Original Article

Neuromuscular blockade characteristics of cisatracurium in patients receiving chemotherapy: A preliminary study in breast cancer patients

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Abstract

Background and Aims: Cancer chemotherapeutic agents cause alteration in the response to neuromuscular blocking drugs, which can have serious perioperative implications. Magnesium, commonly found to be deficient in these patients, plays an indispensable role in neuromuscular transmission. This study aimed to understand the effect of neoadjuvant chemotherapy on the neuromuscular blocking properties of cisatracurium.

Material and Methods: One hundred female patients scheduled for breast cancer surgery were divided into two groups (n = 50 each). Group B received neoadjuvant chemotherapy with taxane, adriamycin, and cyclophosphamide, and Group A did not receive neoadjuvant chemotherapy. Neuromuscular block following cisatracurium 0.15 mg/kg was measured using peripheral nerve stimulator at the ulnar nerve. Onset time, duration of intense block, clinical duration of action, time to TOF4 after the last dose of cisatracurium, along with preoperative serum magnesium concentration were measured. Correlation and multiple regression were run to analyze the relationship between history of neoadjuvant chemotherapy, preoperative magnesium, and the abovementioned time points. Mediation analysis was done to ascertain if magnesium was mediating the observed effects.

Results: Onset time was prolonged by nearly 18% in Group B compared to Group A (P = 0.001). The duration of intense block was 35.27 ± 8.9 min in Group B and 42.07 ± 10.99 min in Group A (P < 0.001). The clinical duration of action of cisatracurium was significantly shorter in Group B (46.06 ± 8.68 min) compared to Group A (55.87 ± 11.04 min, P < 0.001). The time to TOF4 was 32.86 ± 5.66 min in Group B and 36.57 ± 8.49 min in Group A (P < 0.05). Preoperative serum magnesium levels were significantly lower in Group B (P < 0.001).

Conclusion: Patients who had received neoadjuvant chemotherapy had a delayed onset, shorter duration of action, and faster recovery for cisatracurium. Although preoperative magnesium levels were lower in Group B, it was found to be an independent predictor rather than a mediator of these effects.

Keywords: Cisatracurium, neoadjuvant therapy, neuromuscular blockade

Introduction

Breast cancer is the most frequent and the second leading cause of cancer-related deaths globally among females. Expeditious advancements in diagnostics and screening leading to early detection and subsequent treatment with new-age chemotherapeutic agents have improved survival rates. The toxicity of chemotherapy drugs and their relevance to perioperative anesthesia management relates to the specific agents used, cumulative dosage, and drug toxicity.[1,2] It has

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been proposed that patients who are treated with neoadjuvant chemotherapy (NACT) show resistance to the effect of neuromuscular blocking agents (NMBAs).[3] Although the exact underlying mechanism is still poorly understood, hypomagnesemia has been postulated to be one of the causative factors and is also a side effect of many cancer chemotherapeutic agents such as platins and PEGylated liposomal doxorubicin.[4] A low intracellular magnesium (Mg) leads to increased muscle contractility and delayed relaxation for a given stimulus.[5] Limited knowledge of the mechanism of neurotoxic effects of chemotherapeutic agents and inadequate evidence regarding the variation in response to NMBAs among patients exposed to different chemotherapeutic agents warrant further research. Our study aims to shed light on the alteration in response to NMBAs in such patients and also attempts to study its correlation with preoperative serum magnesium levels, if any.

We hypothesize that administration of NACT delays the onset and duration of action, as well as recovery from neuromuscular block following cisatracurium, a relatively new intermediate-acting NMBA in India. Primary outcome variables were onset time (disappearance of single twitch or ST0), duration of intense block (time to post-tetanic count [PTC] 1), clinical duration of action (time to train of four [TOF] 1), and time to TOF4. Secondarily, we compared the preoperative serum Mg levels between the two groups and analyzed if it had a significant role to play in this altered response to cisatracurium, either as a mediator or as an independent predictor.

Material and Methods

This prospective, observational study was conducted at a tertiary cancer care center over a period of 6 months (from January 2019 to June 2019) after obtaining due clearance from the hospital ethics committee. The trial was registered prior to patient enrollment with Clinical Trials Registry- India (No. CTRI/2019/01/017027).

After taking written informed consent, 100 female patients, ASA grade I and II, between 18 and 70 years of age scheduled for either modified radical mastectomy or breast conservative surgery with or without reconstruction with a duration <4 h were included in the study and divided into two groups based on whether or not they received NACT within 30 days prior to surgery.

- **Group A (n = 50)**: Patients who did not receive any chemotherapy
- **Group B (n = 50)**: Patients who received NACT with taxanes, adriamycin, and cyclophosphamide

Patients with neuromuscular diseases, those taking aminoglycosides, tetracycline, or other drugs interfering with neuromuscular conduction, those in whom difficult intubation was anticipated, and those requiring rapid sequence induction were excluded from the study.

A detailed history, complete physical examination, and routine preanesthetic investigations were done along with serum electrolytes (Na, K, Ca, and Mg). None of the patients had evidence of peripheral neuropathy on clinical history and examination.

After taking the patient to the operating room and recording the baseline vitals, electrodes for neuromuscular monitoring were placed over the ulnar nerve at the flexor wrist crease. A standardized anesthesia regimen was used for providing general anesthesia in both the groups consisting of premedication with midazolam 1 mg intravenous (IV) and fentanyl 2 μg/kg IV and induction with propofol 40 mg boluses IV every 10 s till there was loss of response to verbal commands.[6] Muscle relaxation was achieved with cisatracurium 0.15 mg/kg IV (3 × ED95).[7] Qualitative neuromuscular monitoring was carried out using the NS 100™ (Inmed, Vadodara, India) nerve stimulator with a current strength of 40 mA. Tactile assessment of the response to stimulus was done at the adductor pollicis muscle. Bag mask ventilation was performed until adequate muscle relaxation was achieved, that is, disappearance of single twitch (ST0). Upon achieving ST0, an experienced anesthesiologist performed direct laryngoscopy and intubation with an appropriate size cuffed endotracheal tube without external laryngeal manipulation. Intubating conditions were graded excellent when the vocal cords were relaxed, abducted, and there was no coughing or bucking, while they were graded good when the vocal cords were relaxed and abducted with slight bucking or nasal flaring.

Lungs were ventilated with 50:50 oxygen: N_2O and sevoflurane to achieve minimum alveolar concentration of 1 and to maintain normocapnia. Maintenance dose of cisatracurium (0.03 mg/kg) was given at TOF score 1. Normothermia was maintained with the use of forced air warming blanket and warmed intravenous fluids.

The onset time was determined as the time interval from the end of muscle relaxant injection until disappearance of single twitch (ST0). Time for the reappearance of first post-tetanic count (PTC1) and first train of four response (TOF1) indicated duration of intense block and clinical duration of action, respectively. Duration from the last dose of NMBA to achieve all four twitches without detectable fade on TOF stimulation (TOF4) was recorded as time to TOF4. TOF was monitored every 30 s by using the repeat demand

mode. Patients were monitored for any signs of histamine release by observing for skin changes (flush lasting >120 s, erythema, or wheals), presence of any hemodynamic changes, or bronchospasm.

At the end of surgery, reversal of neuromuscular blockade was achieved by administration of neostigmine 0.05 mg/kg and glycopyrrolate 7 mcg/kg through slow IV injection, after the appearance all four TOF without detectable fade. The trachea was extubated when clinical signs of adequate neuromuscular recovery were also present.[8]

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 16.0 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± standard deviation and analyzed using unpaired *t*-test. Qualitative variables were expressed as frequency/percentage. Pearson's correlation coefficient was used to measure the correlation between a pair of quantitative variables. Multiple linear regression and mediation analysis were used to test the association of NACT and serum Mg with ST0, PTC1, TOF1, and TOF4. Significance of indirect effect was tested using bootstrapping to 1000, and 95% confidence intervals were computed. A $p < 0.05$ was considered statistically significant.

Sample size was calculated using G Power statistical software (3.0.10) and was based on a previous study taking the time to PTC1 as the reference value (31.59 ± 7.13 vs. 45.17 ± 11.74).[3] In the current study, power analysis on the assumption of a type I error of 0.05 and power of study as 0.90 revealed a sample size of 10 for each group. The sample size, however, was taken to be 50 for each group to avoid misrepresentation due to outliers and to increase the validity of our results.

Results

All the patients enrolled in the study were females. The demographic data were comparable between the two groups [Table 1]. The mean duration of surgery was 1.9 ± 1.03 h.

Table 1: Demographic data

	Mean±SD		*P*
	Group A	Group B	
Age (years)	52.5±11.31	49.02±12.02	0.07
Weight (kg)	68.05±12.23	66.71±9.18	0.268
Height (cm)	157.26±6.77	155.96±7.5	0.183
BMI (kg/m^2)	27.41±3.87	27.53±3.16	0.438
Duration of surgery (h)	1.64±0.62	1.40±0.41	0.014

The onset time (ST0) was prolonged by nearly 18% in Group B compared to Group A (5.2 ± 1.45 vs. 4.43 ± 0.97 min, $P = 0.001$). The duration of intense block (time to PTC1) was 35.27 ± 8.9 min in Group B and 42.07 ± 10.99 min in Group A ($P < 0.001$) and was shorter by 16% in Group B. Similarly, the clinical duration of action of cisatracurium (time to TOF1) was shorter by 17% in the study group (46.06 ± 8.68 min in Group B vs. 55.87 ± 11.04 min in Group A, $P < 0.001$). Many of our patients did not receive any repeat dose after the intubating dose, and thus, 11 patients in Group A and 15 patients in Group B were not included in the analysis of time to TOF4 after the last dose of cisatracurium. Time to TOF4 was 32.86 ± 5.66 min in Group B and was 10% shorter compared to Group A (36.57 ± 8.49 min, $P = 0.016$) [Figure 1].

Cisatracurium requirement was 23% higher in Group B patients compared to Group A patients (0.16 ± 0.02 mg/kg/h in Group B vs. 0.13 ± 0.04 mg/kg/h in Group A, $P < 0.001$); also, they showed a more frequent dosing requirement. It was observed that patients in Group A required an average of 1.92 top up of cisatracurium for an average duration of surgery of 1.64 ± 0.62 h, whereas 2.48 top ups were required for an average duration of surgery of 1.40 ± 0.41 h in Group B ($P = 0.014$). Using 3xED95 as the intubating dose, all patients had excellent intubating conditions except two in Group B, who had good intubating conditions.

There was no difference in the preoperative sodium, potassium, and calcium values between the two groups. However, there was a significant difference in the preoperative serum Mg concentration: 1.93 ± 0.31 mg/dl in Group A

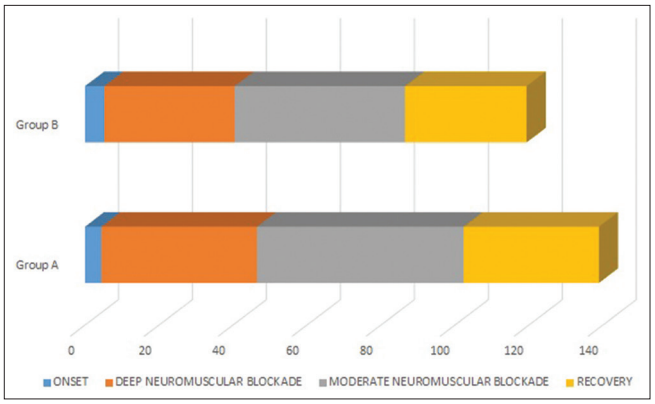

Figure 1: Clinical profile of cisatracurium. Blue indicates the onset time (in minutes), orange indicates time to reappearance of PTC (in minutes) after the initial bolus of cisatracurium, gray indicates time to return of TOF1 (in minutes) after the initial bolus of cisatracurium, and yellow indicates recovery from the effect of cisatracurium, that is, appearance of TOF4 after the last top up dose of cisatracurium. As is evident from the graph, patients who received NACT had a delayed onset, shorter duration of action, and a faster recovery. NACT = neoadjuvant chemotherapy, PTC = post-tetanic count, TOF = train of four

and 1.68 ± 0.38 mg/dl in Group B ($P < 0.001$). Reference range was taken as 1.8–2.2 mg/dl. Eleven patients in the control group had serum Mg values less than 1.8 mg/dl, compared to 37 in the study group. Out of these 37, six had extremely low serum Mg (<1.3 mg/dl), with the lowest value being 1.2 mg/dl. Analysis of the outlier values did not reveal a corresponding change in onset or duration of action. There was a significant overall correlation between serum Mg and onset time ($r = -0.22, P < 0.05$) and duration of action ($r = 0.32, P = 0.001$). However, similar intergroup correlation was not discernible [Table 2, Figure 2].

A regression analysis was used to predict the effect of NACT and serum Mg on onset, duration of action, and time to TOF4. NACT was a significant predictor for onset time, duration of action, and time to TOF4. Serum Mg was a significant predictor for duration of action, but not for onset time and time to TOF4. The overall model fit explained by combination of NACT and serum Mg was small but significant for the onset time and duration of action [Table 3].

Mediation analysis[9] was also carried out to establish if Mg was a mediator of the effects of NACT on neuromuscular blocking properties of cisatracurium. The standardized regression coefficient for the direct and total effect of NACT on onset time, duration of action, and time to TOF4 was significant. We tested the significance of the indirect effect by bootstrapping to 1000 and it was statistically insignificant [Table 4].

Discussion

This study demonstrates that patients who received NACT exhibited resistance to the action of intermediate-acting NMBA, cisatracurium. The onset time for cisatracurium was significantly delayed in Group B, implying that these patients are ready for intubation after a longer time, for the same intubating dose of cisatracurium. In the absence of neuromuscular monitoring, it may lead to failed attempt at laryngoscopy and intubation due to suboptimal intubating conditions. The duration of intense neuromuscular block and the overall clinical duration were also shortened, and thus, these patients required more frequent top ups, leading to a significantly higher drug requirement. In many developing countries, quantitative neuromuscular monitoring is rarely available and most anesthetists rely on clinical signs and capnography to monitor the depth of block. Awareness of the effect of NACT on the neuromuscular action of cisatracurium can alert them about the abovementioned effects and help avoid unwanted complications related to inadequate neuromuscular blockade. Although the literature on the topic is scarce, indirect evidence does exist on chemotherapy-induced neuromuscular dysfunction.[10-12] A previous study demonstrated that patients treated with cyclophosphamide–adriamycin–5-FU–based chemotherapy were ready to be intubated after a longer lag time and needed repeat doses of cisatracurium at shorter intervals to maintain the desired level of blockade.[3]

We also found that the incidence of hypomagnesemia (serum Mg <1.8 mg/dl) was higher in Group B, as was the number of patients having extremely low serum Mg concentrations (<1.3 mg/dl). It was associated with a prolonged onset time and decreased clinical duration of action. Cancer-associated poor oral intake, chemotherapy-induced diarrhea, intestinal malabsorption, and increased renal losses may account for low serum Mg seen in such patients.[4,13] Among other effects, this leads to neuronal membrane hyperpolarization, causing resistance to NMBAs.[5,14,15]

Onset time demonstrated a negative correlation with serum Mg, indicating a slower onset in patients with hypomagnesemia. Our results also established a weak, but significant positive correlation between serum Mg and duration of action. Multiple regression analysis revealed NACT and hypomagnesemia independently shortened the duration of action of cisatracurium and accounted for 23% of the variation in the model. The above findings imply that Mg is an independent predictor for onset time, duration of action, and time to TOF4. This is further supported by the fact that

Table 2: Correlation between magnesium and onset time, duration of action, and time to TOF4

Mg versus time	Group A		Group B		Overall	
	R*	P	R	P	R	P
ST0	−0.02	0.879	−0.197	0.170	−0.224	0.025
PTC1	−0.008	0.956	0.17	0.238	0.181	0.072
TOF1	0.238	0.111	0.182	0.206	0.320	0.001
TOF4	−0.083	0.567	0.155	0.282	0.082	0.379

*PTC=post-tetanic count, ST=single twitch, TOF=train of four. *R represents the Pearson's correlational coefficient*

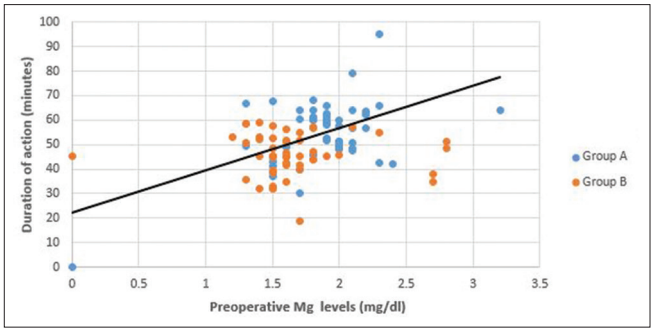

Figure 2: Correlation between clinical duration of action and magnesium levels. The figure shows the correlation between the clinical duration of action, neoadjuvant chemotherapy, and serum magnesium levels. Patients who had received neoadjuvant chemotherapy showed consistently lower levels of serum magnesium as well as a shorter duration of action compared to the control group

Table 3: Regression analysis to establish the combined effect of NACT and hypomagnesemia at the four time points

Dependent variable	Independent variable	B	SE (β)	*P*	R^2	*P*
Onset (ST0)	Constant	5.358	0.714	<0.001	0.108	0.004
	Chemotherapy	0.654	0.262	0.014		
	Mg	−0.482	0.359	0.182		
Duration of intense block (PTC1)	Constant	37.64	5.808	<0.001	0.111	0.003
	Chemotherapy	−6.255	2.13	0.004		
	Mg	2.293	2.919	0.434		
Clinical duration of action (TOF1)	Constant	44.806	5.67	<0.001	0.231	<0.001
	Chemotherapy	−8.387	2.709	<0.001		
	Mg	5.732	2.849	0.047		
Time to TOF4	Constant	35.739	4.657	<0.001	0.063	0.101
	Chemotherapy	−3.618	1.776	0.045		
	Mg	0.429	2.322	0.854		

NACT=neoadjuvant chemotherapy, PTC=post-tetanic count, SE=standard error, ST=single twitch, TOF=train of four. The regression equation used was as follows: $y = \beta_0 + \beta_1{*}x_1 + \beta_2{*}x_2$. where y=response/dependent variable β_0=constant/intercept β_1=regression coefficient for history of receiving neoadjuvant chemotherapy. β_2=regression coefficient for serum magnesium concentration. x_1=independent variable – history of neoadjuvant chemotherapy.x_2=independent variable−serum magnesium concentration. R^2 is the coefficient of determination and represents the variability in the model explained by the independent variables

Table 4: Mediation analysis

	Estimate	SE	*Z*	*P*
Direct effect NACT				
ST0	−0.507	0.20	−2.538	0.011
TOF1	0.76	0.185	4.095	<0.001
TOF4	0.484	0.233	2.079	0.038
Indirect effect NACT-Mg				
ST0	−0.093	0.073	−1.277	0.202
TOF1	0.129	0.072	1.778	0.075
TOF4	0.014	0.076	0.188	0.851
Total effect NACT				
ST0	−0.60	0.19	−3.162	0.002
TOF1	0.888	0.178	4.989	<0.001
TOF4	0.498	0.224	2.222	0.026

NACT=neoadjuvant chemotherapy, SE=standard error, ST0=onset time, TOF=train of four, TOF1=duration of action, TOF4=time to TOF4

patients with hypomagnesemia in the control group too had a slower onset and shorter duration of action.

This study has a few limitations which need to be discussed. All the patients in our study were females and received cisatracurium. Further research is needed to ascertain if the results are applicable across genders and for different NMBAs. Quantitative TOF ratio monitoring instead of qualitative would be able to provide more comprehensive data for neuromuscular monitoring. Due to disparity in the mechanism of action of chemotherapeutic drugs, patients receiving a variety of chemotherapeutic agents need to be studied to determine if similar results are obtained. Ours was not a cause-finding study; therefore, a look into the possible causes behind the effect of NACT on neuromuscular blocking properties of non-depolarizing muscle relaxants may be the future focus.

In conclusion, chemotherapy induces a state of neuromuscular hyperexcitability resulting in an increased resistance to cisatracurium. The onset is delayed, duration of action is shortened, and a higher frequency of top ups with cisatracurium is required, compared to those in patients who did not receive NACT. Hypomagnesemia was found to be an association rather than a mediator of the effects of NACT. Hypomagnesemia may, however, independently delay the onset and cause a shorter duration of action of cisatracurium. The clinical impact of these findings is that it may not be possible to maintain desired depth of neuromuscular blockade in these patients based on clinical criteria alone. Furthermore, considering the high prevalence of hypomagnesemia in patients receiving preoperative NACT, the authors advocate preoperative screening for hypomagnesemia and necessary correction.

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Conflicts of interest
There are no conflicts of interest.

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