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Original Research Article

Utilizing calcium gluconate with low dose neostigmine to enhance neuromuscular recovery from non-depolarizing blockade: A prospective randomized control study

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ABSTRACT

Background: Ionized calcium has a pivotal role to play in neuromuscular transmission. Co-administration of calcium gluconate may allow for tapering the dose of neostigmine used for neuromuscular reversal, thus minimizing adverse effects associated with it while also reducing the chances of residual neuromuscular blockade (NMB). This study aimed to assess the effectiveness of calcium gluconate upon co-administration with neostigmine in enhancing rate of neuromuscular recovery and reducing the incidence of postoperative residual curarization.

Materials and Methods: This parallel group, double-blind randomized controlled study was conducted on 60 patients undergoing surgery at a tertiary care center. Patients in Group CN received 5 mg kg^{-1} of 10% calcium gluconate with neostigmine while Group N received 5 ml 0.9% saline with neostigmine for reversal of NMB. Time from neostigmine administration to achieving a TOF ratio of ≥0.9 was taken as the primary outcome. Additional neostigmine requirement and symptoms of residual neuromuscular blockade (RNMB) in the post-anesthesia care unit (PACU) were considered as secondary outcomes.

Results: A significant difference was found in the meantime taken to achieve TOF ratio ≥0.9 after giving reversal, taking 5.43 ±2.12 mins in Group CN and 8.49 ±4.72 mins in Group N (p = 0.001). Although in Group N, 13.33% patients showed signs of RNMB in PACU versus 3.33% patients in Group CN. This difference was not found to be clinically significant (p=0.081).

Conclusions: The findings of our study suggest that the administration of exogenous calcium may improve neuromuscular transmission even in normocalcemic patients. In conclusion, co-administration of calcium gluconate with low dose neostigmine helps in reducing neuromuscular recovery time in the early period of NMB reversal without incurring any significant disadvantages of administering higher doses of neostigmine.

1. Introduction

Non depolarizing muscle relaxants (NDMRs) are used to temporarily paralyze patients to facilitate endotracheal intubation and provide adequate surgical exposure during general anesthesia. They compete with the acetylecholine (Ach) molecule for postsynaptic nicotinic Ach receptors, thus blocking the neuromuscular transmission at neuromuscular junction (NMJ). However, residual effects of NDMRs in the postoperative period, known as postoperative residual curarization (PORC), may cause life threatening respiratory complications in the first few hours after surgery.[1–4]

Acetyl cholinesterase inhibitors (AChIs) are capable of reversing neuromuscular blockade (NMB) by increasing the quantity of Ach at the NMJ, to a level that pharmacologically antagonizes the competitive

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block caused by any NDMR. These agents increase the lifespan of Ach as well as its concentration at the NMJ. The resulting systemic increase in Ach concentration may lead to unwanted cholinergic side effects such as bradycardia, arrhythmias, hypotension, bronchoconstriction, hypersalivation, diarrhoea, and increased gastric secretions. In fact, it has been shown in various studies that higher doses of AChIs do not improve neuromuscular recovery rather cause paradoxical muscle weakness.[5,6]

Although, ionized calcium has an important role to play in NM transmission, its blanket effects on NMB are unpredictable. While calcium triggers release of ACh from the motor nerve terminal,[7,8] it may also decrease the degree of Ach-induced depolarization at the motor end plates.[9] Few previous reports have suggested that increased ionized calcium concentrations might reduce sensitivity to NDMRs.[10–12]

In patients with residual NMB, administration of calcium may improve NM recovery.[1] Consequently, giving adjuvants such as calcium gluconate pre-emptively may help reduce the risk of residual NMB and also allow administration of a lower dose of AChIs. We postulated that co-administration of calcium gluconate with an AChI could enhance early NM recovery and reduce the incidence of PORC after surgery.

2. Materials and Methods

Ethical approval was provided by the hospital ethical committee. This randomized comparative study was conducted at a tertiary care centre on 60 adult patients of either sex, aged 18-65 years, ASA physical status I-III, admitted for elective surgery under general anaesthesia. Patients with neuromuscular disease, hepatic or renal dysfunction, h/o malignant hyperthermia, allergy to study medication, obese patients and pregnant patients or postpartum patients during lactating period were excluded from the study. Patients taking medications that might influence the effect of NM blocking agents like beta blockers, magnesium sulphate, aminoglycosides and calcium channel blockers, patients with documented hypercalcemia or hypocalcemia and patients planned for elective ventilation in the post-operative period were also excluded.

The primary outcome was the neuromuscular recovery time defined as the time from neostigmine administration to recovery of TOF ratio to ≥0.9. Secondary outcomes were symptoms of PORC in the PACU like general weakness, visual symptoms, difficulty in swallowing and inability to cough effectively and the requirement of additional doses of neostigmine. A previous study[1] compared NM recovery time in patients treated with neostigmine with and without calcium chloride. The NM recovery time to a TOF ratio of 0.9 was 5±2.97min in the calcium group as against 7.85±3.19 min in the control group. Assuming these as reference values, the minimum required sample size at 5% level of significance and 95% power was obtained as 30 patients in each group.

Written informed consent was obtained from all patients. A detailed pre-anesthetic check-up was done. On the morning of surgery, patients were randomly allocated to one of two study groups by computer generated number tables. The group of each patient was decided by opening sequential sealed opaque envelopes. The attending anesthesiologists were blinded to the study medications that were prepared by another anesthesiologist who was not involved in the subsequent anesthetic management. Preoperative fasting guidelines were followed by the patients as per ASA recommendations. All patients were premedicated with tablet alprazolam on the night before and 2 hours before surgery. In the operating room, intravenous access was obtained once ASA standard monitors were attached. All patients received 1 mg midazolam followed by fentanyl 2 mcg kg^{-1} intravenously. Anesthesia was induced with titrated doses of intravenous propofol, thereafter a propofol infusion was commenced @ 100–200 mcg $kg^{-1}min^{-1}$ titrated to achieve a bispectral index of 40 to 60 for the maintenance of anesthesia. Upon achieving loss of consciousness, the patient's lungs were ventilated by bag and mask and NM monitoring was initiated after calibration. For a continuous NM monitoring, we used acceleromyography (TOF-Watch) at the adductor pollicis muscle on the opposite side to the blood pressure cuff and intravenous line. TOF was initially recorded every 20 seconds during induction until intubation, and was set for recording every 5 minutes from intubation till the end of procedure. All patients received 0.6 mg kg^{-1}rocuronium and once a TOF count of 0 was achieved, a definitive airway (endotracheal tube or supraglottic airway) was inserted. Mechanical ventilation was commenced thereafter to maintain an end-tidal carbon dioxide concentration between 35 to 40 mmHg. Additional 0.15 mcg kg^{-1}rocuronium was administered when the TOF count returned to ≥ 2. Core temperature of all the patients was maintained more than 35 degrees C at all times using a heating blanket. At the end of surgery, once a TOF count of 4 was achieved, all patients received 25 mcg kg^{-1} neostigmine and glycopyrrolate 10 mcg kg^{-1}intravenously for reversal of NMB. In addition, patients in Group CN received intravenous 10% calcium gluconate 5mg kg^{-1} in 5 ml and patients in Group N received 5 ml 0.9% saline. The patients' trachea was extubated once a TOF ratio (TOFr) of ≥0.9 was achieved. For both the groups, the NM recovery time was recorded as the time from neostigmine administration to recovery of TOFr to ≥0.9. Once shifted to the PACU, the patients were assessed for presence of any symptoms indicating residual NMB. This task was assigned to A PACU nurse blinded to the study. She was asked to provide details about

residual NMB i.e. general weakness, visual symptoms, difficulty in swallowing and inability to cough effectively. Any requirement for additional neostigmine was also noted. The data was collected and analysed. The quantitative variables (neuromuscular recovery time) in both groups were denoted as mean±SD. The comparison between both variables was done using unpaired t-test/Mann-Whitney test. On the other hand, the qualitative variables (symptoms of PORC, requirement of additional doses of neostigmine) were expressed as frequencies/percentages and compared using Chi-square test/Fischer exact test. A p-value < 0.05 was considered statistically significant. The data was expressed in tabular form in MS Excel and analysed using IBM Statistical Package for Social sciences (SPSS) version 20.0 software.

3. Results

This study had a total of 60 patients as participants with no dropouts. Patient characteristics were similar in both the groups (Table 1). Also, there was no significant difference in the mean total dose of rocuronium used and mean number of top-ups administered in the two groups (Table 2). Neuromuscular recovery time was significantly faster in Group CN (p=0.001) (Table 2). In Group CN, 27 patients achieved a TOFr≥0.9 within 10 mins. The remaining three patients attained a TOFr≥0.9 at 10.45 mins, 10.45 mins and 10.5 mins respectively. In Group N, 24 patients achieved a TOFr≥0.9 within 10 mins and the remaining 6 patients attained a TOFr≥0.9 at 10.04, 10.11, 11.3, 13.04, 16.44 and 22.32 mins respectively. No additional neostigmine was given to any of these patients. Even though, there was no apparent difference in the incidence of PORC in the PACU between the two groups, only one patient in Group CN complained of generalized weakness while 4 patients in Group N complained of generalized weakness despite reaching a TOFr≥0.9 (Table 2).

4. Discussion

This trial was conducted in order to study the effects of co-administration of calcium gluconate with low dose neostigmine (i.e. 25 mcg kg^{-1}) on reversal from nondepolarizing NMB induced by rocuronium. In the calcium group, the NM recovery time was significantly faster than in the group that did not receive calcium (p=0.001). Patients in both groups were comparable with respect to age, weight, gender and ASA physical status as well as the total duration of anaesthesia and surgery. Also, there was no significant difference in the mean total dose of rocuronium used in the two groups.

It is a well-known fact that using neostigmine at higher doses for neuromuscular reversal is associated with certain disadvantages. Being an AChI it leads to an increase in the concentration of Ach at the neuromuscular junction. Aside from its effects on nicotinic ACh receptors on skeletal muscles, ACh can stimulate muscarinic ACh receptors in the heart, lungs, and gastrointestinal tract resulting in systemic adverse effects such as bradycardia, arrhythmias, hypotension, bronchoconstriction, hypersalivation, diarrhea, and increased gastric secretions.[13] Furthermore, at maximal inhibition, when 100% of acetylcholinesterase has been inhibited, there is a clinical ceiling effect of AChIs after which additional doses will not improve recovery and may lead to a paradoxical muscle weakness due to desensitization of ACh receptors leading to transmission failure, a depolarization block or open channel block.[7] This effect can be seen at doses of neostigmine of 0.04 to 0.07 mg/kg which are routinely being used in clinical practice.[14] The use of high-dose neostigmine, above 0.06 mg/kg, has been associated with a threefold increase in the risk of postoperative atelectasis, longer time to PACU discharge readiness, and longer postoperative hospital stay.[15] Thus, higher and additional doses of neostigmine should be administered with due caution.

Although calcium undoubtedly plays an important role in neuromuscular transmission, there is paucity of studies investigating the effects of administration of ionized calcium during reversal from nondepolarizing NMB. Hence, our study was aimed at studying the effects of ionized calcium on neuromuscular recovery with an aim to minimize the dose of neostigmine being routinely administered during neuromuscular reversal.

During a nerve action potential, depolarization opens calcium channels allowing entry of calcium ions into the nerve and this causes Ach to be released. The number of quanta of Ach released by a stimulated nerve is influenced by the concentration of ionized calcium in the extracellular fluid. If calcium is not present, then depolarization of the nerve, even by electrical stimulation, will not produce transmitter release.[16]

The effects of increasing calcium concentration in the nerve ending can be understood by the phenomenon called as post-tetanic potentiation, when the nerve of a patient paralyzed with a NDMR is stimulated at high, tetanic frequencies. Due to the incremental increase in concentration of calcium at the nerve terminal with every stimulus during tetanic period, a stimulus applied to the nerve sometime after this period causes the release of more than the normal amount of Ach. The abnormally large amount of Ach antagonizes the relaxant and causes the characteristic increase in the size of the twitch.[16]

Several studies suggest that increases in serum calcium concentration may cause some degree of resistance to NMB.[11] Al-Mohaya et al. found that in patients of hyperthyroidism, the duration of action of atracurium has been found to be reduced due to increased serum calcium levels.[12]

Table 1: Demographic and patient data

	Group CN	Group N	p-value
Age (years) Mean±SD	40.33 ±10.98	37.23±10.79	0.137
Body Weight (kg) Mean±SD	63.33±8.27	60.8±8.13	0.118
Height (m) Mean±SD	1.7±0.11	1.68±0.1	0.211
BMI (kg/m^2) Mean±SD	21.84±1.51	21.51±1.7	0.215
Sex (M/F)	15/15	14/16	0.398
Duration of anaesthesia (mins) Mean±SD	93.67±19.38	97.33±19.77	0.236
Duration of surgery (mins) Mean±SD	75.57±19.13	79.47±17.59	0.207

*SD – Standard Deviation

Table 2: Table comparing the primary and secondary outcomes in the two groups

	Group CN	Group N	P value
Total dose of Rocuronium (mg)Mean±SD	58.67±10.53	58.45±12.96	0.471
Number of top-ups Mean±SD	2.17±0.7	2.40±1.04	0.156
Neuromuscular recovery time (mins) Mean±SD	5.43±2.12	8.49±4.72	0.001
Residual NMB in PACU Yes/No	1/29	4/26	0.081
Additional neostigmine Yes/No	0/30	0/30	-

*NMB – Neuromuscular blockade, PACU – Post-anaesthesia care unit

Kim and colleagues reported that volatile anesthetics can alter the effective onset time of AChIs.[6] We used total intravenous anaesthesia rather than a balanced anaesthesia technique as use of inhalation agents may have served as a confounding factor when studying recovery from NMB.

In our study, the NM recovery time, as signified by achievement of TOF ratio ≥ 0.9, was significantly faster in the calcium group compared to the patients who did not receive calcium suggesting its beneficial effect on NM recovery in the early period of NMB reversal. The mean time to achieve TOF ratio ≥0.9 was 5.43 ±2.12 mins in Group CN and 8.49 ±4.72 mins in Group N. This quicker neuromuscular recovery time can be attributed to the anti-neuromuscular blockade effect of calcium. Signs of residual NMB in the PACU were seen in 1 patient in Group CN and in 4 patients in Group N. However, this difference was found to be statistically insignificant. A study undertaken by Jae-Woo Ju et al. collaborates our results demonstrating the beneficial effects of calcium on neuromuscular recovery.[1]

In their study 5mg/kg of 3% calcium chloride was co-administered with neostigmine as it has been suggested that this dose can be safely used even in normocalcemic patients and higher doses may paradoxically be associated with muscle weakness.[17] Both 3% calcium chloride and 10% calcium gluconate contain similar amounts of elemental calcium (0.41 vs 0.45 mEq/ml respectively) so in our study we used 5mg/kg of 10% calcium gluconate as it is the formulation available to us.[1]

There were some limitations in our study. Firstly, as calcium was administered at a TOF count of 4 in our study, the effectiveness of calcium on NM recovery has been assessed only for a shallow NMB and hence additional studies may help in assessing the efficacy of calcium on recovery from a moderate or dense block. Secondly, in our study serum magnesium levels were not assessed to begin with, which could be of probable significance since magnesium is a physiological antagonist of calcium at the NMJ. Lastly, we only assessed the effect of one fixed dose of calcium and neostigmine and in our view further assessment of their dose-response relationship is required.

5. Conclusion

The findings of our study suggest that the administration of exogenous calcium may improve neuromuscular transmission even in normocalcemic patients. In conclusion, co-administration of calcium gluconate with low dose neostigmine helps in reducing neuromuscular recovery time in the early period of NMB reversal without incurring any significant disadvantages of administering higher doses of neostigmine.

6. Sources of Funding

None.

7. Conflict of Interest

None.

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