Literature Review with Case Report

Delayed Recovery

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Introduction

Delayed recovery indicates delay in return of consciousness, recovery of protective airway reflexes and resumption of motor activity. There is no single definition of what might constitute delayed awakening or emergence after general anesthesia. Physiologic recovery was complete in 40% of patients by 40 minutes.¹

The principal factors responsible for delayed awakening are anesthetic agents and medications that are administered in the peri-operative period. Non-pharmacological causes may also have a serious sequel and it has to be identified at the earliest. There are numerous factors which lead to delayed recovery. This includes hypoglycemia, severe hyperglycemia, electrolyte imbalance especially hypermagnesemia, hyponatremia, hypoxia, hypercapnia, central anticholinergic syndrome, chronic hypertension, liver disease, hypoalbuminemia, uremia, and severe hypothyroidism.² Various scoring systems and criteria are available which aid in recognizing complications early in the immediate post operative period thereby preventing untoward events post discharge from the Post Anesthesia Care Unit (PACU). One such scoring would be Aldrette Scoring System which employs five crucial parameters which help in guiding discharge of patients from PACU.³

Patient factors like age, status of the renal and hepatic system, underlying metabolic diseases or cumulative effects due to prolonged surgery also affect drug related delay in recovery from anesthesia. Here we describe a case of delayed recovery following general anesthesia in a morbidly obese patient with hypothyroidism discussing the causes and management.

Case Report

A female patient 51 year old was posted for right clavicle implant exit surgery, known case of Hypothyroidism for the past 8 years on Tablet.Eltroxin (levothyroxine) 125 micrograms once a day, Type II Diabetes Mellitus on Tablet Metformin 500 mg twice daily and Tablet Glimepiride 1 mg twice daily, she was also a known case of Systemic hypertension, on Tablet Amlodipine 5 mg twice daily.

During preoperative assessment, she was conscious, oriented, afebrile, weighing 96 kg, height 158 cm (BMI 38.5 kg/m²) with a heart rate of 86 beats per minute and blood pressure of 140/80 mm Hg. Systemic examination was within normal limits. On local examination, breast and thyroid were normal. We anticipated difficult mask ventilation as she was morbidly obese. Airway examination showed short neck, an adequate inter incisor distance, Modified Mallampatti class 3, Thyromental distance of 5.5 cm, Mandibular lux was +1. Blood investigations were within normal limits including her thyroid profile which was suggestive of euthyroid state. Chest radiograph was normal. Electrocardiogram showed S wave depth in V1 plus tallest R wave height in V5-V6 > 35 mm suggestive of left ventricular hypertrophy and Echocardiogram showed no significant abnormality.

Patient was assessed fit under American Society of Anesthesiologists (ASA) Physical Status II.

Anaesthetic Management

Pre-operatively she was advised to take Tablet Eltroxin (levothyroxine) 125 micrograms and Tablet Amlodipine 5mg on the morning of surgery. Tablet Glimepiride was withheld the night before and morning of surgery and Tablet. Metformin was also withheld on the morning of surgery.

Her fasting blood sugar on the morning of surgery was 120 mg/dl and BP was 130/90 mm Hg respectively.

Patient was shifted to operation theatre and standard ASA monitors were connected.

She was pre-medicated with Injection glycopyrrolate 0.2 mg and injection midazolam 2 mg intravenously. Injection fentanyl 100 micrograms (as per lean body weight) was given for analgesia and to blunt the intubation response. She was preoxygenated with 100% Oxygen, induced with Injection propofol 150mg intravenously. Oropharyngeal airway was inserted to facilitate mask ventilation following which she was paralyzed with injection vecuronium 8mg intravenously and intubated with 7.0 size cuffed portex endotracheal tube. Anesthesia was maintained with isoflurane 1.5%, N₂O:O₂ in the ratio of 2:1. Paralysis was maintained with injection vecuronium 1mg (as per ideal body weight) intravenously at 30-45 minute intervals. Neuromuscular monitoring was not employed due to non-availability. Surgery duration was about 120 minutes. Towards the end of surgery after assessing for adequate spontaneous breathing, muscle power and eye-opening, patient was reversed with injection neostigmine 0.05 mg/kg and injection glycopyrrolate 0.01 mg/kg intravenously, re-assessed and trial extubation was done following which she immediately developed respiratory distress. She desaturated to 82%, oxygen was supplemented via face mask with 6 liters/minute despite which she continued to have difficulty in breathing and became drowsy therefore mask ventilation was instituted with 100% oxygen, Positive Pressure Ventilation for about 10 minutes. Other causes like hypoglycemia, hypothermia and stroke were ruled out as evidenced by good muscle power, intact papillary reflex and normal deep tendon reflexes. Arterial blood gas analysis was done, which showed mild acute respiratory acidosis. With the above mentioned maneuvers patient recovered after 20 minutes and observed for two hours in Post Anesthesia Care Unit and shifted to post-op surgical ICU for further monitoring.

Discussion

Delayed recovery from anesthesia is often considered to be multifactorial. Our patient was a known hypothyroid with morbid obesity which in itself has a high chance of delayed recovery along with drug related factors due to altered pharmacodynamics and pharmacokinetics. Although she met the extubation criteria residual effect of neuromuscular blocking agents or volatiles is a definite possibility. The various factors which can lead to a delayed recovery are mentioned in Table 1.

Patient factors	Age Gender Co-morbid conditions Genetic variations Body habitus Obstructive sleep apnea
Pharmacological factors	Anesthetic agent Dosage Time of administration Blood gas solubility Metabolism Excretion Drug interaction
Metabolic causes	Hypoglycemia Hyperglycemia Hypocalcaemia Hypernatremia Hyponatremia Acidosis Hypothermia
Surgical factors	Prolonged surgery Major surgery with large fluid shifts Intra-operative embolism

Table 1: Risk factors for delayed recovery

The most common factors which could be implemented in delayed recovery and some of the causes that could have contributed to delayed recovery in our patient are discussed below.

Age

Elderly patients tend to have an increased sensitivity towards general anesthetics, opioids and benzodiazepines owing to slow return of consciousness due to progressive decline in central nervous system function. They also have a reduced demand for opioids by almost 50%.⁴ The decrease in volume of distribution, clearance rate, and plasma protein binding results in high free plasma concentration of drugs.

Fredman et al. assessed the effect of different doses of midazolam in geriatric patients undergoing brief urologic procedures and found that irrespective of the dose, midazolam significantly depresses mental function and delays PACU discharge.⁵

Gender

Apfelbaum et al. stated in his study saying men are 1.4 times more likely to have delayed recovery than women. Also, women showed a relatively lower sensitivity to the effect of anesthetics, which may contribute to their faster recovery period.^{6,7}

Co-morbidities

Patients with pre-existing disease conditions may predispose to delayed emergence requiring dose adjustments accordingly. Patients with respiratory diseases with altered lung parenchyma and lung volumes will have decreased ability to wash out inhalational agents.⁸ Advanced renal or hepatic disease can prolong action of anesthetic agent's dependent on hepatic metabolism or renal excretion.⁹

Muscle relaxants and opioids are metabolized extensively by the liver and depend on renal excretion therefore products of metabolism can accumulate in diseased states predisposing to prolonged duration of action.

Hypothyroidism

Subclinical hypothyroidism has a prevalence of 1–10% and it has been diagnosed post-operatively often for the first time due to delayed emergence after anaesthesia.^{10–12} Although our patient was euthyroid prior to surgery, longstanding hypothyroidism could have been a significant contributing factor. Adrenal insufficiency is another possibility to be considered in patients with delayed recovery especially in individuals with multiple endocrine abnormalities.¹³

Pharmacological causes

Delayed awakening or emergence is often due to anesthetic drug overdose.¹⁴

A heavy premedication or relative overdose of general anesthetic agents is a proven cause of delayed awakening.¹⁵ The selection of anesthetic technique, choice of anesthetic agent, dosage, duration of action and active metabolites determine the time of unconsciousness to awakening. For this patient all drug doses were adjusted as per body weight as she was obese which could lead to altered drug pharmacodynamics and kinetics leading to a prolonged emergence from anesthesia.¹⁶

Time to emergence increases with increasing duration of anesthesia as reported by Garg et al. in his study where patients who underwent surgery for a longer duration under general anesthesia had delayed recovery.¹⁷

Recovery could also be delayed if soluble volatile agents are continued until the end of surgery or long-acting drugs are given toward the end of the procedure.¹⁸

The termination of action of anesthetic agents given as a bolus for induction is predominantly determined by redistribution and should not delay recovery

except cases where high doses were used for a procedure of short duration.

Volatile Agents

The speed of emergence is directly related to alveolar ventilation and inversely related to blood gas solubility.¹⁹ Hypoventilation lengthens the time taken to exhale the anesthetic agent and delays recovery. Hypothyroid patients are also known to have increased sensitivity to volatiles and obesity has an added effect in delaying emergence when volatiles were being used to maintain anesthesia. Prolonged duration of anesthesia causes increased emergence time due to tissue uptake depending upon the concentration used and drug solubility.²⁰

Opioids

Opioids produce analgesia, sedation and respiratory depression, the intensity of each action varies between subjects and can be difficult to predict. Obese individuals are sensitive to even small doses of opioids and prone to respiratory depression. The direct opioid receptor effect varies with drug potency, half-life, metabolism and patient sensitivity.²⁰ Drug metabolism is affected thereby leading to longer duration of action. Active metabolites of morphine and meperidine increase the duration of action, especially in the presence of renal failure. Neuraxial opioids may also cause early respiratory depression and delayed awakening.²¹

Neuromuscular blocking Agents

One ought to think about drug interactions with neuromuscular blocking agents, or any metabolic abnormalities which may contribute with unusual symptoms and signs in an otherwise anaesthetized patient.

Residual neuromuscular blockade results in paralysis which may be perceived as unresponsiveness though the patient is conscious and aware.²² Various pharmacological interactions with neuromuscular blocking agents prolong neuromuscular block, by interfering with calcium, a second messenger involved in acetylcholine release. Individuals with atypical cholinesterase cannot metabolize depolarizing muscle relaxants thereby leading to prolonging emergence from anesthesia. Also, an electrolyte imbalance like hypermagnesaemia can significantly prolong the duration of action of non-depolarizing muscle relaxants.²³

Recurarization was a definite possibility in this case due to the administration of high doses of non depolarizing agent in a morbidly obese and hypothyroid patient; who are already predisposed to delayed recovery due to the coexisting illness associated pharmacodynamic alterations. The induction dose

was also high as per her lean body mass and maintenance doses were given at regular intervals. All the above factors could have synergistically acted and lead to recurarization/residual paralysis. Therefore administration of neuromuscular blocker guided by neuromuscular monitor would have been ideal in this case.

Metabolic causes

Hypoglycemia/Hyperglycemia

Neuroglycopenia manifests as confusion, abnormal behavior, seizures and coma. In the elderly population, lateralizing neurological signs are commonly seen. Postoperative hypoglycemia most often results from poorly controlled diabetes, starvation and alcohol consumption.²⁴ This patient was a known diabetic with good glycemic control and on regular medications. Tablet Glimepiride was withheld the night before surgery owing to its long duration of action to avoid hypoglycemia intra-operatively. Her blood sugars were monitored intra-operatively and post-operatively thereby ruling out hypoglycemia.

Hyperglycemia due to diabetic ketoacidosis or hyperosmolar non-ketotic acidosis causes an osmotic diuresis and intracellular dehydration. The effect of dehydration manifests as drowsiness and delayed recovery.²⁵

Hypothermia

Daniel et al states in his article that severe hypothermia may lead to reduced conscious level. A core temperature of less than 33 degree Celsius has a marked depressive effect itself and will potentiate the central nervous system effects of anesthetic drugs. In addition, hypothermia reduces the minimum alveolar concentration of inhalational agents, antagonizes muscle relaxant reversal and limits drug metabolism.²⁶

Hypokalemia

Delayed recovery due to inadvertent hypokalemia after laparoscopic cholecystectomy was reported in a medically optimized case of hypertension, bronchial asthma, and hypothyroidism.¹⁰ Hypokalemia intensifies the effects of non-depolarizing muscle relaxants. Mild preoperative hypokalemia without any clinical features could rapidly deteriorate after iatrogenic hyperventilation or surgical stimulation during and after anaesthesia.²⁷

Hypernatremia/Hyponatremia

Severe hypernatremia is less likely to occur in postoperative environment; however, sodium excess results in a cellular dehydration including cerebral dehydration, ruptured vessels and intracerebral

hemorrhage. In a study by Grati et al, concluded that, hypernatremia which can occur during hepatic hydatid cyst removal may also hinder the process of recovery from anesthesia.²⁸

Hypermagnesemia

Magnesium inhibits calcium-mediated release of acetylcholine from the pre-synaptic nerve terminal at the neuromuscular junction and plays an important role in potentiating the effect of non-depolarizing muscle relaxants. Therefore high levels of serum magnesium can be a potential cause of delayed recovery which often goes unrecognized.²⁹

Obstructive sleep apnoea

Another important factor worth mentioning and which could have influenced this patient's recovery is obstructive sleep apnea which is known to cause respiratory complications during emergence from anesthesia.³⁰ Morbidly obese patients with obstructive sleep apnea are at a higher risk for airway obstruction during the extubation period due to anesthetic drug related pharyngeal collapse and respiratory depression. This patient did not have any symptoms of sleep apnea yet it cannot be ruled out as a potential causative factor.

Conclusion

Delayed emergence is commonly encountered in hypothyroid patients; the probable cause in this case being pharmacological and likely due to residual paralysis or recurarization due to altered drug metabolism in a morbidly obese hypothyroid patient. Appropriate anticipation, optimization, precaution in selecting drugs and neuromuscular monitoring with good analgesia is mandatory to avoid delayed recovery post-operatively. Management of delayed recovery if it occurs lies in protecting the airway, maintaining adequate oxygenation, ventilation and hemodynamic stability.

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