2	85.4	91	94.4	92.4	89.2	82.4
	S.D	12.8	8.16	20.03	25.63	25.77	27.22	32.87	33.856	25.41	13.94
	P-Value		<.1	<.9	<.9	<.9	<.9	<.8	<.6	<.6	<.9
D	Mean	88.6	82.9	75	86.3	89.1	88	89.7	91	91	92
	S.D	11.87	13.12	13.7	21.06	17.09	17.32	14.21	13.42	8.5	8.25
	P-Value		<.5	<0.02	<.9	<.9	<.9	<.9	<.6	<.6	<.8
E	Mean	89.6	92.8	93.8	92.2	91.5	94.4	95.4	96.8	102.6	101.6
	S.D	10.31	14.2	11.88	15.37	16.57	19.53	18.63	19.99	22.36	21
	P-Value		<0.5	<0.5	<0.6	<.7	<.6	<.9	<.5	<.5	<.5
F	Mean	80	87.6	87.2	86	88.8	87.6	81.6	84.8	92.8	91.2
	S.D	7.89	18.22	14.12	9.88	13.66	12.03	11.27	8.45	14.01	15.88
	P-Value		<.6	<.5	<.5	<.5	<.1	<.9	<.6	<.1	<.5

Table No. - 02

Changes in mean B.P at various intervals

GROUPS		0 Min	15 Min	30Min	45 Min	60 Min	90 Min	120 Min	180 Min	6 Hrs	12 Hrs
A	Mean	127.6	114.4	120	120.4	116.4	114.6	118			
	S.D	16.12	23.03	13.42	14.22	16.22	13.48	17.64			
	P-Value		<.6	<.6	<.6	<.6	<.1	<.6			
B	Mean	117.6	116	111.8	116	117.4	121	129	119	119.4	113
	S.D	14.28	6.63	11.44	9.96	10.81	10.44	11.36	9.04	8.35	9.808
	P-Value		<.8	<.6	<.8		<.8	<.1	<.9	<.8	<.6
c	Mean	118	96	106	120	122	116	123.6	118	121.6	122
	S.D	11.66	24.11	20.59	10.95	16	9.3	13.11	16	11.41	7.49
	P-Value		<.1	<.5	<.6	<.6	<.8	<.8		<.6	<.6
D	Mean	120	120	120.4	124	122	125.2	126	122	128.4	124
	S.D	10.95	8.94	10.31	10.2	11.59	7.75	10.2	7.48	10.38	10.2
	P-Value			<.9	<.6	<.9	<.6	<.6	<.8	<.6	<.5
E	Mean	126.8	128.6	126.8	122.2	123.4	120	125.4	132.8	134.6	124
	S.D	12.07	10.08	9.6	14.55	10.08	11.56	10.12	15.574	16.45	12.81
	P-Value		<.8		<.6	<.6	<.5	<.9	<.5	<.5	<.5
F	Mean	128	115.2	108	108	110	118.8	131.2	141.2	141.2	133.2
	S.D	18.33	18.23	4	11.66	6.33	11.91	15.93	11.21	9.26	15.52
	P-Value		<.4	<.02	<.02	<.02	<.8	<.8	<.5	<.5	<.8

Table No.-04

Comparison of duration of motor paralysis (In inutes) with statistical analysis

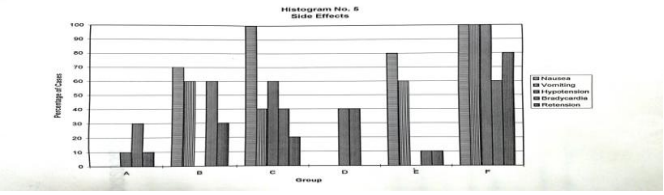
GROUPS	A	B	C	D	E	F
Mean	88	90.5	88	112	108	96
S.D	23.37	21.39	9.27	24.2	20.88	22.67
P.Value		<.8		<.2	<.1	<0.5
P.Value	<0.8		<0.8	<0.2	<0.1	<0.4
P.Value		<0.8		<0.1	<0.05	<0.4
P.Value	<0.1	<0.1	<0.1		<0.8	<0.2
P.Value	<0.1	<0.1	<0.05	<0.8		<0.2
P.Value	<0.5	<0.5	<0.5	<0.2	<0.2	

Table No.-03

Comparison of duration of analgesia (in Hrs.) with statistical analysis

GROUPS	A	B	C	D	E	F
Mean	2.68	11.87	9.6	7.6	11.6	11.6
S.D	5.37	4.46	2.37	1.24	2.78	1.85
P-Value		<0.001**	<0.001**	<0.001**	<0.001**	<0.001**
P-Value	<0.001**		<0.5	<0.05*	<0.9	<0.9
P-Value	<0.001**	<0.2		<0.2	<0.1	<0.2
P-Value	<0.001**	<0.05*	<0.2		<0.02*	<0.02*
P-Value	<0.001**	<0.9	<0.2	<0.02*		
P-Value	<0.001**	<0.9	<0.02*	<0.02*		

* Significant
** Highly Significant



RESULTS

Pulse rate

In control group (group A) and 0.25 neostigmine groups (B,C&D) initially slight fall in pulse rate was noted and there after pulse rate start rising gradually reaching to pre-spinal level beyond 90 minutes but in 0.5 mg neostigmine (Group E) and 0.75 mg neostigmine (Group F) initial fall in pulse rate was not observed, rather increase in pulse rate over period of time with maximum at 6 hrs was a peculiar observation.(Shown table No. 1)

In group E there was not much variation in pulse rate up to 2 hrs but at 3 and 6 hrs pulse rate increased. In group F pulse rate decreased till 90 minutes but beyond that it increased which was sustained to raised value even at 12 hrs.

These changes in pulse rate in control group when compared to study groups were statistically insignificant. When compared with each other statistically significant values were observed when group B was compared to group E and highly significant when group E was compared to group F.

Blood Pressure

In control group (A) and 0.25 mg neostigmine groups (B&C)initially slight fall in blood pressure was noted at 15 minutes then BP increased gradually reaching to little higher than pre spinal value at 120 minutes. However, in group D (0.25 mg neostigmine) Blood pressure was almost stable throughout.

In group E (0.5 mg neostigmine) & Group F (0.75 mg neostigmine) there were more variations in B.P., when group F values were compared with pre spinal value observations at 30 min. , 45 min and 60 minutes were found to be significant statistically. (Shown table No. 2)

Duration of analgesia

Mean duration of analgesia was found to be maximum in group B (11.8 hrs.) and minimum in group A, where it was 2.68 hrs. When all other groups were compared to group A, statistically highly significant values were obtained Group B when compared to group D and group D compared to group E and F statistically significant values were obtained. (Shown table No. 3)

Duration of motor paralysis

Mean duration of motor paralysis was found to be maximum in group D (112 min.) and minimum in groups C and A (88 min. each). When all the groups were compared to group A, and also when compared with each other derived insignificant values. (Shown table No. 4)

Side effects

Nausea, vomiting, hypotension, Bradycardia and retention of urine were the side effects observed in present study. Maximum side effects were observed in group F and minimum group A and D (Histogram) In group F all the 5 patients developed hypotension – 2 within 5 minutes, 3 within 5 to 45 minutes with bradycardia, severe nausea, vomiting and 4 retention of urine.

Nausea and vomiting in study groups when compared to control group was found to be significant. Bradycardia and hypotension in control group when compared to study groups was statistically insignificant.

Stephen E. Abram et al[8] , while studying the synergistic effect of intrathecal acetyl choline esterase inhibitor with morphine and clonidine, on rats, found that some side effects occurred at analgesic doses of cholinesterase inhibitors (irritability, abnormal posturing, (sedation, diuresis) but no side effects were noted with any of the drug combinations.

Hood et al[3] in their phase I safety assessment of intrathecal neostigmine concluded that nausea and vomiting occurred in a dose related manner 30 to 90 min. after spinal neostigmine. Most likely site of this effect is in brain stem. Treatment of established nausea by glycopyrrolate, atropine, phenargan and Ondansetron approved minimally effective in this open label trial. They did not observe any cardiovascular stimulation with 500 micro gm neostigmine which is consistent with our study. Though they did observe increase in B.P. and heart rate after 750 micro gm neostigmine given intrathecally.

DISCUSSION

The word "pain" is derived from Latin word "poena" meaning punishment. Pain is always subjective and is unique among all senses because it has a strong emotional component along with the sensory component. Research has revealed spinal cholinergic pathways and transmitters involved in antinocioceptive processing. Intrathecal neostigmine, the cholinergic agent (a cholinesterase inhibitor) causes analgesia in humans[3]. It is advantageous over other currently used spinal drugs as it causes no hypotension, no sedation, no respiratory depression or neurological dysfunction[4, 5].

Mean Pulse Rate

In our study the mean heart rate during spinal anesthesia in all the six groups varied, but the common thing was that pulse rate after 15 minutes of intrathecal neostigmine decrease in control group and groups (B,C,D) when 0.25 mg neostigmine was administered, while pulse rate increased in groups (E,F) where higher doses of neostigmine (0.5 mg/ 0.75 mg) was administered.

Yaksh et al[6] in their study on rats and dogs found no persistent change in the heart rate of dogs administered intrathecal saline, although there was a modest but statistically significant decline over time after initiation of infusion of neostigmine.

Hood et al[3] in their experimental study found that there was an increase in heart rate and blood pressure after intrathecal administration of neostigmine methyl sulphate, which results from amplification of the action of acetylcholine release on pre-ganglionic sympathetic neurons where it is an excitatory neurotransmitter. They concluded that it appears that degree of cardiovascular stimulation from intrathecally administered neostigmine is greater in the rats, then in sheep or human, perhaps reflecting diminished penetration of neostigmine into the inter mediolateral cell column in species with larger spinal cords. We are in full agreement to these views of above authors.

The increased pulse rate at 3 and 6 hours in group E and beyond 90 minutes up to 12 hours in group F reflects that higher doses of neostigmine (0.5 mg and 0.75 mg) led to this, hence 0.5 mg and above doses of neostigmine should be avoided for intrathecal route, because cardiovascular stimulation of intrathecally administered neostigmine is dose dependent.

Mean Blood Pressure

In group A Blood pressure variations were not much significant, but in group B slight fall in BP was noted initially, but beyond 1 hr it started rising, at 2 hrs statistically significant difference

(P < 0.1) was noted. In group C initial fall in BP was significant at 15 minutes (96 vs 118), statistically comparative values were also significant. In group D and E the variations in BP were not very significant. However in group F slight fall in BP was noted at 30 minutes and then it reached to 141.2 mm at 3 hrs, On statistical comparison with pre-spinal levels values at 30, 45 and 60 minutes were found to be significant. (Shown table No.2)

However Changes in blood pressure in control group, when compared to, study groups were found to be statistically insignificant, when compared among themselves significant values were obtained. When group B was compared to group F and when group C was compared to group E, reflecting dose dependent effect on blood pressure of higher doses of intrathecal neostigmine.

Hood and co-workers[3] in their experimental study on sheep, found an increase in blood pressure after intrathecal administration of neostigmine resulting from amplification of the action of acetylcholine release on pre-ganglionic sympathetic neurons where it is an excitatory neurotransmitter. However, to strengthen this statement of experimental study, more human studies are needed in this direction.

Duration of Analgesia

The mean duration of analgesia in control group (Group A) was 2.68 hours. While in the study group, it was 11.8 hrs, 9.6 hrs, 7.6 hrs, 11.6 hrs and 11.6 hrs in groups B, C, D, E and F respectively. Statistically, these values were highly significant (p<.001) when compared with the control group.

Yaksh et al[6], based on their experimental study reached to the inference that intrathecal injection of neostigmine resulted in an elevation in the hot plate response latency. These response latencies were dose dependent. Similarly other auther[7] hypothesized that post operative pain itself enhances spinal cholinergic tone and hence the analgesic effect of intrathecal neostigmine.

In the first ever published clinical trial of neostigmine on healthy humans, David D. Hood et al[3] demonstrated dose related analgesia. This was contrary to the present study in which no dose dependent analgesia was observed. David D. Hood further concluded the therapeutic dose of spinal neostigmine, based on response to experimental pain, probably lies between 50 and 500 micro gm, and should cause near total relief of post operative pain, lasting 4-6 hours. We agree to this view that less than 500 ugm of neostigmine is sufficient to achieve desired analgesic effect.

Further duration of analgesia was not affected by increasing dose of neostigmine as in group B where 0.25 mg neostigmine was used , it was 11.87 hrs VS 11.6 hrs in group E and F, where 0.50 mg and 0.75 mg neostigmine dose was used.

Duration of Motor Paralysis

The duration of motor paralysis in control group was 88 + 23 min, while in study groups it was 90 + 21 min., 88 + 9 min., 112 + 24min., 108 + 20 min and 96 + 23 min in group B, C, D, E and F respectively.

Statistically these values were insignificant when compared to the control group also when compared amongst themselves.

Hence, duration of motor paralysis was not affected by increasing dose of neostigmine as it was maximum 112+ 24 min in group D where only 0.25 mgm IT. neostigmine was given.

SUMMARY AND CONCLUSION

In this study effects of varying doses of intrathecal neostigmine in prolonging post operative analgesia produced by 5% xylocaine was evaluated in 45 patients of either sex, belonging to ASA grade I and II, with age ranging between 21 and 67 years.

All the patients were divided in 6 groups. These patients were operated for various lower abdominal, perineal, lower limb and uro surgical procedures.

Bradycardia in control group when compared to study groups was statistically insignificant. When compared with each other statistically significant values were observed when group B was compared to Group E and highly significant when

group E was compared to group F. (Shown table No. 1)

Hypotension in control group when compared to study groups were found to be statistically insignificant. When compared amongst themselves significant values were obtained when group B was compared to group F , and when group C was compared to group E.

Duration of motor paralysis was maximum 112 + 24 min in group D and minimum in group C when it was 88 + 23 min. statistically these values were insignificant.

Duration of analgesia in group A was 2.68 hrs. while in study groups it was – B- 11.8 hrs, C-9.6 hrs, D-7.6hrs, E-11.6 hrs and F-11.6 hrs respectively. Statistically these values were highly significant ($p<.001$) when compared with the control group. But when study group were compared amongst themselves they were found to be insignificant except when group B and D were compared ($p<.05$) when group D was compared with group E and F ($p<.02$) and group F compared with group C where it was found to be significant.

Side effects were found to be maximum in group F in which all the patients developed nausea, vomiting and hypotension. 60% of the patients developed bradycardia while 80% of them developed urinary retention. Thus higher dose of neostigmine (0.75 mg) should not be used.

Hence low dose neostigmine (0.25 mg) when added to xylocaine IT enhances duration of analgesia without affecting significantly cardiovascular status, duration of motor paralysis and adverse effects. Thus more and more use of low dose neostigmine as an adjunct to xylocaine (heavy) IT is being recommended and studies on larger number of patients are required in this direction.

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