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Prolonged Neuromuscular Block Due to Drug-Drug Interaction in a Post-Chemotherapy Patient Posted for Septoplasty: A Case Report

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Abstract--

Introduction*- It is not uncommon to encounter cancer patients who have been subjected to chemotherapy being planned for non-oncological surgery. Chemotherapeutic drugs stimulate a cascade of catastrophic events leading to apoptosis via drug-receptor interaction. We are presenting a case-report on one such side-effect missed on the pre-operative assessment that lead to prolonged recovery phase in a patient posted for septoplasty under general anaesthesia.*

Case Report*- 62 year old female planned for septoplasty had been on chemotherapeutic treatment for unilateral cancer breast stage 2. Drugs related toxicities were ruled out and general anesthesia was planned. Pre-medication in the form of injection glycopyrrolate 0.005mg/kg and fentanyl 1 microgram/kg, Induction by injection propofol (total 90mg) and succinylcholine 1.5mg/kg. After securing ETT, maintenance was achieved with isoflurane, N20:O2 (50:50) with vecuronium used as NDMR. Post cessation of surgery which lasted for 1 hour 40 minutes, inhalational gases were stopped but the patient remained deeply sedated, hypotonic despite reversal with neostigmine for 45 minutes. Thereafter, her eye opening returned but her tachypnoea persisted, so she was bridged to BiPAP mode in ICU till she regained muscle tone and distress subsided which took around 2 hours. This delayed muscular recovery was thought to be due to cyclophosphamide induced pseudocholinesterase inhibition which caused the action of succinylcholine to be prolonged.*

Conclusion*- Chemotherapeutic agents and their drug-drug interactions must be kept in mind while formulating plan of anesthesia for cancer patients undergoing surgery for general indications.*

Keywords*- chemotherapy, cyclophosphamide induced pseudocholinesterase deficiency, succinylcholine, delayed recovery, drug-drug interactions*

Abbreviations-

ETT- Endotracheal Tube, ENT- Ear Nose and Throat, OPD- Out Patient Department, PAC- Pre-Aanesthetic Checkup, CSF- Colony Stimulating Factor, CVC- Central Venous Catheter, CY- cyclophosphamide, PSC- Pseudo Cholinesterase, BiPAP- Bilevel Positive Airway Pressure, NDMR- Non- Depolarising Muscle Relaxation, ICU- Intensive Care Unit, PORP- Post- Operative Residual Paralysis, VAP- Ventilator Associated Pneumonia, CPAP- Continuous Positive Airway Pressure, NIV- Non- Invasive Ventilation, RNMB- Residual Neuro Muscular Blockade, FFP- Fresh Frozen Plasma, Manuscript.

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I. INTRODUCTION

Returning to the pre-anaesthetic state after completion of surgery requires the patient to be easilyarousable, to be able to protect his airway and maintain adequate ventilation. Time to recover completely from anaesthesia is variable depending upon blood solubility of inhalational anaesthetic agents and pharmacodynamics for intravenous agents, patient related factors and the length of surgery. Delayed emergence from anaesthesia is one of the most dreaded complications faced by anaesthesiologists world over. It is defined as the failure to regain consciousness 20-30 minutes after a surgical procedure.[1] Although residual effect of anaesthetic agents and sedatives are most commonly involved, many a times it remains a dilemma. Major risk factors associated with higher incidence of delayed recovery are summarised as [TABLE-1].

Table – 1 Risk Factors Associated with Higher Incidence Of Delayed Recovery After Anaesthesia

Patient factors	**Drug related factors**	**Surgery related factors**	**Metabolic factors**	**Neurological factors**
Extremes of age Genetic variations Comorbidities (renal/hepatic /respiratory or cardiac failure/ seizures/ stroke)	Dosage Time of administeration Blood-gas solubility Route and products of metabolism Route of excretion and half-life Drug-drug interactions Local anaesthetic toxicity	Prolonged surgery Hypotension Hypoxia Prolonged painful stimulation Regional techniques with intravenous sedation Excessive blood loss/ massive transfusion Excessive use of muscle relaxants	Hypo/hyperglycemia Dyselectrolytemia Sepsis Central anti-cholinergic syndrome Hypo/hyperthyroid state Hypothermia Acidosis Coagulation defects	Cerebral hypoxemic insult Cerebral haemorrhage Cerebral vein thrombosis Cerebral venous thrombo-embolism Factitious disorder

1. **Patient Related Factors**- These include age-dependent changes in the volume of distribution, plasma protein binding andrate of metabolism which prolong the effect of inhaled and intravenous anesthetics, opioids and benzodiazapenes with extremes of age bearing significantly high risk. Also genetic abnormalities in target receptors and hydrolytic enzymes, body habitus and comorbidities influence the rate of recovery. It is vital to titrate anaesthetic drugs to cater to individual needs.

2. **Drug Related Factors-**These are related to alteration in one of the steps of pharmacokinesis of drugs administered during anaesthesia, drug-drug interactions, overdose or incomplete neuro-muscular blockade reversal and rarelysuxamethoniumapnea. To suspect a drug overdose or residual effect as the cause of delayed recovery requires careful inspection of all the systemic effects of the drug in question while ruling out any synergism with other drugs.

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3. **Surgery Related Factors**-Some surgeries involve repeated painful stimulations like exploratory laparotomies, some are prolonged to >3 hours or are associated with adverse intra- operative events like hypotension, hypoxemia, acidosis or massive blood loss. All these factors increase the risk of slow post-operative recovery to several times even when individualised approach and modified doses of anaesthetic drugs have been used.

4. **Metabolic Factors-**These factors are the most difficult to detect in case of delayed awakening and require careful clinical examination, working out the differentials and supportive data from labs and radiology to confirm one's diagnosis. Electrolyte disturbances like hypo/hypernatremia, hypo/hyperkalemia, acidosis, hypothermia, hypo/hyperglycemia, endocrinal emergencies like thyrotoxicosis/ myxedema etc must be considered in a case of delayed recovery as these are reversible with prompt treatment.

5. **Neurological Factors**-These are the grave conditions reported in the literature which have been linked to delayed awakening after general anaesthesia. Periods of hypoxemia or ischemia have been known to occur as a result of intraoperative arrhythmias, deliberate hypotension, or in patients with abnormal cerebral vasculature particularly in neurosurgery, cardiac, and carotid surgery. Similarly small hemorrhages into ventricles, subependymal area, and around the ventricular catheters are frequently seen following ventriculoperitoneal shunt surgery[2], causing delayed awakening from anaesthesia. Rarely, previously unknown intracranial mass lesion has been implicated in prolonging emergence[3]It is important that in high-risk surgeries, all vital parameters are aggressively monitored and maintained throughout the procedure to prevent adverse sequalae

In every case of delayed anaesthetic recovery, it is of prime importance to note the level of consciousness of the patient by means of Modified Aldrete Score[Table-2].

Table 2.-Modified Aldrete score for assessing recovery and discharge from the post anesthesia care unit

Parameters	**Quantification**	**Grading**
Motor activity	4 extremities 2 extremities No	2 1 0
Breathing	Able to breathe deeply and cough Dyspnoea, shallow breathing Apnea	2 1 0
Circulation (change in b.p.)	<20% control 20-50% control >50% control	2 1 0
Consciousness	Fully awake Arousable on calling Unresponsive	2 1 0
Oxygen saturation	>92% room air >90% on o2 <90% on o2	2 1 0

A strong tactile stimulus like eyeball pressure or sternocleidomastoid pinch can help the patient to return to wakefulness. His airway patency and minute ventilation must be adequate at all times and assisted by use of nasal/oral airway, assisted ventilation with mask and ambu, non-invasive BiPAP and invasive mechanical ventilation

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as required till completely recovered. The haemodynamic parameters like heart rate, blood pressure, saturation of O2 and respiratory rate monitoring gives a clue to the depth of anaesthesiaand analgesia, so must be recorded at all times. Ambient environment and all infusion fluids must be warmed to room temperature to prevent hypothermia. Also such a scenario commands review of all the components of pre-anaesthetic check-up including any point missed on history taking, clinical examination of organ systems and lab investigations that could have lead to delayed anaesthesia recovery. All drugs administered must be documented with their dosage and time of administration to rule out any discrepancy. Antidotes to common drugs like flumazenil, naloxone must be present in the crash cart for use in case reversing a particular drug is desired. The basic investigations like blood glucose, blood gas analysis and renal/liver functions must be sent post-procedure and followed – up for any derangements. In case all the above are non-indicative, and the patient does not show any signs of recovery, it is logical to proceed to CT/MRI to rule out any intracerebral event.

Thus, failure to awaken post general anaesthesia requires an integrated approach to all the underlying risk factors that the patient concerned might have, all the peri-procedural anaesthetic agents used and their anticipated time of clearance as well as duration and hameostatic derangements involved in surgery. It takes an experienced anaesthesiologist or team per say to decipher the code to this mystery and treat it appropriately.

In this case report, we present a case of delayed recovery from neuromuscular blockers which, in all likelihood, was related to cyclophosphamide induced pseudocholinesterase deficiency.

II. CASE REPORT

62 year oldfemale who came to ENT OPD with deviated nasal septum was planned for surgery coming morning after PAC clearance. On eliciting detailed medical history, she was a known case of carcinoma breast and had received 6 cycles of chemotherapy 1 year back with doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 followed by trastuzumab 4mg/kg over 90 minutes weekly for 52 weeks. Post chemotherapy, she was undergoing treatment for her myelosuppression in the form of CSF and erythropoietin injections. Apart from that, she had no history of any other co-morbidities, drug allergy or blood transfusion. She had undergone modified radical mastectomy 2 years back under general anaesthesia which was uneventful. She was a teacher by profession, non–alcoholic, non- smoker with good socio-economic background.

On physical examination, she had pallor and bilateral mild non-pitting edema. Her cardiorespiratory examination was normal with NYHA Grade 2. All routine investigations were ordered which were as follows- Hb- 9 gm%, TLC 3650 /cumm, DLC -80/12/2/4, platelet 80000/cu mm, INR- 1.1, creatinine-1.3, S. electrolytes- Na+135 mg/dl, K+ 3.2 mg/dl, corrected Ca2+ 7.8 mg/dl, Liver Function Tests, Arterial Blood Gas and Chest XRay – WNL and ECG showing normal sinus rhythm. TTE was advised to review any features of cardiomyopathy due to doxorubicin which revealed an ejection fraction of 55% with DD grade 1. LV and RV functions and diameters were recorded as normal. She was corrected for her K+ and Ca2+ levels and taken up for surgery with due risk.

On the day of surgery, she was premedicated with alprazolam 0.25 mg. She was shifted to OT in a calm, awake state and monitors were attached. Intravenous line was secured and Ringer Lactate solution was started at 80 ml/ hour. After giving injection glycopyrrolate 0.005mg/kg and fentanyl 1microgram/kg, induction was done with propofol till loss of verbal stimulus (total 90mg) and thereafter, succinylcholine was administered in a dose of

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1.5mg/kg. She had no fasciculations and after 1 minute, ETT was secured with bilaterally equal air entry. Maintainence of anesthesia was accomplished with N2O:O2(50:50) and isoflurane 0.4V/V % on which she had achieved haemodynamic stability with no response to noxious stimuli. She had decreased anesthetic requirement which made us cautious for increased sensitivity to all anaesthetic agents. She was given bolus dose of vecuronium 0.1 mg/kg and thereafter when she started weaning off. There was no requirement of supplemental muscle relaxant throughout the surgery which lasted for 1 hour 40 minutes. Intra-operative analgesia was given in the form of intravenous diclofenac infusion 75mg.

After the surgery was complete, inhalational agents were switched off and oropharyngeal suctioning done with removal of throat pack. The patient remained deeply unresponsive to noxious stimulus till 40 minutes after cessation of gases with Modified Aldrete recovery score 2/10. At 45 minutes, patient started breathing spontaneously but with only 90-100ml expiratory tidal volume. Because it was already past 1 hour to the last dose of muscle relaxant, patient was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.01mg/kg. Despite reversal, patients respiratory efforts remained inadequate, she had hypotonia (tone 1/5) in all four limbs; the protective reflexes were present (cough and swallow reflex) albeit sluggish. She opened her eyes to tactile stimulus, tone increased to 2-3/5 and Aldrete score improved to 5/10. It was labelled as a case of inadequate reversal and furtherinjection neostigmine was repeated to a total dose of 0.07 mg/kg but with no improvement in her breathing. She was maintaining well on CPAP mode of anesthesia workstation with Psupp 12 cm H2O. It was decided to extubate the patient and bridge her to NIV mode till her breathing efforts were normal. She was shifted in Intensive Care Unit and kept on Bi-level Non-invasive mode with an IPAP 12 and EPAP 6 cm H2O on FiO2 0.5. After two hours, she regained her tone and consciousness completely and NIV was detached. Her respiratory distress had disappeared and her clinical parameters to predict RNMB (head lift >5 sec, hand grip>10 sec, able to lift arms and legs>5 sec) were recorded to be within normal limits. She was able to maintain on face mask with O2 6L/min. She was started orally by evening and shifted to ward next morning.

III. DISCUSSION

Residual neuromuscular blockade is a common sequalae of surgeries performed under general aneaesthesia which may lead to delayed emergence. The incidence of residual neuromuscular blockade is as high as 60% even after administration of reversal agent.[4]Themost reliable test to detect residual paralysis is a mechanomyographic TOF> 0.9, but unfortunately, our PNS machine was malfunctioning and we had to rely on our clinical judgement including tests like head lift(>5sec) or hand grasp (10sec) for neuromuscular function.

Factors that alter the incidence of postoperative residual paralysis include use of different TOF criterion (0.7, 0.8 or 0.9) for PORP[5,6], genetic abnormalities, extubating without neuromuscular blockade reversal, time duration between last assessment of neuromuscular blockade and reversal[6-8], malnutrition, presence of kidney, cardiac or neuromuscular dysfunction, drugs that alter pharmacokinetics/dynamics of NMBs like CCB s, magnesium, lithium, antibiotics like aminoglycosides, local anaesthetics, inhaled anaesthetics, opioids, benzodiazapenes, and chemotherapeutic agents etc, age, electrolyte abnormalities[9], metabolic[9] or respiratory acidosis, and hypothermia[9].

In our patient, reversal was given in the maximal dosage , all cardiac, kidney functions were normal; electrolytes, metabolic parameters including LFTs, RBS, acid-base analysis were normal and hypothermia was prevented by used of nasopharyngeal temperature probe and use of bare huggers , fluid warmers etc. So, the only possibility fitting into causation of hypotonia and respiratory muscles weakness remained the inhibition of pseudo-

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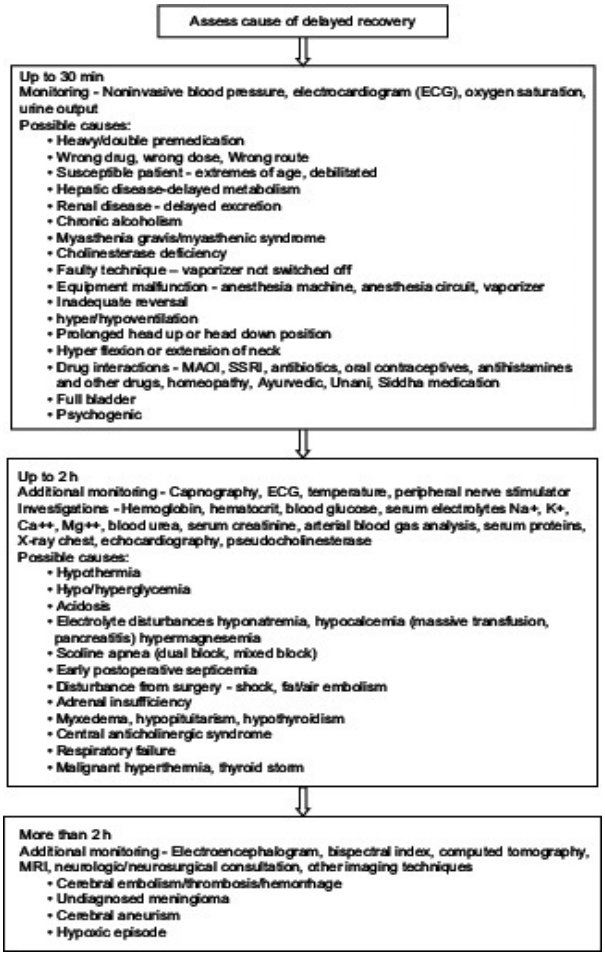
cholinesterase activity by cyclophosphamide which causedpost operative respiratory distress due to residual action of succinylcholine.We counselled the patient to get her PchE levels evaluated but she refused to do so.

Pseudocholinesterase is a tetrameric glycoprotein enzyme produced in the liver that hydrolyses choline esters like succinylcholine. The plasma half-life of this enzyme is 12 days and its activity is essential for weaning off from mivacurium or scoline induced neuromuscular blockade. Drugs like cyclophosphamide combine with the enzyme to render it ineffective or upto 50% of the pre-treatment value leading to dose-dependent prolonged neuromuscular blockade and hence, delayed recovery from anaesthesia. Koseoglu et al reported a case of young female with left adrenal neuroblastoma with bone marrow metastasis. She underwent 2 successful procedures under general anaesthesia while on treatment with cisplatin, etoposide, doxorubicin, and cyclophosphamide (1.2gm/m^2). While planning autologous stem cell transplantation, she was shifted to high-dose CY (7gm/m^2) and subsequently underwent CVC insertion under general anaesthesia with thipentone 3.5 mg/kg, fentanyl 2 microgm/kg and succinylcholine 1.8 mg/kg. After insertion, she maintained flaccid paralysis with apnea. Her PSC levels were found to be very low 0.4 IU/ml(normal range 1400-5600IU/l) and required ventilator support for 90 minutes after receiving succinylcholine.[10]

Etiologies of delayed recovery have been categorised according to the period of recovery into – 30 minutes , 2 hours and more than 2 hours delay (Figure-1). [11]



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Out of these, scolineapnea has been noted to produce prolongation of upto 2 hours which was seen in our case too.A case series by Zencirci B et al illustrates four different cases of mivacurium induced prolonged neuromuscular blockade fully recovered after 1 hour 22 minutes, 2 hours 20 minutes, 4 hours 20 minutes and 1 hour 5 minutes respectively. All of them had deficient levels of PSC enzyme on testing and 3 of them recovered to normal levels after 1 month while 1 of them could not. Hence, congenital deficiency related to mutations at a single autosomal location on the long arm of chromosome 3 as well as acquired deficiencies related to pregnancy, renal or liver disease, malignancy, burns, chronic malnutrition, myocardial failure, myxedema can cause prolonged apnea after general anaesthesia.[12]

Similarly, Somers R et al in 2009 reported a case of lower segment caesarian section under general anaesthesia where the patient did not return to spontaneous breathing due to prolonged neuromuscular blockade and cholinesterase deficiency was suspected. She had to be mechanically ventilated for 6 hours before she resumed spontaneous respiration. [13]During the first 2-3 days after delivery, there is documented fall in serum PSC levels over and above lower pregnancy levels which revert back to normal at the end of puerperium.[14] Lower PSC levels have also been found in pre-eclamptic and HELLP syndrome patients, probably due to diminished liver profile.[15]

The main targeted line of treatment in succinylcholine induced apnea is regulation of minute ventilation by means of ventilatory support until whole of the drug diffuses out of myoneural junction permitting return of neuromuscular function. Another proposed treatment is prophylactic transfusion of FFPs in order to augment patient's endogeneous PSC levels. However, it has to be weighed against the risk of iatrogenic transfusion related infections. In our case, the patient remained hypotonic but was not entirely flaccid, so it was decided to put her on non-invasive ventilation keeping in mind that she was in immunocomprised state with high-risk of developing early – onset VAP on invasive mode of ventilation.

IV. CONCLUSION

Chemotherapeutic agents and their systemic toxicities must be sought during pre-anaesthetic evaluation of cancer patients posted for surgery to ensure safe conduct of anaesthesia and improve post-operative outcome.

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