Original Research Paper

Volume - 14 | Issue - 03 | March - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Anaesthesiology

CITICOLINE: A CAUSE OF INADEQUATE MUSCLE RELAXATION IN A YOUNG PATIENT UNDER GENERAL ANESTHESIA

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ABSTRACT Citicoline prevents phospholipid degradation and promotes regeneration of cerebral phosphatidylcholine, and is used to improve cognition and delay disease progression in cerebral ischemia, and head injury patients by increasing acetylcholine levels. This drug may potentially interact with neuromuscular blocking agents (NMBAs) that act on muscular acetylcholine receptors during general anaesthesia (GA) leading to resistance to NMBAs.A 24-year-old male was posted for oro-maxillofacial fracture reduction and plating. The patient had polytrauma, including head, face, chest, right elbow, and abdominal injuries leading to coma for 15 days, tracheostomised, ventilated, recovered, and started on tablet Citicoline for 15 days. General anaesthesia was induced with propofol and atracurium and maintained on sevoflurane. After induction, a patient came out of muscle relaxation within 15 minutes and thereafter every 10 minutes. Atracurium was replaced with Vecuronium but still patient was inadequately relaxed. Dexmedetomidine infusion was added, and sevoflurane concentration was increased to achieve muscle relaxation. Citicoline may be responsible for inadequate muscle relaxation so for elective cases citicoline could be withheld for five days preoperatively. Also, dose modification of neostigmine is needed under neuromuscular monitoring.

KEYWORDS : Citicoline, Nootropics, brain injury, muscle relaxation

CASE REPORT:

A 24-year-old male had fallen from the third floor at the workplace 45 days back causing injuries like extradural hemorrhage, subdural hematoma, facial fractures, right side multiple rib fractures causing hemo-pneumothorax, right elbow fracture, and grade two splenic lacerations with minimal perinephric hematoma. As per the discharge summary, from the private hospital patient was in a coma and was on a ventilator for 10 days, tracheostomized and weaned from the ventilator on the 15th day. Right-sided Intercostal drain (ICD) was inserted for hemo-pneumothorax. The patient was shifted to our institute for further management. On admission the patient was awake and conscious, Glasgow Coma Scale being 15/15 with pallor and bruises on the right eye, the right elbow was in plaster, and Portex® tracheostomy tube (TT) number 7.5 was in situ. The patient did not have any significant past history.

On examination, the patient weighed 50 kilograms, was afebrile, pulse rate was 102 per minute, blood pressure was 102/68 mm of Hg, and respiratory rate of 14 per minute. On auscultation, air entry was reduced in the right base with, minimal crepitations, and heart sound was heard without any murmur. . The patient was on tablet Zocef 500 milligram (mg) twice a day, tablet Dolo (650 mg twice a day), tablet Pantoprazole (40 mg once a day), tablet cetirizine (10 mg once a day), and tablet Citicoline (500mg twice a day) for 10 days. Preoperative Investigations were as mentioned in Table/figure 1.

Table/Figure 1: Preoperative Investigations.

Complete blood count	Renal function test	Kidney function test
HB: 11.3 gm/dl TLC: 8,250 /ml	Sr. Creatinine: 0.62 mg/dl	Total Bilirubin: 0.8 mg/dl
PLTS: 4,50,000/ml BG: A POSITIVE	Serum Sodium :134 mEq/l Serum Potassium: 4.8 mEq/l Serum Chloride: 100 mEq/l	Direct Bilirubin: 0.3 mg/dl Indirect Bilirubin: 0.5 mg/dl
PT/INR: 15/1.09	2DEchocardiography: Ejection Fraction- 60%, grade 1 Left Ventricular Diastolic Dysfunction	SGOT/SGPT: 52/60 U/L ALP: 265 U/L

Hb-hemoglobin, TLC-total leukocyte count, PLTs-platelets, BG-blood group, PT/INR – Prothrombin Time/ International Normalized Ratio, SGOT-serum glutamic-oxalocaetic transaminase, SGPT-serum glutamic pyruvic transaminase, ALP – Alkaline Phosphatase.

Ultrasound abdomen showed signs of fatty liver, rest is within normal limits. Ultrasound chest showed mild free fluid in the left pleural cavity(non-tappable), and a minimal streak of fluid in the right pleural cavity. Computed tomography Face plain showed communicated minimally displaced fracture of right para symphysis, maxillary, right orbit, zygomatic arch, right temporal bone as seen in table/figure 2

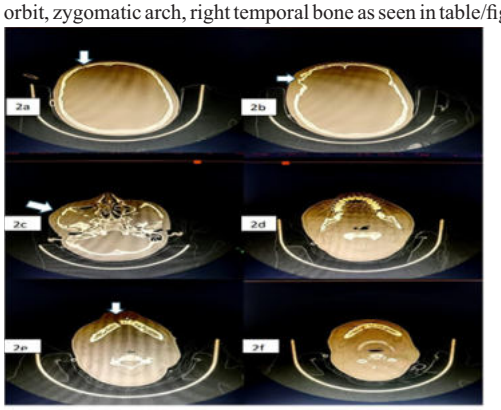


Fig. 2a,2b : Comminuted minimally displaced fracture is seen involving right lamina papyracea with herniation of extraconal fat and right medial rectus muscle.

Fig. 2c,2d : Comminuted minimally displaced fracture is seen involving superior, lateral and inferior wall of right orbit, zygomatic arch, inner and outer table of right frontal sinus with squamous part of right temporal bone extending to the right mastoid air cell with hemo-mastoid.

Fig. 2e,2f : Comminuted minimally displaced fracture is seen involving body of right Para symphysis region, medial, anterior and lateral wall of right maxillary sinus with resultant hemo-sinuses with herniation of retro maxillary fat.

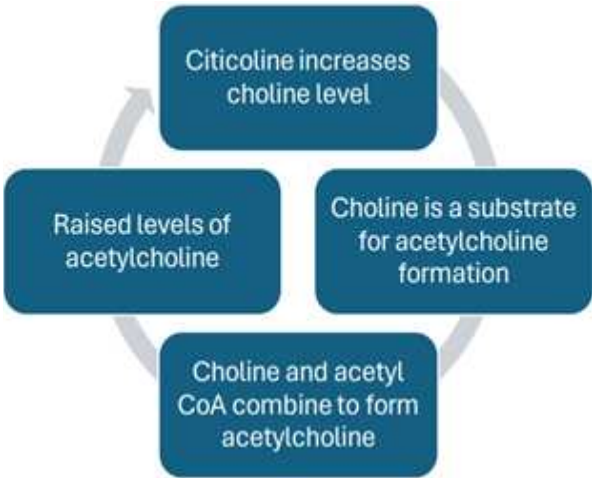
Table/Figure 2 Computed Tomography Face.

The patient was to be operated on for mini plates with screws for bilateral zygoma fracture with mandible fracture under American Society of Anesthesiologists (ASA) grade two. The standard protocol of general anaesthesia was followed preoperatively and the patient was shifted to the operation theatre, standard monitors were attached and preoperative vitals were recorded. The patient was kept warm by warmer with temperature monitoring which was within normal limits throughout the procedure. General anesthesia was induced with fentanyl 100 micrograms (mcg), propofol 80 milligrams (mg), atracurium 25 mg, and sevoflurane was maintained at a minimum alveolar concentration (MAC) of 1.5. After 15 minutes patient started breathing, and atracurium 5 mg was repeated. Thereafter patient kept coming out of muscle relaxants every 10 minutes, so atracurium was replaced with vecuronium one mg, as a muscle relaxant. After starting vecuronium, the patient started coming out every 10-15 minutes, so dexmedetomidine infusion was started at 0.5 mcg per kilogram loading dose for 10 minutes followed by a maintenance dose. The patient kept coming out of muscle relaxant every 15 minutes. We

increased sevoflurane concentration to achieve sufficient muscle relaxation. Due to the unavailability of neuromuscular monitoring, a quantitative assessment of neuromuscular block could not be done. Injection of fentanyl 50 mcg was repeated, and paracetamol 100 milliliters (ml) was infused over 20 minutes. At the end of the procedure, the patient was reversed with neostigmine 2.5 mg, and glycopyrrolate 0.4 mg after gaining sufficient power and alertness. Postoperatively, the patient had good power, and reflexes shifted to the recovery room for monitoring till the patient was completely alert and then shifted to ward.

DISCUSSION:

This patient was on medications like cephalosporin, pantoprazole, and cetirizine which don't have any interactions with neuromuscular blocking agents (NMBA) [1]. In this patient, tablet citicoline was started for a head injury [2]. Despite replacing atracurium with vecuronium the patient was coming out of muscle relaxants every 10-15 minutes. We increased the depth of anaesthesia by adding dexmedetomidine infusion, and fentanyl, still patient was not relaxed. Muscle relaxation was better after increasing sevoflurane concentration as inhalational gas is known for synergistic effects with muscle relaxants [3]. The potency of muscle relaxants, especially atracurium depend on maintaining the cold chain. We confirmed this from the pharmacy and also replaced atracurium with injection vecuronium to rule out reduced potency of atracurium. Serum electrolytes done preoperatively were normal as electrolyte imbalance can affect neuromuscular blockade. Previously, it has been reported by Jang EA et al [4] and Bharadwaj et al [5] that certain drugs like Donepezil, an acetylcholinesterase inhibitor caused inadequate muscle relaxation during general anaesthesia and the addition of desflurane and cisatracurium worked better in Alzheimer's disease [7]. Piotrowska et al concluded it is effective in Parkinson's disease, glaucoma, and addictions [8]. We could have used neuromuscular monitoring for quantitative assessment of neuromuscular block but due to unavailability, we had to rely on the patient's clinical response. We could not find any reference for patients on citicoline therapy undergoing general anaesthesia. There are no clear guidelines on whether this drug should be discontinued before elective surgery. As per the study by Piotrowska et al cticoline is a safe drug, that has no significant systemic cholinergic effects and is a well-tolerated product. The probable cause for inadequate muscle relaxants could be an increased concentration of acetylcholine due to citicoline as explained in table 3/figure 3 [9]. As more patients on citicoline therapy will require anesthesia in the future, it is important to emphasize this drug interaction. Probably citicoline can be discontinued for five days before surgery as ScadesJJ et al suggest urinary, fecal, and exhaled gas excretion of citicoline for the five days following oral administration [9].



Table/figure 3 Citicoline Interaction.

Also, discontinuation before surgery should not have detrimental effects on cognitive function as it has no disease-modifying action. We recommend using peripheral nerve monitoring in these patients as it gives a quantitative assessment of neuromuscular block. Patients with adequate spontaneous recovery to train of four ratios greater than or equal to 0.9 % can be identified with quantitative monitoring and a dose of pharmacological antagonism not required or could be reduced as per Thielen, et al [10].

CONCLUSION:

Citicoline is an essential drug in head injury, stroke, and cognitive dysfunction to improve prognosis. Citicoline probably interacts with neuromuscular blockers by increasing the concentration of acetylcholine resulting in inadequate muscle relaxation and increased dose requirement of neuromuscular blockers during general anaesthesia. Choice of the neuromuscular blocker and dose adjustment might be required under neuromuscular monitoring in patients on citicoline during general anaesthesia.

Informed Consent Statement: Informed consent from the patient was taken.

Conflict Of Interest Statement: There is no conflict of interest.

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