CALCIUM INDUCED ENHANCED RECOVERY FROM MUSCLE RELAXANTS AFTER REVERSING WITH NEOSTIGMINE AND GLYCOPYRROLATE

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ABSTRACT

BACKGROUND

Incomplete recovery from muscle relaxants is a potentially hazardous condition. Calcium ions play a significant role in neuromuscular transmission. This study is to find out whether Ca^{2+} administration after reversal with neostigmine and glycopyrrolate could enhance the recovery from neuromuscular blockade.

MATERIALS AND METHODS

Patients aged between 18 and 60 belonging to ASA status 1 and 2 undergoing elective surgery under general anaesthesia using non-depolarizing muscle relaxant were included in the study. They were randomly divided into 2 groups**.** First group received Calcium gluconate along with neostigmine for reversal of neuromuscular blockade while the second group received normal saline along with reversal. Muscle power was assessed by "tongue depressor mouth clench test". Time to achieve full recovery was compared between the two groups.

RESULTS

The group which received calcium gluconate recovered much faster than the saline group. Since p-value is found to be highly significant, there is significant difference in the time of attainment of full muscle power between the two groups.

CONCLUSION

Calcium administration with Neostigmine enhances neuromuscular recovery from non-depolarizing muscle relaxants.

KEYWORDS

Calcium, Neuromuscular Transmission, Neostigmine, Reversal of Neuromuscular Blockade.

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BACKGROUND

The return of normal neuromuscular function following paralysis of non-depolarizing muscle relaxants is a complex poly pharmacological occurrence. Adequate recovery from neuromuscular block is essential to ensure adequate spontaneous ventilation with normal regulation of breathing and to avoid adverse patient outcomes. Sufficient recovery is confirmed by an adductor pollicis TOF ratio of atleast 0.90.Residual neuromuscular blockade in post anaesthesia care unit is not rare. Approximately 30% to 50% of patients can have TOF ratio less than 0.90 following surgery.[1,2]

Calcium ions play a significant role in neuromuscular transmission. Voltage gated calcium channels in the presynaptic motor nerve ending triggers the release of ACh from vesicles into the synaptic cleft and promotes transmission of action potential into the muscle. Even though we know the importance of calcium ions in neuromuscular signalling, few studies have been done regarding the effect of calcium in early recovery from neuromuscular blockade. A recent study conducted by Ju J-W et al., published in European Journal of Anaesthesia studies the effect of calcium chloride co-administration with neostigmine in enhanced rate of reversal from neuromuscular recovery.[3] In our study we try to find out whether Calcium gluconate administration after reversal with neostigmine and glycopyrrolate could enhance the recovery from neuromuscular blockade.

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MATERIALS AND METHODS

After approval from the Institutional Ethics Committee and written informed consent from patients, this observational study was performed at Sree Gokulam Medical College and Research Foundation, Trivandrum, during the period from April 2017 to September 2017.

60 patients aged between 18 and 60 belonging to ASA (American Society of Anaesthesiologists) class 1 and 2 undergoing elective surgery under general anaesthesia using non-depolarizing muscle relaxant were selected. Those with neuromuscular diseases, hepatic and renal diseases and on any drugs known to interact with neuromuscular blockade were excluded from the study.

Patients were allocated into 2 groups randomly using sealed envelope method. After 8 hours NPO and premedication, they were taken for surgery. Intraoperative monitoring of ECG, SPO2, ETCO2, BP were done for all the patients. Once the surgery was over, patient was weaned off from all the anaesthetic agents and the appearance of attempt of respiration was noted. Then the patients were reversed with Neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg, followed by 10 ml 10% Calcium Gluconate in first group and 10ml Normal Saline in the second group. Time of attainment of full muscle power was assessed by "tongue depressor test".[4] and was compared in both groups.

Data Analysis and Results- Data was fed into a Microsoft excel worksheet and was analysed by SPSS statistical software. Student t- test was used for comparing the two groups.

Response Time (Sec)	Neostigmine + Calcium Gluconate	Neostigmine + Normal Saline
1	0	0
2	3	0
3	10	0
4	12	0
5	3	2
6	2	7
7	0	12
8	0	5
9	0	3
10	0	1

Table 1. Frequency Distribution

Null Hypothesis: 'u1-u2=0' (There is no difference in means). Since absolute value of t stat is 11.9, we reject the null hypothesis (t value of zero means null hypothesis is true).

Since P value is <<0.001 (much less than critical values) the means of two populations are significantly different. t-Test- Two-Sample Assuming Unequal Variances.

	Neostigmine + Calcium	Neostigmine + Normal Saline
Mean	3.7	7.1
Variance	1.044827586	1.40
Observations	30	30
Hypothesized Mean Difference	0	
df	57	
t Stat	-11.90	
P (T<=t) one-tail	2.17999E-17	
t Critical one-tail	1.67	
P (T<=t) two-tail	4.35997E-17	
t Critical two-tail	2.00	

Table 2. Statistical Data When Alpha = 0.05

	Neostigmine + Calcium	Neostigmine + Normal Saline
Mean	3.70	7.1
Variance	1.04	1.40
Observations	30.00	30
Hypothesized Mean Difference	0.00	
df	57.00	
t Stat	-11.90	
P (T<=t) one-tail	2.17999E-17	
t Critical one-tail	2.39	
P (T<=t) two-tail	4.35997E-17	
t Critical two-tail	2.66	

Table 3. Statistical Data When Alpha = 0.01

	Neostigmine + Calcium	Neostigmine + Normal Saline
Mean (u)	3.7	7.1
Median	4	7
Standard Deviation	1.02	1.18
Variance	1.04	1.40

Table 4. Group Statistics

Since p-value is found to be highly significant, there is significant difference in the time of attainment of full muscle power between the two groups.

DISCUSSION

Role of calcium in neuromuscular transmission is well known. But very less studies have been done on the impact of calcium on early recovery from neuromuscular blockade.[3] Neuromuscular junction is predominantly depending on Acetyl choline (ACh) for neural transmission. The nerve synthesizes ACh and stores in small vesicles. Stimulation of the nerve causes these vesicles to migrate to the surface of the nerve, rupture, and discharge ACh into synaptic cleft. Voltage gated calcium channels are arranged alongside the active zone. During a nerve action potential, sodium from outside flows across the membrane, and the resulting depolarizing voltage opens the calcium channels, which allows entry of calcium ions into the nerve and causes acetylcholine to be released. The number of quanta of ACh released by a stimulated nerve is influenced by the concentration of ionized calcium in extracellular fluid.

ACh Receptors (AChRs) in the end plate of the muscle respond by opening their channels for influx of sodium ions into the muscle to depolarize the muscle. The endplate potential created is continued along the muscle membrane by the opening of sodium channels present throughout the muscle membrane to initiate a contraction. ACh immediately

detaches from the receptor and is destroyed by the enzyme, acetylcholinesterase, which is also present in the cleft.[5] Depolarizing muscle relaxants can also act on these receptors to mimic the effect of Acetylcholine and cause depolarization of the end plate (Agonists of receptor). Non-depolarising muscle relaxants (NDMR) also act on the receptors, but they prevent ACh from binding to the receptor and thus prevent depolarization by agonists (Antagonists of receptor).[6] Reversal drugs inhibit Acetylcholinesterase and therefore impair the hydrolysis of ACh. The increased accumulation of undegraded acetylcholine can effectively compete with NDMRs and thereby displace the latter from the receptor and antagonize the effects of NDMR.[7]

Appropriate reversal of a nondepolarising neuromuscular blockade is essential to avoid adverse patient outcomes. Sufficient recovery from neuromuscular blockade for tracheal extubation can be confirmed by an adductor pollicis train-of-four (TOF) ratio of at least 0.90 or 1.0 if acceleromyography (AMG) is used. Quantitative neuromuscular monitoring is the only method of assessing whether a safe level of recovery of muscular function has occurred.

Calcium ion is essential for many biological processes that include cardiac automaticity; excitation-contraction coupling in myocardial, smooth and skeletal muscle; blood coagulation; neuronal conduction; synaptic transmission; hormone secretion and mitotic division. Calcium is also a major intracellular messenger needed for normal cellular function and is required by many enzymes for full activity. During anaesthesia, several factors may alter the serum ionised calcium level, thus potentiating the adverse effects of hypo- and hypercalcaemia in susceptible patients. These factors are: the presence of malnutrition and low albumin; abnormal acid-base status and electrolytes; the drugs used during the peri-operative period; transfusion of large volumes of citrated blood; and the use of cardiopulmonary bypass. Benzodiazepines, inhalational and intravenous anaesthetic agents, opioids, local anaesthetics, neuromuscular blocking drugs etc. decreases intracellular calcium concentration. Acidosis decreases calcium binding to albumin thus increasing ionised calcium, while alkalosis increases binding, producing a subsequent reduction in the ionised calcium. Massive blood transfusions and cardiopulmonary bypass also decreases Ca^{2+} concentration.[8] Anaesthetist should aim to prevent further changes in the plasma calcium concentration and to recognise and treat adverse effects of hypo and hypercalcaemia, particularly those on the heart.

The main goal of neuromuscular blockade during induction of anaesthesia includes paralysis of the vocal cords and muscles of the jaw to facilitate endotracheal intubation. During recovery from neuromuscular block, restoration of complete neuromuscular strength is essential to ensure adequate spontaneous ventilation with normal regulation of breathing during hypoxia and the patency of the musculature of the upper airway with maintained airway protection.

Residual postoperative neuromuscular block causes decreased chemoreceptor sensitivity to hypoxia, functional impairment of the pharyngeal and upper esophageal muscles, impaired ability to maintain an open upper airway, and an increased risk of hypoxemic events, as well as the development of postoperative pulmonary complications.[9] Clinically significant residual neuromuscular block cannot be excluded using clinical criteria only and can persist postoperatively. Objective monitoring of the degree of neuromuscular block during and after anesthesia reduces the incidence of residual neuromuscular block.[10]

Three methods are commonly used in the operating room to evaluate residual neuromuscular blockade: clinical evaluations for signs of muscle weakness, qualitative neuromuscular monitors, and quantitative neuromuscular monitors.

Clinical evaluation of signs of residual muscle weakness

Unreliable

- Sustained eye opening.
- Protrusion of the tongue.
- Arm lift to the opposite shoulder.
- Normal tidal volume.
- Normal or nearly normal vital capacity.
- Maximum inspiratory pressure less than 40 to 50 cm H2O.

More reliable, but still not excluding residual neuromuscular block

- Sustained head lift for 5 seconds.
- Sustained leg lift for 5 seconds.
- Sustained handgrip for 5 seconds.
- Sustained "tongue depressor test" [11]
- Maximum inspiratory pressure 40 to 50 cm H2O or greater.

Qualitative Neuromuscular Monitoring

Peripheral nerve stimulators deliver an electrical stimulus to a peripheral nerve, and the response is subjectively assessed by clinicians either visually or tactility (i.e., placing a hand on the thumb to detect the muscle contraction after ulnar nerve stimulation).[12] Neuromuscular function is monitored by evaluating the muscular response to supramaximal stimulation of a peripheral motor nerve.[11] Two types of stimulation can be used: electrical and magnetic. Electrical nerve stimulation is the most commonly used method. Commonly used patterns of electrical nerve stimulation are single-twitch, Train of Four (TOF), tetanic stimulation, post tetanic count (PTC) and double-burst stimulation (DBS). TOF is the most commonly used method. Return of the fourth response in the TOF heralds the recovery phase.

Quantitative Neuromuscular Monitoring

Quantitative neuromuscular monitors are instruments that permit both stimulation of a peripheral nerve and the quantification and recording of the evoked response to nerve stimulation. They allow an accurate assessment of the degree of muscle weakness using either TOF stimulation (TOF ratio displayed) or single-twitch stimulation (response

compared with control "twitch" as a percentage). Although five different methods of quantifying neuromuscular function in the operating room have been developed, acceleromyography is the only technology that is commercially produced as a stand-alone monitor.[13]

During neuromuscular recovery, a reasonably good correlation exists between the actual TOF ratio and clinical observation, but the relationship between the TOF ratio and signs and symptoms of residual block varies greatly among patients. When the TOF ratio is 0.4 or less, the patient is generally unable to lift the head or arm. Tidal volume may be normal, but vital capacity and inspiratory force is reduced. When the ratio is 0.6, most patients are able to lift their head for 3 seconds, open their eyes widely, and stick out their tongue, but vital capacity and inspiratory force are often still reduced. At a TOF ratio of 0.7 to 0.75, the patient can normally cough sufficiently and lift the head for at least 5 seconds, but grip strength may still be as low as about 60% of control. Other features are diplopia and visual disturbances, inability to maintain apposition of the incisor teeth "Tongue depressor test" negative, facial weakness, speaking difficulty, overall weakness and tiredness. When the ratio is 0.8 and higher, vital capacity and inspiratory force are normal. The patient may, however, still have diplopia and blurred vision.[12]

Patients with TOF ratio less than 0.90 are at increased risk for hypoxemic events, impaired control of breathing during hypoxia, airway obstruction, aspiration, postoperative pulmonary complications and symptoms of muscle weakness. Appropriate management of neuromuscular blockade can decrease the incidence of, or eliminate, residual blockade, which will reduce the risks of these adverse postoperative events. To exclude clinically significant residual neuromuscular block, the TOF ratio must exceed 0.9 when measured mechanically or electromyographically and 1.0 when measured acceleromyographically.[13]

Residual neuromuscular blockade depends on various factors. They include TOF ratio; patient factors like age, gender, preexisting medical conditions, medications interacting with neuromuscular transmission; type and dose of NDMR used; type and dose of reversal agents; method of measurement of residual blockade; postoperative conditions like acid base defects, hypothermia etc.

Anticholinesterases increase the concentration of ACh at NMJ. Acetylcholinesterase is the enzyme responsible for the control of neurotransmission at the neuromuscular junction by hydrolysing acetylcholine.[14] Rapid hydrolysis of acetylcholine removes excess neurotransmitter from the synapse, preventing overstimulation and tetanic excitation of the postsynaptic muscle. Anticholinesterase drugs interact with the anionic and esteratic sites of acetylcholinesterase. Although they inhibit the breakdown of acetylcholine, resulting in an increase in acetylcholine in the neuromuscular junction, there is a clinically relevant ceiling effect to the maximal concentration of acetylcholine.[14] As concentrations of acetylcholine increase, some of the neurotransmitter diffuses away from the neuromuscular junction, while additional acetylcholine undergoes reuptake into motor nerve terminals. As the processes of diffusion and reuptake reach equilibrium with augmented release by enzyme inhibition, a peak level at the neuromuscular junction is reached. Once the acetylcholinesterase enzyme is maximally inhibited by an anticholinesterase agent and peak concentrations of acetylcholine are present, the administration of additional drug will not further increase acetylcholine levels or enhance recovery of neuromuscular blockade. This ceiling effect of anticholinesterases is an important limitation of all clinically used agents; neuromuscular blockade cannot be adequately reversed if high concentrations of NMBDs are present at the neuromuscular junction.[15]

Complications of anticholinesterase include nausea, vomiting, paradoxical muscle weakness, bradyarrhythmias and bronchospasm.

CONCLUSION

The group which received Calcium Gluconate during reversal with Neostigmine attained early recovery from neuromuscular blockade compared to the group which received Normal Saline along with Neostigmine. So calcium can enhance recovery from neuromuscular blockade.

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