Indian J.Sci.Res. 5(1) : 31-38, 2014 ISSN : 0976-2876 (Print)
ISSN : 2250-0138 (Online)

A STUDY OF RECOVERY FROM GENERAL ANAESTHESIA AFTER PREOPERATIVE ADMINISTRATION OF ANTIMICROBIAL

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ABSTRACT

Antimicrobials are used prophylactily in any major surgery to cover perioperative wound infection and other infectious complication ,that may have interaction with muscle relaxant used for general anesthesia and the aim of our study is drug interaction and behavioural response of newly introduced antibiotics used with rocuronium. Gentamicin shortened onset and duration of block after intubating dose of rocuronium and also prolonged duration of extubation after last dose of rocuronium where as meropenem and ceftriaxone did not alter onset, duration and recovery characterstics of rocuronium. . From our study we can conclude that meropenem and ceftriaxone but not gentamicin, can be used safely during general anesthesia.

KEYWORDS : Rocuronium, Gentamicin, Meropenem, Ceftriaxone, General anaesthesia

Many drugs are known to interact with neuromuscular blocking agents that include antimicrobials, inhaled anaesthetics, magnesium, lithium, local anaesthetics, antiepileptics and some diuretics. Antimicrobials are used in almost all major surgeries preoperatively, intraoperatively and postoperatively to reduce postoperative wound infection and other infectious complications. A maximum dose of prophylactic antibiotic is given preoperatively so that effective tissue concentration is present at and after the time of incision. (Ludwig et al.,1993)

Commonly administered antimicrobials are aminoglycoside, clindamycin, lincomycin and polypeptide antimicrobial like colistin and polymyxin. This effect (interaction with neuromuscular blocking agent) is usually not observed in clinical use of these drugs but is manifested only when used with neuromuscular blocking drugs.

Aminoglycoside group of antimicrobials used frequently in many major surgeries to cover gram negative bacterial infection, have highly neuromuscular blocking property. This effect is most likely due to ability of aminoglycosides to inhibit the prejunctional release of acetylcholine while also decreasing postsynaptic sensitivity to the neurotransmitter (Singh et al., 1982)

Non-depolarizing group of muscle relaxant include tubocurare, vecuronium, atracurium, rocuronium, doxacurium, pipecuronium etc. Rocuronium belonging to an intermediate acting non-depolarising group of neuromuscular blocking drug, is often used in general anaesthesia.

The near ideal muscle relaxant must span the range of short, intermediate and long acting duration (as required by surgical procedure),have rapid onset, be highly metabolized, have no cumulative or cardiovascular effect, to be independent of kidney for elimination, and be easily antagonized. The most commonly used clinical agents-atracurium, doxacurium, vecuronium, pancuronium and pipecuronium-demonstrate some, but not all, of these properties.

Rocuronium bromide is a relatively new non-depolarizing muscle relaxant. It is the first of these agents to have an onset time possibly as brief as that of suxamethonium without adverse side effect. Rocuronium bromide is mono-quaternary, aminosteroidal, nondepolarizing neuromuscular blocking agent with a rapid onset of action (Bartkowski et al., 1993) and it has a low tendency to release histamine. Both enflurene (Bartkowski et al., 1990) and isoflurane (Shanks et al., 1993) (Muir et al., 1994) potentiate the effect of rocuronium bromide. Halothane appears to produce less potentiation of neuromuscular block than isoflurane and enflurane (Cooper et al., 1993). Studies on the interaction of rocuronium bromide and some intravenous anesthetic agent have confirmed that standard doses of fentanyl, ,droperidol,

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midazolam, etomidate, thiopentone and propofol do not have any clinically significant effect on the action of rocuronium bromide (Khuenl-Brady et al., 1992)

Recently many newer antimicrobials have been introduced in the clinical practice to combat tough infections particularly in critically ill patients. Increasing use of newer antimicrobials (Ceftriaxone, Meropenem, Polymyxin,Piperacillin, Vancomycin etc.) in preoperative, intraoperative and postoperative sessions has motivated to workout to the best of our efforts, the drug interaction and behavioural response when coadministered with a neuromuscular blocking agent.

MATERIALS AND METHODS

This study is randomized, prospective, double blind, case control study carried out on admitted patients of Gandhi Memorial & Associated Hospitals ,KG medical university , Lucknow,(former CSSMU) undergoing various surgical procedures under general anaesthesia (GA) after getting approval from Ethical Committee, King George's Medical University, UP, Lucknow and obtaining a written consent from the patient relative.

For this purpose a total of 80 patients of eigher sex of age group between 18-50 yrs and ASA grade I&II were submitted. Patients of renal, pulmonary, cardiovascular, neurological, neuromuscular diseases and deranged liver function test were excluded from our study. A general physical and detailed clinical examination supported by routine blood, urine and biochemical test as per need was carried out.

The cases were divided into two groups, the first one called control group (Group A) includes patients who received rocuronium and no antimicrobial and another called study group (Group B) includes patients who received antimicrobial with rocuronium. Group B further devided into 3 subgroup as B1 (Rocuronium with Gentamicin) B2 (Rocuronium with Meropenem) and B3 (Rocuronium with Ceftriaxone).

After arrival in operating room intravenous access was secured and ECG, pulse oximetry, noninvasive blood pressure, temperature and urine output was monitored at regular interval till shifting of the patient to post-operative room. A venous blood sample was taken before medication for estimation of Na^+, K^+, Ca^{++} and Mg^+. Every patient received Ringer Lactate as fluid for maintenance, induction losses, fasting and blood loss as per calculations. Single dose of antimicrobial according to study group was given to patient in moderate dose (gentamicin-1.5 mg/kg, meropenem -15 mg/kg and ceftriaxone-20 mg/kg) approximately 1 hr before induction. All patient after induction with propofol, intubating dose of rocuronium(0.6mg/kg) was given. Anaesthesia was maintained with mixture of N_2O and O_2 (60%:40%), propofol infusion (50-200 mcg/kg) and top-up dose of rocuronium(0.15 mg/kg) during surgery and propofol infusion had stopped at end of operation. Inhalational agent and any drugs that have effect on neuromuscular function was avoided. Neuromuscular block was monitored/assessed with the help of peripheral nerve stimulator (PNS) using train of four (TOF) stimulation.

Train-of-four is a test used for measuring the level of neuromuscular blockade. In this test four consecutive stimuli of 2hz are delivered along the path of a nerve and the response of the muscle is measured in order to evaluate stimuli that are blocked versus those that are delivered. Four equal muscle contractions will result if there is no neuromuscular blockade, but if nondepolarizing blockade is present, there will be a loss of twitch height and number, which will indicate the degree of blockade. Four twitches with different height means there is less than 75% block, three twitches means 75% block, two twitches means 80%,one twich mean95% block and no twich means 100% block.

After administration of propofol, the nerve stimulator was switched on to maximal current output to ensure that a supramaximal stimulus is applied. After intubating dose of rocuronium, time of giving intubating dose of rocuronium, laryngoscopy and intubation, first topup dose, last topup dose,reversal agent and finally time of patient awakening and tracheal extubation was noted.By noting all time T_1 (duration from intubating dose of relaxant to laryngoscopy and intubation), T_2 (Duration from intubating dose of relaxant to first topup dose of relaxant)

and T_3(Duration from last topup dose to patient awakening and tracheal extubation) was calculated.

Temperature of local site and body was controlled with airwarmer, fluid warmer & blanket. A blood sample was taken before induction and before reversal for estimation of Na^+, K^+, Ca^{++} and Mg^{++}. Two patient found to have abnormal electrolyte were excluded from the study.

Effect of antimicrobials on the onset of blockade, duration of blockade & recovery characterstics of rocuronium was assessed. Laryngoscopy was done when there is no twitch response after TOF stimulation. First top-up and successive top-up was given at appearence of first twich response after TOF stimulation. Reversal of residual neuromuscular block was performed by mixture of neostigmine (50 µg/kg) and glycopyrrolate (0.01mg/kg) when at least 3 twitches in TOF stimulation was recorded. Extubation of trachea was done under vision when the patient was fully awake, breathing spontaneously and following the verbal commands. The recovery from anaesthesia was assessed by TOF response as well as clinically by sustained hand grip, head raising and intact bulbar reflexes.

RESULTS

This chapter describes results obtained from analysis of data by using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

Distribution of patient according to age, gender, ASA grade, height and weight was statistically not significant in all the groups.

Table 1, shows Mean age of patients in Groups A, B1, B2 and B3 was 35.55±11.62, 33.00±9.19, 38.20±11.77 and 36.20±8.95 years respectively. On comparing the data statistically, no significant intergroup difference was observed (p=0.134).

Table 2, shows distribution of subjects according to their gender and on comparing data statistically no significant difference was observed (p=0.940).

Table 1: Distribution of Subjects according to age

S.No.	Age (years)	Group A		Group B1		Group B2		Group B3		
		n	%	n	%	n	%	n	%	
1.	≤20	2	10.0	1	5.0	3	15.0	2	10.0	
2.	21 - 30	7	35.0	10	50.0	3	15.0	4	20.0	
3.	31 - 40	3	15.0	5	25.0	2	10.0	7	35.0	
4	41 - 50	8	40.0	4	20.0	12	60.0	7	35.0	
	Mean±SD	35.55±11.62		33.00±9.19		38.20±11.77		36.20±8.95		

χ^2=13.696 (df=9); p=0.134
n = Number of patients SD= Standard deviation

Table 2: Distribution of Subjects according to gender

S.No.	Gender	Group A		Group B1		Group B2		Group B3	
		n	%	n	%	N	%	n	%
1.	Female	10	50.0	9	45.0	10	50.0	11	55.0
2.	Male	10	50.0	11	55.0	10	50.0	9	45.0

χ^2=0.400 (df=3); p=0.940 n = Number of patients

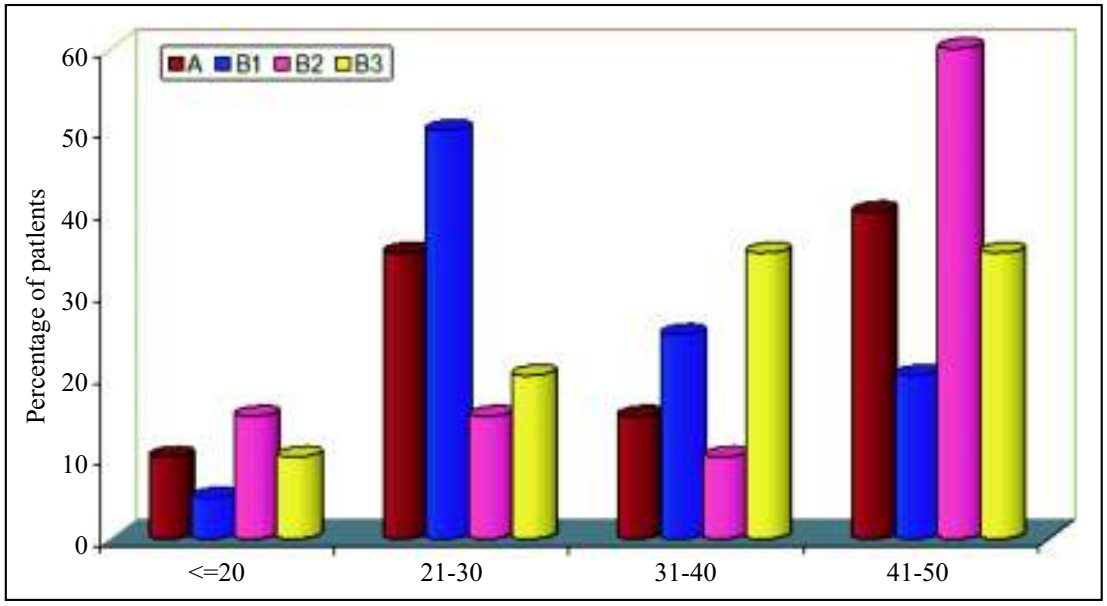

Table 3: Distribution of Subjects according to ASA Grade

S. No.	ASA Grade	Group A		Group B1		Group B2		Group B3	
		n	%	n	%	n	%	n	%
1.	I	12	60.0	14	70.0	13	65.0	13	65.0
2.	II	8	40.0	6	30.0	7	35.0	7	35.0

χ^2=0.440 (df=3); p=0.932 n = Number of patients

Table 4: Comparison of Anthropometric Measurements in different groups

S.No.	Parameter	Group A		Group B1		Group B2		Group B3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.	Height	162.15	9.10	162.63	8.82	163.45	7.72	160.25	9.16
	F (ANOVA) = 0.484; p=0 .694 (NS)								
2.	Weight	60.50	10.12	60.25	8.69	60.70	10.56	57.73	7.09
	F (ANOVA) = 0.456; p=0.714 (NS)								

SD = Standard deviation

Table 3, shows the ASA grade of subjects in all groups and majority of subjects in all the groups were in ASA Grade I. On comparing the data statistically, no significant intergroup difference was observed (p=0.932).

Table 4, shows,comparison of weight and height of all subjects in different age groups. Mean height of the patients ranged from 160.25±9.16 cm (Group B3) to 163.45±7.72 cm (Group B2). Statistically, there was no significant difference in height of patients in different groups (F=0.484; p=0.694).

Mean weight of the patients ranged from 57.73±7.09 kg (Group B3) to 60.70±10.56 kg (Group B2).

On comparing the data statistically, no significant intergroup difference was observed (p=0.714).

Table 5 shows, comparison of hemodynamic and other vital parameters in different groups. At baseline all the groups were matched for mean heart rate, SBP, DBP, MAP, temperature and % oxygen saturation showing no statistically significant difference among groups (p>0.05).

Table 6, shows comparison of mean time in minutes of laryngoscopy and intubation(t_1), first top-up dose of relaxant(t_2) and last top-up dose of relaxant(t_3) after intubating dose of relaxant among all groups.

Table 7, shows comparison of mean time in minutes taken for reversal, motor response with sustained head raising and hand grip and extubation after intubating dose of relaxant among all groups.

Table 8, shows comparison of different duration (T_1,T_2 and T_3) in minutes of all groups.

Mean value of T_1(duration from intubating dose of relaxant to laryngoscopy and intubation) for group A, B1, B2 and B3 was 1.68±0.10, 1.56±0.10, 1.67±0.10 and 1.67±0.12 minutes respectively. Group B1 took minimum time while group A took maximum time. Intergroup

Table 5: Comparison of Hemodynamic and other vitals parameters in different groups

SN	Parameter	Group A		Group B1		Group B2		Group B3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.	Heart rate (bpm)	78.05	7.20	82.00	9.51	79.25	9.03	82.80	8.76
F=1.339; p=0.268									
2.	SBP (mm Hg)	119.90	10.18	122.65	9.91	122.90	10.14	120.20	9.19
F=0.514; p=0.674									
3.	DBP (mm Hg)	76.50	5.57	79.00	6.46	77.40	7.02	78.55	6.35
F=0.630; p=0.598									
4.	MAP (mm Hg)	90.97	5.84	93.55	6.21	92.57	6.86	92.43	6.32
F=0.569; p=0.637									
5.	Temp. (^oC)	36.23	0.30	36.25	0.26	36.30	0.38	36.43	0.34
F=1.538; p=0.212									
6.	SpO_2	99.10	0.45	99.10	0.55	99.25	0.44	99.05	0.39
F=0.699; p=0.555									

SBP=Systolic blood pressure; DBP=Diastolic blood pressure MAP=Mean arterial pressure; Temp= Temperature SpO_2=Oxygen saturationSD = Standard deviation

Table 6: Comparison of Mean time (minutes) taken of parameter (t_1, t_2 & t_3) among the groups after intubating dose of relaxant

SN	Level	Group A		Group B1		Group B2		Group B3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.	t_1	1.68	0.10	1.56	0.10	1.67	0.10	1.67	0.12
	F=6.557; p=0.001								
2.	t_2	30.66	3.23	58.60	9.43	33.28	3.78	33.43	4.35
	F=104.045; p<0.001								
3.	t_3	95.15	24.01	108.58	19.83	106.58	27.34	100.63	18.92
F=1.424; p=0.242									

t_1= Time of laryngoscopy and intubation t_2= Time of first top-up dose of relaxant
t_3= Time of last top-up dose of relaxant SD= Standard deviation

Table 7 : Comparison of Mean time (minutes) taken for reversal, motor response with sustained head raising and hand grip and extubation

SN	Level	Group A		Group B1		Group B2		Group B3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.	Reversal	122.44	24.04	143.38	18.06	135.19	27.71	127.38	19.20
	F=3.298; p=0.025								
2.	Motor response with sustained head raising and hand grip	127.41	23.90	148.78	17.56	140.15	28.00	132.21	19.17
	F=3.458; p=0.020								
3.	Extubation	128.10	23.87	149.41	17.50	140.85	28.01	132.81	19.13
	F=3.462; p=0.020								

SD= Standard deviation

Table 8 : Comparison of Mean time (minutes) taken for different landmarks

SN	Level	Group A		Group B1		Group B2		Group B3	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.	T_1	1.68	0.10	1.56	0.10	1.67	0.10	1.67	0.12
	F=6.557; p=0.001								
2.	T_2	30.66	3.23	58.60	9.43	33.28	3.78	33.43	4.35
	F=104.045; p<0.001								
3.	T_3	32.95	3.86	40.84	5.22	34.28	3.16	32.19	2.61
	F=21.124; p<0.001								

T_1= Duration from intubating dose of relaxant to laryngoscopy and intubation
T_2= Duration from intubating dose of relaxant to first top-up dose of relaxant
T_3=Duration from last topup dose of relaxant to patient awakening and tracheal extubation
SD= Standard deviation

comparison of B1 with other groups (B1vsA,p=0.002, B1 vs B2 p=0.005 and B1 vs B3 p=0.004) show statistically higher significance.

Mean value of T_2 (duration from intubating dose of relaxant to first topup dose) for group A, B1, B2 and B3 was 30.66±3.23, 58.60±9.43, 33.28±3.78 and 33.43±4.35 minutes respectively. For T_2, Group B1 took maximum time (58.60±9.43minutes) while Group A took the minimum

time (30.66±3.23 minutes). On comparing the data statistically, a significant intergroup difference was observed ($p<0.001$).

Mean value of T_3 (Duration from last topup dose to extubation) for group A, B1, B2 and B3 was 32.95±3.86, 40.84±5.22, 34.28±3.16 and 32.19±2.61 minutes respectively. For T_3, Group B1 took maximum time (40.84±5.22 minutes) while Group B3 took the minimum time (32.19±2.61 minutes). On comparing the data statistically, a significant intergroup difference was observed ($p<0.001$).

DISCUSSION

Concomittant drug therapy as happen in administration of General Anesthesia is well known affair. The repercussion adjust like motor car running in multiple lane road drifting from its route will meet with an accident or its speed will be slow or fast according to lane chosen. This exercise have been undertaken to resolve the issue of multiple drug therapy in administration of general anesthesia and to study the consequences of drug involved in.

Aminoglycosides antimicrobials (Amikacin, Gentamicin, Tobramicin, Neomycin, streptomycin etc.) have been established to cause prolongation of the duration of non-depolarizing muscle relaxant (Fiekers et al., 1983) (Dupuis et al., 1989)

Recently many newer antimicrobials (Ceftriaxone, Meropenem, Polymyxin, Piperacillin, Vancomycin etc.) have been introduced in the clinical practice to combat tough infection particularly in critically ill patients. The available literature does not mention many studies on the effect of these newer antimicrobials on the duration of Non-depolarizing muscle relaxant (Tryba et al., 1985) (Condon et al., 1995)

In our study , interaction between rocuronium and antimicrobials, the mean time taken for all the parameter (TOF3, TOF2 and TOF1 response) was minimum in group B1. In intergroup comparison of TOF1 response (95% block), B1 with other group (B1 vs A p=0.001), (B1 vs B2,p=0.002) and (B1 vs B3, p=0.003) had statistically significant minimum time.

In our study time for laryngoscopy and intubation when there was no TOF response and also clinically absent diaphragmatic movement just after TOF1 response was noted and duration from intubating dose of relaxant to laryngoscopy and intubation (T_1) was calculated. Mean value of T_1 for group A, B1, B2 and B3 was 1.68±0.10, 1.56±0.10, 1.67±0.10 and 1.67±0.12 minutes respectively. Intergroup comparison of B1 with other groups (B1vsA,p=0.002, B1 vs B2 p=0.005 and B1 vs B3 p=0.004) show statistically higher significant.

In our study the time (t_2) of first visible twitch after intubating dose of relaxant was noted and first topup dose of relaxant given. Duration T_2 (duration from intubating dose of relaxant to first topup dose) was calculated for each patient in each group. Mean value of T_2 for group A, B1, B2 and B3 was 30.66±3.23, 58.60±9.43, 33.28±3.78 and 33.43±4.35 minutes respectively.

In our study recovery from general anesthesia is evaluated in steps. After last dose of relaxant when TOF3 (75% block) response appeared, reversal was given, we waited till the TOF4 response (<75% block) with sustained hand grip and head raising and diaphragmatic movements reappeared. After this the patient was extubated. T_3 (Duration from last topup dose to extubation) was calculated for each patient in all group. Mean value of T_3 for group A, B1, B2 and B3 was 32.95±3.86, 40.84±5.22, 34.28±3.16 and 32.19±2.61 minutes respectively.

CONCLUSION

Since gentamicin shorten the onset time of blockade, time for laryngoscopy and intubation is also shortened,it also prolong the duration of rocuronium block after intubating dose and prolong the duration of recovery from last top-up dose upto extubation where as two other used antimicrobials meropenem and ceftriaxone lack all this property. It was concluded that only Gentamicin but not Meropenem and Ceftriaxone appear to alter the onset, duration and recovery characteristics of rocuronioum, so Meropenem and Ceftriaxone can be used safely during surgery under general anaesthesia.

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