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Original Research Article

Assessment of Safe Neuromuscular Reversibility after Vecuronium Bromide with and without Neostigmine

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ABSTRACT

Postoperative residual neuromuscular block is a frequent occurrence in the practice of anaesthesia.
There is convincing evidence that quantitative neuromuscular monitoring reduces the frequency of residual neuromuscular block in patients receiving non-depolarizing neuromuscular blocking agents. The present study has investigated the recovery from vecuronium bromide induced neuromuscular block with & without anticholinesterase drug "Neostigmine" in 60 cases. In our study we have included the age group from 10-70 years with mean age of 35.33 years of group A and mean age of 32.83 of Group B. We have included the patients of both sexes with male/female ratio 21:9 in group A and 16:14 in group B. All the patients were allocated randomly in two groups. Group A with 30 patients received neostigmine in dose of 0.04 mg/kg was to reverse vecuronium bromide induced neuromuscular block while group B of 30 cases did not receive neostigmine. Result shows that evoked recovery from vecuronium bromide induced neuromuscular block was most rapid & adequate after 0.04 mg/kg neostigmine. Recovery was prolonged & incomplete when neostigmine was not given for reversal of vecuronium induced neuromuscular block and omission of neostigmine would clearly be unsatisfactory. Vecuronium bromide did not show any significant effects on cardiovascular system. There was slight increase in pulse rate & arterial blood pressure after intubation which returned to normal value after 5-10 minutes. There was no side effect of neostigmine in dose of 0.04 mg/kg given for reversal.

Keywords: Neuromuscular reversibility, neuromuscular blocking agents, vecuronium bromide, neostigmine

INTERODUCTION

Neuromuscular blocking agents (NMBAs) are widely used to induce muscle relaxation in anesthetized patients undergoing surgery. However, patients receiving NMBAs may be at risk of residual block, a key contributing factor for the development of postoperative pulmonary complications[1] and increased postoperative morbidity and mortality. [2]

The scope and technique of anaesthesia was revolutionised on 23rd January, 1942 when Harold R. Griffth & Enid Johnson deliberately used curare to achieve muscle-relaxation during surgery at suggestion of Dr. Lewis Wright.

Since then various other synthetic muscle-relaxants such as gallamine triethiodide, alcuronium, pancuronium bromide, vecuronium bromide and atracurium etc. have been introduced and their use have become firmly established as an integral part of balanced anaesthesia.

Drawbacks of d-tubocurarine and alcuronium were both associated with increased heart rate and decreased arterial blood pressure and peripheral resistance and anaphylactic reaction.

Whereas gallamine triethiodide increases heart-rate and blood pressure owing to its cardiac vagal blocking properties prolonged paresis may follow the use of gallamine in cases with renal failure. [3]

Pancuronium bromide synthesized by and used clinically in 1967 increases heart-rate, occasionally blood pressure. It has been shown to exhibit a prolong action in patient with impaired renal function. Similarly the biliary obstruction can double the plasma half life of pancuronium in man.

The new drug atracurium whose pharmacological properties have been described by [4] Hughes et al has many attractive properties i.e. it is slowly hydrolysed by two separate reactions: (1) Hofmann degradation (2) Easter hydrolysis. It is non cumulative and has no cardiovascular effects. The duration of action does not prolonged in absence of hepatic and renal excreting pathways but unfortunately atracurium can cause histamine release and produces flushing, bronchospasm and hypotension in few sensitive individuals.

In most of the surgical procedure, requiring muscular relaxation, the use of a single non-depolarising muscle relaxant would be preferred provided the relaxant enables easy and quick intubation, and provides good muscle relaxation, quick and safe recovery.

Therefore, there is still a need for short acting nondepolarising neuromuscular blocking agent with a rapid onset of action which should not affect cardiovascular system in therapeutic dose. Ideally it should be rapidly metabolised to inactive metabolites and should be rapidly reversible by minimum dose of anticholinesterase neostigmine or without neostigmine.

There is convincing evidence that quantitative neuromuscular monitoring reduces the frequency of residual neuromuscular block in patients receiving non-depolarizing neuromuscular blocking agents. [5,6]

In the series of nondepolarising neuromuscular blocking agents, the recently introduced drug vecuronium bromide fulfills all these criteria to some extent.

It has intermediate duration of action. It is more potent and having quick onset and shorter duration of action than pancuronium bromide [7] vecuronium bromide has very minimal side effects, almost no cardiovascular effects (Savage et al) [8] no histamine release and no vagolytic action. It is a muscle relaxant of wide margin of safety with no cumulative action either from repeated dose or continuous intravenous infusion. It shows close related duration of action.

The antagonism of vecuronium bromide induced neuromuscular block is more rapid after pronounced spontaneous recovery. Vecuronium Bromide is devoid of cumulative effects, has good cardiovascular stability, does not release histamine and is excreted mainly in the bile. [9]

It has been observed that very small dose of neostigmine is adequate for safe reversal of vecuronium bromide induced neuromuscular block but sometime it is not required. The required dose of neostigmine is significantly less in case of vecuronium bromide as compare to pancuronium bromide for reversal. [10]

Neostigmine is an anticholinesterase agent used widely to antagonise the nondepolarising neuromuscular block. In a dose of 2.5 - 5.0 mg Neostigmine has been found to adequate to antagonise all currently available nondepolarising neuromuscular blocking drugs. However, use of neostigmine as a reversal agent is not free from side effects e.g. bradycardia, miosis, increased salivation and bronchospasm etc. even some time in large doses neostigmine may itself causes neuromuscular block by depolarising action.

This study was undertaken to assess the safe neuromuscular reversibility after vecuronium bromide with and without neostigmine.

Neostigmine is a synthetic quaternary ammonium parasympatho-

mimetic agent. It is an anticholinesterase used to reverse neuromuscular blockade. Anticholinesterase may increase the release of acetylcholine from presynaptic nerve terminals. [11,12]

Reversal of neuromuscular blocking effect of vecuronium bromide is readily achieved by anticholinesterase agents. It has been suggested that a lower dose of neostigmine than that required to reverse other neuromuscular agents might be appropriate after vecuronium bromide but other authors dispute this. [13] Gen Carelli (1982), [3] Fahey (1981).

MATERIALS AND METHODS

Sixty cases were selected for this study among healthy individuals (ASA Grading I & II) for elective surgery under general anaesthesia in L.L.R. & Associated Hospital, G.S.V.M. Medical College, Kanpur. Patients in this study were of both sexes and above 10 years age group with no neuromuscular weakness & no electrolyte imbalance and not taking any medicine affecting the neuromuscular blocking action of vecuronium bromide.

Assessment of Patient

General examinations of patient and complete examination of central nervous system, cardiovascular and respiratory system were carried out. All the cases were allocated randomly in two groups.

1. Group A-Consists of 30 cases. In these cases Neostigmine in dose of 0.04 mg.kg-1 was given to reverse vecuronium bromide induced neuromuscular block.
2. Group B-includes 30 cases. Neostigmine was not given in this group.

Investigation:

All the cases were investigated for routine blood & urine examination. Chest X-Ray PA-View, ECG and some special investigation if considered essential were carried out. Blood urea, S. creatine in liver function tests were carried out in specific cases.

Preparation for anaesthesia:

All the admitted patients were prepared as for conventional anaesthesia. Sound sleep on the night before operation was ensured by giving either sedative or tranquilizer as per requirement of patient. All were advised to take nothing by mouth for atleast six hours before induction of anaesthesia.

Premedication:

All the patients were premedicated with .012 mg/kg atropine and .6mg/ kg pentazocine and .5 mg/kg promethazine i.m. 3/4 hour before induction of anaesthesia. Pulse rate, arterial blood pressure & weight are recorded before induction. Tidal volume was taken with respirometer for the control values.

Induction of Anaesthesia-

Patients were brought on operation table. An intravenous line with 5% Dextrose solution was started. Patient was induced with 2.5% Sodium-Thiopantone 4-7 mg kg-1 I.V. slowly followed by succinylcholine 1-2 mg kg-1 and then after 100% Oxygenation with face mask by doing intermittent positive pressure ventilation, a proper size endotracheal tube was passed after direct visualization of cord by Macintosh laryngoscope. Patient was maintained on N20 & 02 with 67: 33 ratio. When effect of succinylcholine was worn off than vecuronium bromide was given in dose of .06 -.08 mg kg -1. Now when effect of this was worn off it was given in t p p dose (1/5 of first dose). Patients were monitored 'for pulse rate and arterial blood pressure during operation.

Recovery and reversal of muscle-relaxant action:

When the surgery was completed and spontaneous respiration was returned. The tidal volume was measured at-12 minutes, 16 minutes, 20 minutes & 24 minutes after last dose of vecuronium bromide. Pulse rate & arterial blood pressure was recorded. N20 was switched off. 100% 02 was given in every case.

Now in Group A- The neostigmine with dose of .04 mg kg-1 -1 was given with Atropine .02 mg kg and extubation was done after complete I (recovery of neuromuscular block as observed seeing adequate chest expansion opening of eyes, hand grip, sustained head raising time, speech, muscle tone & absence of tidal volume was recorded with respirometer, time taken for extubation was noted.

In Group B- The assessment of reversibility was done without giving Neostigmine and any complication of inadequate reversibility was observed.

Pulse & arterial blood pressure were recorded in both grows.

If Antagonism of neuromuscular block was inadequate -1 .04 mg kg Neostigmine was given in these cases to achieve adequate reversal.

RESULT

It is evident from table 1 that group A has 30 cases with 21 males and 9 females and group B has 30 cases with 16 males and 14 females.

Table 1: Distribution Of Patients According To (Age & Sex)

Age range (yrs)	Group A			Group B		
	Male	Female	Total	Male	Female	Total
10-20	3	2	5	2	3	5
20-30	5	1	6	4	5	9
30-40	4	3	7	4	2	6
40-50	6	2	8	2	1	3
50-60	2	1	3	3	2	5
60-70	1	0	1	1	1	2
Total	21	9	30	16	14	30
Mean Age S.D.	35.33±14.25			32.84±13.32		

Table 2: Distribution of Patients According to Weight

Weight (kgs)	Group A		Group B	
	No. of Cases	Percentage	No.of case	Percentage
20-30	4	13	5	17
30-40	5	17	3	10
40-50	8	27	9	30
50-60	10	33	9	30
60-70	1	3	3	10
70-80	2	1	1	3

It is evident from table 2 that Group A has mean weight 46.52 kg and Patients of Group B has mean weight 47.13 kg.

Table 3: Types of Surgical Procedure Performed

	Group A (N= 30)		Group B (N= 30)	
	No. of cases	Percentage	No.of cases	Percentage
General surgery	18	60%	20	66%
Orthopaedic	7	23%	6	20%
Gynaecology	5	17%	4	14%

Table 3 shows that majority of cases in both group had undergone general surgery.

Table 4: Mean Time For Surgery In Both Groups

Duration(min)	Group A		Group B	
	No. of cases	Percentage	No. of cases	Percentage
30-60	12	41	10	33
60-90	10	33	11	36
90-120	7	23	7	23
120-150	1	3	2	7
Mean±SD	57±10.03 minutes		63.72±12.08 minutes	

It is clear from table 4 that mean time for surgery in group A was 57 minutes and 63.72 minutes in group B.

Table -5: Tidal volume on return of spontaneous respiration after last dose of vecuronium

Time (min.) After 1st dose of vecuronium	Tidal volume	% to the control
12	106± 60.45	23%
16	270± 122.34	59.80%
20	292± 140	63.30%
24	294±138.79	63.40%

Table 5 shows that even after 24 minutes of last dose of vecuronium the tidal volume was 63.40% to the control.

Table 6: Tidal Volume With and Without Neostigmine in Both Groups

Intervals	Group A N= 30 Mean±SD	Group B N= 30 Mean±SD	P value
Preoperatively (control) in m1	462±170.65	466±167.45	<0.05 Significant
After reversal in m1	408±120.17	300.8±128.65	
Percentage to control	84.40%	64.54%	

It is evident from table 6 that tidal volume was 84.4% to the control in the patients of Group A. In the cases of Group A tidal volume was above 75% to control. In Group B tidal volume was 64.54% to control. Tidal volume was taken 24 minutes after last dose of vecuronium with and without Neostigmine. Tidal volume more than 75% to control is taken as adequate.

Table 7: Changes in Parameters after Reversal.

Parameters	Conditions	Group A		Group B		P Value
		No of cases	%	No of cases	%	
Respiratory effort	Adequate	24	80%	4	14%	<0.01 (HS)
	Poor	6	20%	26	86%	
Muscle Tone	Good	23	77%	3	10%	<0.01 (HS)
	Inadequate	7	23%	27	90%	
Speech	Clear	21	70%	5	17%	<0.01 (HS)
	Slurred	9	30%	25	83%	
Head raising	<4 sec	7	23%	24	20%	<0.05 (S)
	>4 sec	23	77%	6	20%	
Hand grip	Good	21	70%	6	20%	<0.01 (HS)
	Poor	9	30%	24	80%	

HS: Highly Significant; S: Significant

It is evident from table 7 that reversal was adequate in Group A & it was not adequate in patients of Group B.

Table- 8: Change in vital parameter such as – pulse rate

Stage	Group A	Group B
	Mean value per min.	Mean value per min.
Preoperatively (Control)	82.6±10.15	81.2±7.34
After intubation	83.5±8.23	82.7±7.93
Before Extubation	76.4±7.64	77.3±8.43
After extubation	78.2±9.36	76.9±8.84

Table 8 states that there is increase in pulse rate after intubation in both the group which reached to control value after sometime.

Table- 9: Change in blood pressure

Stage	Group-A Mean value mm Hg		Group-B Mean value mm Hg	
	SAP*	DAP*	SAP	DAP
Preoperatively (Control)	116.8±2.55	72.2±3.10	112.8±1.75	67.8±3.20
After intubation	120.2±2.85	72.9±2.80	115.2±2.24	68.4±2.45
Before Extubation	116.2±1.96	72.3±3.20	113.1±3.2	67.6±2.66
After extubation	115.8±2.45	71.9±2.60	112.9±2.10	67.4±1.95

-There was slight increase in arterial pressure after intubation.
- No change in arterial blood pressure after giving neostigmine in group A.
* = Systolic Blood Pressure
** = Diastolic Blood Pressure

DISCUSSION

We have studied the recovery from vecuronium bromide induced neuromuscular block with & without anticholinesterase drug "Neostigmine" in 60 cases. In our study we have included the age group from 10-70 years with mean age of 35.33 years of group A and mean age of 32.83 of Group B. We have included the patients of both sexes with male/female ration 21:9 in group A and 16: 14 in group B.

The mean weight of Group A was 46.52 kg and Group B was 47.13 kg. In this study body weight was taken as basis for the calculation of dose of vecuronium bromide

and neostigmine. It is easily measureable and is fairly accurate and reliable method for the use of muscle relaxants in clinical practice.

Same standard premedication was used in all cases to avoid the influence on the dosage and action; of muscle relaxant drug. The anaesthetic regime was chosen as that least likely to affect the neuromuscular junction. Barbiturates have been shown to have a slight depressant effect on the neuromuscular junction. But by giving the induction dose of thiopentone a body weight basis this small effect should be almost equal in all patients. N20 has no effect on result of our study. Keeping in mind the above precautions, this study thus undertaken by us should therefore leave the neuromuscular junctions, least influenced by other drugs. In our study we recorded tidal volume on return of spontaneous respiration after last doses (.02mg/kg) of vecuronium bromide at various intervals. Tidal volume was 23% to control after 12 minutes, 59.8% to control after 16 minutes and it was 63.3% to control after 20 minutes. It was 63.42 to the control even after 24 minutes indicating incomplete recovery.

Agostan et al (1980) reported that the duration (recovery to 90% of control twitch height) following vecuronium bromide averaged 15 minutes after .03 mg kg land 27 mintues after .05 mg -1 and the total durations (recovery to 90% of control twitch height following vecuronium bromide .1 mg kg averaged 44 minutes.

Agoston, et al (1980) [14] observed recovery time from 25 to 75% twitch force of vecuronium bromide averaged 9 minutes and 15 minutes following single bolus injection of .03 mg kg-1 -1 and .12 mg kg respectively.

Crul & Booij (1980) [15] observed that vecuronium has shorter duration of action than pancuronium and recovery from neuromuscular blockade is more rapid with newer drug. It has suggested that when vecuronium is given in bolus doses, an anticholinesterase may not be necessary to antagonize vecuronium bromide induced neuromuscular block (Baired et al 1982). [16]

Johnson J.E et al 1987 observed that neostigmine is used widely to antagonize non depolarizing neuromuscular block. In the presence of at least 5% recovery of single twitch a dose of 2.5 - 5.0 mg has been found adequate for all currently used neuromuscular blocking agents including vecuronium bromide.

Antagonism is more rapid after pronounced spontaneous recovery has occurred (Rupp SM, Miller 1986) [17] and it has been suggested that smaller dose of neostigmine might be adequate or it might be omitted (AstleyB. 1981). [18] (Johnson & Harper, 1989) suggested that the dose of neostigmine should not be reduced below 0.04mg kg-1 even when all response of the TF are present for safe reversal of vecuronium induced neuromuscular block. They concluded that evoked recovery from vecuronium induced block was most rapid after neostigmine .04 mg kg-1 at both minimal and moderate degrees of spontaneous recovery. Recovery was prolonged when dose was reduced and omission of Neostigmine would clearly be unsatisfactory. The dose of neostigmine should not reduce to less than .04 mg kg-1 even when single response had recovered to 50 % of control and there are four response to ToF stimulation.

Fahey et al (1981) [3] found that less neostigmine was required to antagonize vecuronium bromide blockade as compared with that required to antagonize blockade from pancuronium.

Jones Hunter et al (1987) [19] observed that neostigmine 2.5 mg was rapidly effected to antagonize vecuronium induced Neuromuscular block even initial recovery was only slight. Similarly in our study we observed the same results as observed by above mentioned workers. We have taken tidal volume & some other clinical evidence as parameter to access the reversal status because we do not possess myographic facilities. In our study we observed that tidal volume measured after

giving .04 mg kg-1 of Neostigmine to reverse vecuronium induced neuromuscular block was 84.4% to the control value. This value was above adequate level i.e. more than 75% to the control. We also observed that tidal volume measured without giving neostigmine was 64.5% to the control value which indicates incomplete reversal. This result is supported by other clinical evidence taken as parameter, such as time taken for extubation, respiratory effort, muscle tone, speech, sustained head raising time When .04 mg kg-1 neostigmine was given to reverse vecuronium bromide induced neuromuscular block. The respiratory effort was adequate in 80% cases. The muscle tone was good in 77% cases, speech was clear in 70% cases. Sustained head raising time was more than 4 seconds in 77%. We conclude from this observation that recovery from vecuronium bromide induced neuromuscular block with .04 mg kg-1 neostigmine was adequate. When neostigmine was not given for recovery of vecuronium induced neuromuscular block. The respiratory effort was poor in 86% cases, muscle tone was inadequate in 90% cases. Speech was slurred in 83% cases. The sustained head raising time was less than 4 seconds in 80% cases. From this study we conclude that reversibility after vecuronium bromide without neostigmine was incomplete.

Taking same parameter V Singh et al (1991) [20] observed that neostigmine is necessary to reverse vecuronium induced neuromuscular block even with normal ToF more than .7 and used reversal in all cases, since even with normal TOF, 70% receptor can still be blocked. Vecuronium is the most selective neuromuscular blocking drugs which is almost free from autonomic blocking properties. In our study we observed that after vecuronium bromide there is slight decrease in pulse-rate, which is not significant. This observation is supported by Barnes et al (1982) [21] there was no significant change in pulse rate after giving neostigmine, too. Buzillo & Noldge (1982) [22] observed that there is no change in pulse rate after administration of vecuronium bromide.

Zurant et al (1980) suggested that lack of Tachycardia with vecuronium may be related to low cardiovascular anti-muscarinic potency of vecuronium previously reported in cat. Even doses of drug many times greater than those required to produce neuromuscular block do not increase heart rate (Booij et al, 1980). [7] Our observation showed that after vecuronium there was an insignificant change in Systolic & Diastolic arterial blood pressure. There is slight increase in blood pressure after intubation & returned back to normal value after some time.

This is supported by Crull & Booij (1980), [15] they did "not observed any change in heart rate and arterial blood pressure with the dose of vecuronium upto .13 mg kg-1, and showed that vecuronium is free from Vagolytic and Cardiovascular side effect. Schaer & Hossll (1980) observed that vecuronium at neuromuscular dose is unlikely to produce marked cardiovascular side effect. Baired & Herd (1980) [16] found that there were neither 0 significant change in heart rate and arterial pressure following vecuronium nor any decrease in myocardial performances. Buzello & Boldge (1982) [23] also did not observe any cardiovascular or other side effect after repetitive administration of vecuronium bromide.

Morris et al (1983) [24] even in large doses, vecuronium bromide is having only minimal cardiovascular effects, in comparison with pancuronium.

The findings of all the workers support our results that vecuronium bromide has negligible or no side effect on cardiovascular system. The overall incidence of complication was the least with vecuronium bromide. Our study also showed that there was no side effect of neostigmine in dose of .04 mg kg-1 like bronchospasm, neuromuscular block, when given to reverse vecuronium induced neuromuscular block.

It is supported by Pyane et al (1980). [25] They observed that there was no

electromyographic or clinical evidence that largest dose of neostigmine (.04mg kg-1) produced slower recovery because of neostigmine block. Hohnson & Harper (1989) also observed the same results.

Bowman et al (1980) [26] observed that neostigmine does not exert a predominant influence on either pre or post junctional receptors.

CONCLUSION

Consequent upon careful appraisal of discussion over various observations on entire work carried on 60 cases otherwise healthy patients the following conclusions were drawn:-

1. We conclude from our study that evoked recovery from vecuronium bromide induced neuromuscular block was most rapid & adequate after 0.04 mg/kg neostigmine.
2. Recovery was prolonged & incomplete when neostigmine was not given for reversal of vecuronium induced neuromuscular block and omission of neostigmine would clearly be unsatisfactory.
3. Vecuronium bromide did not show any significant effects on cardiovascular system. There was slight increase in pulse rate & arterial blood pressure after intubation which returned to normal value after 5 - 10 minutes.
4. There was no side effect of neostigmine in dose of 0.04 mg/kg given for reversal.

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