

Review Article

Delayed awakening after anaesthesia- A challenge for an anaesthesiologist

Safiya Imtiaz Shaikh* and Lakshmi R R

Department of Anaesthesiology, Karnataka Institute of Medical Sciences, Hubli, India

***Correspondence Info:**

Safiya Imtiaz Shaikh
Professor and HOD,
Department of Anaesthesiology,
Karnataka Institute of Medical Sciences, Hubli, India.
E-mail: ssafiya11@yahoo.com

Abstract

Delayed awakening from anaesthesia remains one of the biggest challenges that involve anaesthesiologists. Most commonly, delayed awakening is due to drugs effects persistence. The time taken to emerge to fully consciousness is affected by patient factors, anaesthetic factors, duration of surgery and painful stimulation. Non pharmacological causes may have serious sequel; thus recognising these organic conditions is important. Unexpected delayed emergence after the use of general anaesthesia has a plethora of causes.

The most common cause for delayed awakening following anaesthesia is medications and anaesthetic agents used in the perioperative period. There may be an over dose of medications. Emergence from anaesthesia depends on the tissue uptake of the drug, average concentration used and the duration of exposure. Certain underlying metabolic disorders such as hypoglycaemia, severe hyperglycaemia, electrolyte imbalance especially hyponatremia, hypoxia, hypercapnia, central cholinergic syndrome, chronic hypertension, liver disease, hypoalbuminemia, uraemia and severe hypothyroidism may also be responsible for delayed recovery after anaesthesia. Preoperative medications such as opioids and sedatives and hypothermia can further interfere with postoperative recovery. Intraoperative cerebral hypoxia, haemorrhage, embolism or thrombosis also can manifest as delayed awakening from anaesthesia.

The ultimate goal of treatment is to find the cause and treat the cause, but primary management is to maintain airway, breathing and circulation.

Keywords: Delayed awakening; General anaesthesia; Drug effects; Neuromuscular blockers

1. Introduction

Ideally on completion of surgery and anaesthesia, the patient should be awake or easily arousable, protecting the airway, maintaining adequate ventilation and with their pain under control³. Delayed emergence from anaesthesia remains a cause of concern both for anaesthesiologist and surgeon. The principal factor for delayed awakening from anaesthesia is assumed to be the medications and anaesthetic agents used in the perioperative period.⁴Time to emerge from anaesthesia is very variable and depends on many factors related to the patient, the type of anaesthetic given and the length of surgery.⁵

Although delayed emergence from general anaesthesia is not uncommon, recognizing the cause and instituting timely treatment is imperative in condition where delayed therapy can increase morbidity and mortality.

2. Causes of delayed awakening

Causes of delayed awakening can be classified into

- Pharmacological causes
- Metabolic causes
- Respiratory causes
- Neurological causes

2.1 Pharmacological causes

Pharmacological effects depend on dose, absorption, distribution, metabolism, excretion and context sensitive half –life of a drug. Pharmacodynamics and pharmacokinetic interactions also play an important role.

2.1.1 IV anaesthetic agents

The termination of action of iv anaesthetic agents given as a bolus for induction is predominantly determined by redistribution and should not delay recovery.² The duration of unconsciousness is affected by context sensitive half -life, amount of drug, co administration with other drugs and patient factors.⁶

Eg : patients given propofol for induction and/or maintenance recover faster than those receiving other agents because propofol is rapidly metabolised by the liver and possibly also at other extra hepatic sites.

With thiopentone the initial drug effect is terminated by redistribution within 5 to 15 minutes. Elimination is by oxidative metabolism in the liver at a rate of 15% per hour. Cumulative effects may therefore become apparent when more than one dose is given.⁵

Propofol and ketamine may affect the intracellular Ca levels through NMDA receptors. Calcium is known to induce neuronal excitability and to increase anaesthesia depth.⁷

2.1.2 Volatile anaesthetic agents

Emergence from volatile agent anaesthesia depends upon pulmonary elimination of the drug and MAC. Pulmonary elimination is determined by alveolar ventilation. Alveolar hypoventilation lengthens the time taken to exhale the anaesthetic agent and delays recovery.²When the duration of anaesthesia is prolonged emergence also depends on the total tissue uptake of the drug which is related to drug solubility, average concentration used and duration of exposure.³Time to emergence increases with increasing duration of anaesthesia.²

2.1.3 Opioids

Opioids produce analgesia, sedation and respiratory depression; the intensity of each action varies between subjects and can be difficult to predict. The direct opioid receptor effect varies with drug potency, half-life, metabolism and patient sensitivity. Active metabolites of morphine and meperidine prolong the duration of action, especially in presence of renal failure.²

2.1.4 Neuromuscular blockers

Residual neuromuscular blockade results in paralysis which may be perceived as unresponsiveness though the patient is conscious and aware. A large number of pharmacological interactions with neuromuscular blocking agents prolong neuromuscular block, by interfering with calcium, a second messenger involved in acetylcholine release.⁸

Electrolyte disturbances cause cell wall hyperpolarisation and prolong block.² Patients with myasthenia gravis are very sensitive to non depolarising muscle relaxants, doses only 10 to 50% of the usual dose are required. Increased sensitivity to muscle relaxant is seen in muscular dystrophies. Prolonged apnoea following suxamethonium is due to abnormal or absent plasma choline esterase enzyme.⁵ Acquired cholinesterase deficiency is seen in pregnancy, liver disease, renal failure and thyrotoxicosis.²

Extension of the block is variable and depends upon the genotype.² Repeated doses of suxamethonium may produce dual block which is prolonged and slow to recover.² Hypokalemia intensifies the effects of non depolarising muscle relaxants.⁹ Several drugs that quicken recovery from neuromuscular blockade caused by vecuronium in anesthetized patients are Ulinastatin and Gabexatemesilate protease inhibitors and Milrinone, a phosphodiesterase III inhibitor. Ulinastatin, is thought to promote the release of acetylcholine at the neuromuscular junction and increase hepatic blood flow and urine volume.¹⁰

2.1.5 Benzodiazepines

Benzodiazepines are used for anxiolysis and premedication, co induction facilitates the hypnotic and sedative properties of other agents. Benzodiazepines potentiate the central nervous system depressant effects of anaesthetic and analgesic drugs and may delay emergence from anaesthesia.⁵ Benzodiazepines combined with high dose opioids can have a pronounced effect on respiratory depression, producing hypercapnia and coma.²

2.2 Metabolic causes

2.2.1 Hypoglycemia

Hypoglycemia is diagnosed by confirmation of venous blood glucose concentration of <2.2 mmol/L. The brain is totally dependent upon glucose as its energy source. The effects of hypoglycaemia can be divided into those resulting from sympathetic response and those caused by neuroglycopenia. Neuroglycopenia manifests as confusion, abnormal behaviour, seizures and coma.² Postoperative hypoglycaemia most often results from poorly controlled diabetes, starvation and alcohol consumption.⁵

2.2.2 Hyperglycemia

Severe hyperglycemia can prolong unconsciousness after anaesthesia. A venous blood glucose >14 mmol/L causes an osmotic diuresis and dehydration in the untreated patient. The effects of dehydration range from drowsiness to acidosis. Intraoperative cerebrovascular accident may occur as a result of cerebral vascular occlusion, especially in diabetics with microvascular and macrovascular disease.² Severe hypoglycaemia may occur in decompensated state like hyperosmotic hyperglycemic coma or diabetic ketoacidosis.⁵

2.2.3 Electrolyte imbalance

This may be secondary to the underlying illness or as a consequence of the surgical procedure.⁵

2.2.3.1. Hypernatremia

Hypernatremia is defined as plasma $\text{Na}^+ >145$ mEq/L. Extreme hypernatremia is less likely to occur in postoperative environment; however sodium excess results in a cellular dehydration including cerebral dehydration, ruptured vessels and intracerebral haemorrhage. Symptoms include thirst, drowsiness, confusion and coma.² Hypernatremia which can occur during hepatic hydatid cyst removal may also hinder the process of recovery from anaesthesia.¹¹

2.2.3.2 Hypokalemia

Serum potassium levels below 3.5 mEq/L are considered as hypokalemia.¹ The common signs of hypokalemia are confusion, decreased level of consciousness, muscle weakness, constipation, nausea, vomiting, polyuria, depression, decrease in cardiac contractility and change in cardiac rhythm. The potassium shift and /or excretion due to the alkalotic state require a considerable period of time to produce cardiac arrhythmias. Mild preoperative hypokalemia without any clinical features could rapidly deteriorate after iatrogenic hyperventilation or surgery stimulation during and after anaesthesia.¹²

2.2.3.3 Uraemia

Uraemia can occur in acute renal injury or chronic renal disease. Uraemia is due to increased blood urea nitrogen and other toxins which leads to symptom complex, known as uraemia. Uraemia results in dehydration and cerebral effects attributable to cellular damage and distortion. The clinical effects of uraemia are varied but intracerebral changes may produce drowsiness, confusion and coma.²

2.2.3.4 Hypothermia-

Severe hypothermia may lead to reduced conscious level. A core temperature of less than 33°C has a marked anaesthetic effect itself and will potentiate the CNS effects of anaesthetic drugs. In addition hypothermia reduces the MAC value of inhalational agents, antagonises muscle relaxant reversal and limits drug metabolism.¹³

The direct hypothermic effects on brain tissue are compounded by cardiovascular and respiratory disturbance at less profound degrees of hypothermia. Cardiac output decreases with a decrease in temperature and arrhythmias occur. Low cardiac output affects circulation and drug pharmacokinetics as well as tissue perfusion.²

2.3 Respiratory causes

Patients who do not breathe effectively during or after anaesthesia may become hypercarbic to a level that may produce sedation or even unconsciousness.⁵ Ventilation is affected by primary muscle problems, metabolic imbalance, obesity and residual neuromuscular block. Pulmonary disease states result in venous admixture, dead space or both and include pulmonary embolism, atelectasis, obstruction, aspiration, consolidation, acute respiratory distress syndrome and transfusion related acute lung injury.² The diagnosis is usually suspected clinically and may be confirmed by arterial blood gas analysis or measurement of end tidal CO_2 .⁵

2.4 Neurological causes

Diverse pathologies can precipitate intraoperative cerebral insult, causing coma. Coma may be attributed to a dissociative stupor. Reported delays in return to consciousness span time periods from 2 to 30h and longer amnesia thereafter.¹⁴ Periods of hypoxemia or ischemia can occur during surgery. These are often result of inadequate cerebral perfusion secondary to low mean arterial pressure.²

Cerebral hypoxemia of any cause will result in reduced conscious level which may first present as delayed awakening from anaesthesia, especially if hypoxic insult has occurred during anaesthesia.⁵ Intracerebral event such as haemorrhage, embolism and thrombosis can occur. Small haemorrhages into ventricles, subependymal area and around the ventricular catheters are frequently seen following ventriculo peritoneal shunt surgery.¹⁵ This is very rare except in neurosurgery, cardiac surgery, cerebrovascular and carotid surgery.⁵

Anticholinergic syndrome symptoms range from cerebral irritation with delirium and agitation to CNS depression with stupor and coma. These accompany with tachycardia, blurred vision, dry mouth and urinary retention. Nowadays it is not commonly seen as less anticholinergic medications are used.¹⁶

3. Evaluation and management

Immediate care

- Clear airway to be maintained, oxygen should be given. Re intubate if indicated.
- Ensure adequate respiration. If indicated, ventilate the patient via ET tube.
- Assess heart rate, blood pressure, ECG and peripheral perfusion, consciousness level and urine output. Resuscitate as indicated.

Intensive monitoring of all hemodynamic parameters, ET_{CO}2, SPO₂, CVP, input and output is mandatory.

Review history, investigations and perioperative management, including the anaesthetic chart and timings of the drug administration, looking for possible cause of the delay in recovery.

Look for signs of opioids narcosis-pinpoint pupils and slow respiratory rate. Arrange for antidote. Inj .naloxone 800mcg in 500ml of normal saline over 6 hours.¹⁷

In case of suspected benzodiazepine overdose; Supportive treatment should be with maintenance of airway and ventilation until drug has been metabolised. Antidote Inj.flumazenil is available. However flumazenil is expensive and may cause arrhythmias, hypertension and convulsions.

Measure temperature and necessary measures should be taken like wrapping in blankets, ensuring that room is kept warm and warm IV fluids.

Check blood glucose and correct with IV dextrose if it is less than 3mmol/L.

Check arterial blood gas analysis. Correct electrolyte imbalances and acidosis accordingly.

If no other cause can be found for delayed emergence from anaesthesia, an intra cerebral event may be suspected and full neurological examination should be performed, looking particularly for localising signs. However radiological imaging CT or MRI is often required to confirm diagnosis.

4. Conclusion

Delayed awakening of varying degree is not uncommon after anaesthesia and may have a number of different causes, individual or combined.⁵ The most common cause for delayed awakening are medications and anaesthetic agents used in perioperative period.^{18,19} Emergence depends on the tissue uptake of drug, average concentration used and duration of exposure.²⁰ Delayed emergence, often blamed on the anaesthetic agents may not always be the culprit.⁴ The primary management is always support of airway, breathing and circulation, whilst cause is sought and treated.⁵

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