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Review

Delayed emergence after anesthesia

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Abstract In most instances, delayed emergence from anesthesia is attributed to residual anesthetic or analgesic medications. However, delayed emergence can be secondary to unusual causes and present diagnostic dilemmas. Data from clinical studies is scarce and most available published material is comprised of case reports. In this review, we summarize and discuss less common and difficult to diagnose reasons for delayed emergence and present cases from our own experience or reference published case reports/case series. The goal is to draw attention to less common reasons for delayed emergence, identify patient populations that are potentially at risk and to help anesthesiologists identifying a possible cause why their patient is slow to wake up.
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1. Introduction

Delayed emergence—although in general a rare event—is a well known occurrence [1]. The low incidence complicates the design of meaningful clinical studies that could investigate potential mechanisms or clearly identify predisposing comorbidities or patient populations at risk. In addition, this low incidence also impedes the learning from personal experience. The lack of clinical studies makes it difficult to comprehend the complexity of this postoperative complication. Most published articles about delayed emergence are in the form of case reports or small case series which usually do not gain widespread distribution or attention. A potential "this could never happen to me" attitude of caregivers further facilitates negligence of this clinical problem. While we agree that there are obvious reasons for delayed emergence such as overdosing of narcotics or altered pharmacokinetics in elderly patients, most of us have had at least a few patients that were slow to wake up without any obvious reason. In this review, we want to shed light on some of the more uncommon reasons for delayed emergence. In particular we will discuss drug interactions, serotonin syndrome, postoperative delirium, central anticholinergic syndrome, psychiatric disorders, narcolepsy/sleep paralysis, surgical complications, and total spinal anesthesia.

1.1. Drug interactions

Elyassi et al [2] presented a case where a possible interaction between gabapentin and ketamine was the reason for delayed emergence. A 58-year-old man with chronic pain for cervical spinal stenosis was scheduled for cervical laminoplasty. At the end of the surgical procedure, the patient was breathing spontaneously but not responsive to

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verbal commands or noxious stimuli. After an extensive work-up, which included magnetic resonance imaging and angiography, a definitive organic cause for the patient's state could not be established. Since the patient had received anesthesia in the past without the use of ketamine, Elyassi et al concluded that the most likely explanation for the delayed emergence in their patient was a possible gabapentin/ketamine interaction. Their patient took 900 mg of gabapentin three times per day and received a total of 100 mg of ketamine intravenously for his surgery.

Weingarten et al presented a case of a 52-year-old woman that was – after an uneventful surgery – transferred to the recovery room where she was found to be sedated but arousable. One hour after arrival in the post-anesthesia care unit (PACU), however, she became unresponsive to tactile and painful stimuli. Flumazenil and naloxone were given without any improvement. Arterial blood gas, thyroid hormones, hemoglobin, and electrolytes were within normal limits. Starting five hours after the operation and in the following 12 hours her neurological status gradually improved. She did not have any recollection of what had happened. The patient had multiple procedures done under general anesthesia in the past with only one being complicated by a similar delayed emergence. Prior to her surgery she was seen by a psychiatrist who could not find any Axis I or Axis II *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses. Weingarten et al report that her preoperative medications included pregabalin, duloxetine, tramadol and acetaminophen/hydrocodone. In this patient a drug interaction cannot be ruled out.

The increasing age of patients undergoing surgery and their increasing complexity in terms of comorbidities and baseline medications should raise anesthesiologists' awareness of potential drug interactions in the perioperative period. One should also keep in mind that patients will not readily report the use of herbal medicine/dietary supplements unless they are specifically being asked for it. Since these substances also bear the potential for interacting with drugs given in the perioperative period [3–8] it is crucial to address this during the preoperative interview (see also section "Serotonin syndrome"). Both Valerian [4], commonly used for sleep disorders, and Kava [5], used as an herbal anxiolytic, can have sedative effects that can interfere with residual anesthetic effects in the immediate postoperative period potentially causing prolonged emergence from anesthesia. Raduege et al [5] have published an excellent article reviewing the anesthetic implications of kava medication.

1.2. Serotonin syndrome

Serotonin syndrome usually presents as a triad of neuromuscular abnormalities, autonomic hyperreactivity, and mental status changes. It usually occurs when 2 or more serotonergic agents are administered concomitantly, is typically diagnosed clinically and a high level of suspicion is warranted from clinicians. Table 1 summarizes drugs involved in the serotonin pathway. Severity of serotonin syndrome can be mild to severe. The severe form presents with muscle rigidity, hyperthermia and multi organ failure and thus shares features of malignant hyperthermia. The mild form presents usually with tachycardia, myoclonus, restlessness, dilated pupils, anxiety, and diaphoresis. Some of these symptoms are not uncommon in the immediate postoperative period and shared with other potential reasons for delayed emergence emphasizing the clinical dilemma anesthesiologist find themselves in when assessing these patients. Two diagnostic criteria are being used clinically to facilitate diagnosis of serotonin syndrome: Hunter's and Sternbach's toxicity criteria. Application in the immediate postoperative period is however limited. Wilson et al recently reviewed diagnosis and management of perioperative serotonin syndrome [10]. Rastogi et al have written an excellent review about possible opioid and serotonergic drug interactions [11] and their clinical implications.

Roy and Fortier [12] presented a case where a 41-year-old woman that had been taking venlafaxine, a serotonin norepinephrine reuptake inhibitor, exhibited profound muscle rigidity that was attributed to fentanyl but aggravated by venlafaxine. Duloxetine has been suggested as a potential risk factor for postoperative serotonin syndrome [13] as well. In this case report, a 68-year-old woman had to be re-intubated in PACU and transferred to the intensive care unit (ICU) secondary to confusion, agitation and not following verbal commands and eventually apnea. Gollapudy et al suggested that an interaction of fentanyl, which has serotonin reuptake inhibiting effects, ondansetron with its 5-HT_3 receptor blocking effects, and the co-medications of duloxetine, paroxetine, and bupropion with their selective serotonin reuptake inhibiting effects might have caused the serotonin syndrome in their patient. Fentanyl is a known to be a 5-HT_{1A} agonist, which augments serotonin release, and by weak serotonin reuptake inhibition, even further increases synaptic serotonin levels [11]. Other serotonergic opioids are tramadol, methadone, and fentanyl (Table 1). Interestingly, there is an increasing number of case reports about serotonin syndrome with concomitant use of oxycodone [14,15], which is not a phenylpiperidine opioid and should thus not interfere with serotonin reuptake [15,16]. For several reasons, such as lack of awareness among healthcare providers and also vague clinical symptoms, serotonin syndrome is difficult to diagnose in an awake patient and even more so in patients just waking up from anesthesia.

The increasing use of herbal medicine, and particular its popularity in the chronic pain population [17], might also present an easily overseen problem. St John's wort is used as an herbal anti-depressant, has been shown to inhibit serotonin, dopamine, and norepinephrine reuptake [18,19] and can thus lead to serotonin syndrome when combined with anesthetic drugs that increase serotonin release and/or further decrease its reuptake, which can present as delayed emergence [7]. Crowe and McKeating presented a case of a 21-year-old woman that received anesthesia for incision, drainage and marsupialization of a Bartholin abscess [6]. After an anesthesia that lasted approximately only 10 minutes and for which they

Table 1 Drugs and corresponding mechanisms associated with serotonin syndrome

Mechanism	Medication found in medical record	Substances not readily reported by patient	Medication given in the perioperative period
Increased release of serotonin	Levodopa Carbidopa-levodopa	Amphetamines and derivatives Cocaine MDMA (ecstasy)	
Impaired reuptake	SSRIs (citalopram, fluoxetine, sertraline etc.) SNRIs (duloxetine, venlafaxine etc.) Dopamine-norepinephrine reuptake inhibitors (bupropion) Serotonin modulators (nefazodone, trazodone etc.) TCAs (amitriptyline, clomipramine, desipramine etc.) Valproate Carbamazepine Methadone	Cocaine MDMA (ecstasy) St. John's wort Dextromethorphan	Meperidine Tramadol Pentazocine Metoclopramide 5-HT_3 receptor antagonists (ondansetron etc.)
Inhibited serotonin metabolism	Monoamine oxidase inhibitors (MAOIs (selegiline, moclobemide etc.)	Syrian rue (peganum harmala)	Linezolid Methylene blue
Direct serotonin agonist	Buspiron Triptans (sumatriptan etc.) Ergot derivatives	LSD (lysergic acid diethylamide)	Fentanyl
Increased sensitivity of postsynaptic receptors	Lithium		

Modified after [9]. SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants; MDMA, 3,4-methylenedioxy-methamphetamine.

administered fentanyl 1 μg/kg, propofol 3 mg/kg and maintained with sevoflurane and nitrous oxide with a FiO_2 of 0.5, their patient was still unresponsive to painful stimuli 30 minutes after conclusion of the procedure. The patient could not be discharged from the recovery room until 90 minutes after anesthesia. The most likely reason for the delayed emergence in their patient was reported to be St. John's Wort that the patient had been taking for her depression. Crowe and McKeating also point out in the discussion of their case report that St. John's Wort is prescripition controlled in Ireland since 2000, while it is still being considered a dietary supplement by the Food and Drug Administration in the United States [6].

1.3. Postoperative delirium

A recently published large prospective cohort study looked into morbidity and mortality found an incidence of postoperative delirium of 7.2 and 8.7% for patients undergoing elective and emergency procedures, respectively, with the highest incidence (28%) in patients undergoing emergency oncology spine procedures [20]. In contrast, delirium incidence after coronary artery bypass surgery is reported to be 5.8% [21]. Whether these differences are related to the procedures, different patient population or to different definitions of and assessments for delirium is unclear. One has to keep in mind though that the incidence of postoperative delirium is not well studied at all and is reported to range from 0 [22] to 40% [23]. The hypoactive subtype of delirium is particularly difficult to diagnose especially in the immediate postoperative period as it can easily be attributed to residual effects of anesthetic agents [24]. It has been shown that in patients after cardiac surgery, a pre-operative diagnosis of depression predicts development of hypoactive delirium with an Odds ratio of 3.57 [25]. This study also showed that hypoactive delirium is a strong predictor for longer ICU stay and prolonged mechanical ventilation. Unfortunately, it is difficult to assess for delirium in the immediate postoperative period in a non-ICU setting and there are no validated methods. Screening tools, such as the CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) have been shown to be of limited use in the PACU and were not sensitive enough to identify delirium post-operatively [26] when compared to a neuro-psychiatric examination. Obviously, a neuropsychiatric consult is not always readily available or helpful in determining a cause for delayed emergence. There is some evidence that haloperidol and neuroleptics might be helpful in preventing postoperative delirium [27,28] or reduce severity and duration [29]. The results of an ongoing multi-center, randomized, double-blind, placebo-controlled clinical trial designed to investigate early pharmacological

intervention to prevent delirium (HARPOON) [30] will hopefully clarify the role of haloperidol in this setting.

1.4. Central anticholinergic syndrome

Central anticholinergic syndrome is not usually considered a primary reason for delayed emergence because of the broad variety of neurological signs and symptoms, which can range from coma to agitation [31]. If it presents with depressed vigilance, it can again easily be mistaken as residual anesthetic effects, especially since most anesthetic drugs have been associated with the syndrome. The classic description of central anticholinergic syndrome is "red as a beet" (cutaneous vasodilation), "dry as abone" (anhidrosis), "hot as a hare" (anhidrotic hyperthermia), "blind as a bat" (mydriasis), "mad as a hatter" (delirium), and "full as a flask" (urinary retention). It is interesting that most patients with central anticholinergic syndrome in the immediate postoperative period present with central nervous system depression while those patients presenting to the emergency or psychiatry departments usually exhibited excitation or delirium [32]. Respiratory depression unrelated to opioid or muscle relaxant use can be present [33]. Link et al described that—unlike in the population presenting to the emergency department—in the immediate postoperative period peripheral signs of central anticholinergic syndrome, such as tachycardia, mydriasis, dry and warm skin, etc, can be decreased or non-existent making a clinical diagnosis more difficult [32]. A possible reason is the use of reversal agents (eg, neostigmine) that do not cross the blood-brain-barrier at the end of a surgical procedure [34]. Schneck et al [33] report that the incidence of central anticholinergic syndrome was the highest in women with a peak in the 40- to 50-year age group and particularly after hysterectomy. The agitated version of central anticholinergic syndrome was mostly observed in men under the age of 30 years. Schneck and colleagues also point out that, although use glycopyrrolate instead of atropine should theoretically decrease incidence of central anticholinergic syndrome, it can still occur.

Cohen et al presented a case of a 32-year-old otherwise healthy woman scheduled to undergo a dilation and evacuation for missed abortion under sedation [35]. She received a total of 2 mg of midazolam and 30 mg of propofol and did not regain consciousness 30 minutes after the end of the procedure. Five minutes after 2 mg of physostigmine, she regained consciousness, was fully alert, and was cooperative. The authors suspected midazolam triggered central anticholinergic syndrome.

At our institution we encountered a case of central anticholinergic syndrome precipitated by the administration of gylcopyrrolate. A 51-year-old man underwent thoracic laminectomy for placement of a spinal cord stimulator. The patient had a past medical history significant for obesity, chronic back pain, chronic abdominal pain secondary to pancreatitis, depression, anxiety and hypertension. Prior to admission medications included oxycodone, hydromorphone, methadone, gabapentin, lisinopril, metoprolol, and oxybutynin.

Preoperatively, the patient received 2 mg IV midazolam. Prior to induction he received 0.4 mg glycopyrrolate since it was noted that he was bradycardic. After induction (150 μg fentanyl, 150 mg propofol, 40 mg rocuronium), the patient was positioned prone. For maintenance of general anesthesia, 50% N_2O, 0.5% isoflurane and remifentanil (0.05-0.07 $\mu g\ kg^{-1}\ min^{-1}$) were utilized and an additional 100 μg fentanyl, 0.8 mg hydromorphone and 60 mg ketamine IV were administered over the course of the 3 hour case.

Upon completion of the operation, 3 mg neostigmine, 0.6 mg glycopyrrolate, and 4 mg ondansetron were administered. Upon tracheal extubation, it was noted that the patient was agitated, moving his extremities, trying to get up off the operating room table, intermittently following basic commands and not speaking. Two mg of midazolam were given and the patient was brought to the PACU. In the PACU, the patient was agitated, tachycardic, and hypertensive, but he maintained adequate oxygen saturations and his serum glucose level and arterial blood gas measurements were within normal limits. The patient received 1 mg physostigmine over the course of 2 minutes. Within 3 minutes of receiving this medication, the patient was conversant, following commands, and noted to be alert and oriented. He had no recollection of anything after receiving midazolam in the preoperative area.

It is interesting that this patient developed central anticholinergic syndrome, since he received glycopyrrolate to treat his baseline bradycardia and for reversal (along with neostigmine) of the non-depolarizing muscle relaxant. Glycopyrrolate as opposed to atropine does not cross the blood-brain barrier and therefore does not/is less likely to induce central anticholinergic syndrome. However, many other drugs such as benzodiazepines, halogenated inhaled anesthetics, opioids, and others have also been associated with and might have caused central anticholinergic syndrome in this patient [31].

1.5. Psychiatric disorders

Han et al [36] presented a case where a 42 year old woman developed quadriplegia and lower facial diplegia after spinal cord stimulator implantation. She was only able to open and blink her eyes. After an extensive workup which included an emergent computed tomographic (CT) scan of the head and spine, no organic cause was found to explain her postoperative condition. Therefore, this group concluded that their patient most likely suffered from a conversion disorder presenting as a locked-in syndrome. After a prolonged recovery and hospitalization of 2 days, she was discharged without sequelae. Conversion disorder is defined as neurological symptoms, such as paralysis, without a definable organic cause. Risk factors for conversion disorder include recent emotional trauma or stress and pre-existing mental health condition.

Locked-in syndrome is defined as a state where the patient is aware and awake but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles in the body except for the eyes. A postoperative conversion disorder can also present as a hysterical paralysis. Zhu et al [37] reported 2 cases of hysterical paralysis after spinal surgery. One patient completely recovered 1 hour after IV injection of placebo, the other patient was about to be transferred to the operating room for emergent evacuation of possible hematoma when his symptoms gradually resolved and the revision was cancelled. Zhu et al emphasize that whenever there is a clear discrepancy between objective findings and clinical presentation one has to keep psychological differential diagnoses on the work list.

At our institution we encountered a case of delayed emergence secondary to a presumed psychiatric disorder. A 50-year-old man, with a past medical history of chronic lower back and upper extremity joint pain, hypertension, posttraumatic stress disorder, obstructive sleep apnea with home continuous positive airway pressure device use, depression, cognitive dysfunction, and anxiety was scheduled for removal of spinal cord stimulator removal. Medications prior to admission included: oxycodone/acetaminophen, gabapentin, quetiapine, duloxetine, sulindac, hydrochlorothiazide, furosemide, tamsulosin, ipratropium bromide inhalation, and a lidocaine patch. The patient was given 2 mg of midazolam, 150 μg fentanyl, 300 mg propofol, and 150 mg succinylcholine for induction. Anesthesia was maintained with sevoflurane (1.5%) and a propofol infusion at 60 $\mu g\ kg^{-1}\ min^{-1}$.

The surgery was uneventful and approximately 90 minutes in duration. During the last 20 minutes, sevoflurane was titrated to off, but the patient was administered an additional 50 mg propofol IV because of bucking and movement of all four extremities. At the end of surgery, the propofol infusion was discontinued, and 15 minutes later the patient began to have spontaneous respirations with a rate of 20 breaths/min and tidal volumes of 550 mL. The patient did not regain consciousness after 20 minutes of undetectable levels of expired sevoflurane. The patient was found to have dilated pupils to 5 mm bilaterally, reactive to light, and without movement. At this point, 4 mg physostigmine was given in divided doses of 2 mg 10 minutes apart. After administration of this medication, the patient appeared to make attempts to open his eyes, but was still unable to follow commands or move any of his extremities. Finger-stick blood glucose was 137 mg/dL. The patient was then given 0.2 mg flumazenil followed by an additional 0.2 and 0.1 mg after no change in the patient's condition was noted. Over the next 20 minutes, the patient began to open his eyes and was able to follow commands to track with his eyes bilaterally and was also able to respond to questions in a binary fashion with eye blinks. He was still unable to move any of his four extremities and was unresponsive to noxious stimuli. Plans were made to have the patient transferred from the operating room to radiology for emergent CT and magnetic resonance imaging head imaging, however, prior to transfer the patient began to be able to protrude his tongue and move it in different directions to command, followed by initially slight thumb and great toe movements bilaterally. Ninety minutes after stopping the patient's propofol infusion and 170 minutes after his last dose of succinylcholine the patient was able to demonstrate 3/5 strength in his upper and lower extremities to flexion and extension. He continued to draw adequate tidal volumes with oxygen saturations of 100% based on pulse oximetry throughout and was finally extubated and taken to the ICU for close monitoring.

The patient was reassessed upon arriving to the ICU and had 4/5 strength in his upper and lower extremities bilaterally and 5/5 strength 5 hours post-extubation. After questioning, the patient denied any recall of the events in the operating room. Pseudocholinesterase level was found to be 4986 IU/L (normal range: 2900-7100 IU/L). The patient was discharged home on post-operative day 1 without any sequelae.

We believe that our patient suffered from conversion disorder presenting as a locked-in syndrome similar to the patient presented by Han et al [36]. We initially suspected central anticholinergic syndrome (dilated pupils) and hence gave a probative dose of physostigmine. The initial improvement in our patient's condition was most likely secondary to a non-specific arousal effect of physostigmine [33]. Since this arousal reaction only lasted for a few minutes, we had excluded central anticholinergic syndrome as the possible reason for the delayed emergence in this patient and continued to search for other reasons.

1.6. Narcolepsy/sleep paralysis

Another possible reason for complicated emergence is undiagnosed narcolepsy/sleep paralysis. Spector and Bourke [38] report a case where they successfully treated a patient with a postoperative episode of sleep paralysis with physostigmine. Their patient presented with "glass eye stare, unresponsive to verbal commands or noxious stimuli and with alternating patterns of apnea, tachypnea and sighs without any mechanical airway obstruction". This patient had recurrent episodes of sleep paralysis in the past and her husband, who was a physician, could clearly tell that his wife suffered from another attack. Little is known about sleep paralysis. It seems to be associated with narcolepsy, however not with other psychiatric comorbidities such as depression or anxiety. Mesa et al [39] reported of a patient with narcolepsy that had suffered from delayed emergence on several occasions in the past. They provided anesthesia without the use of benzodiazepines for premedication and they did also not administer any opioid analgesics. Anesthesia was induced with propofol and maintained with propofol and nitrous oxide (70%). The patient stayed in PACU for 1 hour after excision of a thigh mass compared to her previous PACU stays of 8 to 10 hours after a vaginal hysterectomy and a bilateral breast reduction, respectively. Administration of physostigmine lead to rapid improvement of the neurological state of our first but not of the

Table 2 Risk factors/symptoms and treatment for reasons for delayed emergence

	Risk factors/symptoms	Management
Drug interaction	Multiple co-morbidities/medications/dietary supplements Use of multiple anesthetic agents (eg, ketamine + opioids)	Consider naloxone +/− flumazenil
Serotonin syndrome	Parkinson's disease (levodopa) SSRIs SNRIs Triptans TCAs Lithium Methadone MAO inhibitors Methylene blue, linezolid, fentanyl (see Table 1)	Discontinue serotonergic agents Sedation (benzodiazepines) Consider serotonin antagonists (eg, chlorpromazine)
Postoperative delirium	Age Type of surgery Temperature derangements Withdrawal symptoms Pain Daylight deprivation ... [24]	Sedation, if agitated Consider psychiatric consult Consider haloperidol
Central anticholinergic syndrome	Reversal of muscle paralysis Atropine scopolamine Antihistamines (promethazine) TCAs (amitriptyline) Sleep aids (doxylamine) Neuroleptics (chlorpromazine) Eye drops (cyclopentolate)	Physostigmine (beware of relapse, multiple doses may be required)
Psychiatric disorder	Psychiatric co-morbidities	Psychiatric consult
Narcolepsy/Sleep paralysis	History of narcolepsy/sleep paralysis	Physostigmine? Avoid/limit perioperative use of benzodiazepines/opioids?
Surgical complication Total spinal anesthesia	Type of surgery Hypotension Dilated pupils	Surgical consult Sedation Re-intubation

MAO, monoamine oxidase.

second patient. It is unclear how one can clearly differentiate between central anticholinergic syndrome and undiagnosed narcolepsy/sleep paralysis, but a detailed preoperative medical and psychiatric assessment should be performed.

1.7. Surgical complications

Surgical complication should be considered in a patient with complicated emergence. It has been suggested that spinal cord ischemia induced by vasospasm secondary to painful stimuli within or near the spinal cord [40] can lead to temporary paralysis. Significant intra- or postoperative loss of cerebrospinal fluid is the proposed mechanism for remote cerebellar hemorrhage which can present with seizures and delayed emergence [41–43]. However, spontaneous intracranial epidural [44,45] and subdural [46] hematomas after spine surgery have also been reported. Epidural hematoma can occur as late as 72 hours after electrode implantation [47]. It is important to be aware of these potential complications since the clinical presentation of both intracranial epidural and intracranial subdural hematomas, as a surgical complication, is usually headache which can easily be misconceived as a post-dural puncture headache secondary to a dural tear. While these complications might be more obvious after surgery involving the central nervous system, there are also case reports for intracranial hemorrhage after cochlear implantation [48].

Regional anesthesia techniques performed by anesthesiologists or surgeons can also lead to neurological changes which might be difficult to diagnose especially when general anesthesia is provided in combination with these techniques. Brookshire et al and others [49,50] have reported the well-known yet rare brainstem anesthesia as a complication of retrobulbar block. Dukes and colleagues [51] report a patient that presented with a locked-in syndrome after stellate ganglion block. Shortly after injecting bupivacaine their patient became unresponsive and apneic but did still blink her eyes while being mask ventilated. Five minutes after the

event, the patient regained consciousness and was able to move all four extremities. She had no memory of the incident.

Turley et al [52] present a case of a patient that regained consciousness after shoulder surgery, was extubated, coughed vigorously and then became unconscious again. He had to be re-intubated and transferred to the intensive care unit. All immediate diagnostic efforts (blood tests for metabolic or glycemic disturbances, CT scan of the head, and 12-lead electrocardiogram) did not establish a reason for his decline in neurological status after initial extubation, but he was extubated in the ICU the next day without any neurological compromise. A neurological consult suggested the clinical diagnosis of an ischemic brainstem event and the patient was further evaluated. A large patent foramen ovale with right-to-left shunt even without provocative testing (eg, coughing) was detected on transthoracic ultrasound and thus a paradoxical embolus seemed to be the most likely reason for the neurological deterioration in the immediate postoperative period.

Another possible reason for delayed emergence is transurethral resection syndrome. Although it is a well-known complication after transurethral prostate resection, it occurs less frequently but is not yet obsolete [53]. Risk factors include duration of operation, weight of resected mass, and type of irrigation fluid [9]. The underlying pathophysiology is hyponatremia leading to nausea, restlessness, confusion, or even coma secondary to absorption of irrigation fluid via the venous plexus.

1.8. Complications of regional anesthesia

Another possibility for delayed emergence with neurological symptoms such as paralysis is total spinal anesthesia. There are reports where patients were hypotensive, slow to wake up, showed complete paralysis and little to no breathing effort [54,55] after thoracic procedures. Chaudri et al [54] report a patient that failed to wake up after thoracotomy and had fixed and dilated pupils, complete paralysis, and made no respiratory effort. He was sedated and taken to the ICU where he required colloid and norepinephrine infusions for persistent hypotension. Twelve hours after conclusion of the surgery the patient was extubated and had no neurological sequelae. Accidental intrathecal administration of the local anesthetic during intracostal block was identified as the most likely reason for the delayed emergence.

Lekhak et al [56] report a case where a patient that had undergone thoracotomy became severely hypotensive after administering 20 ml of bupivacaine 0.25% through a previously placed paravertebral catheter. She was kept intubated and transferred to the ICU where she was extubated about one hour later. Two hours after the procedure she complained about pain at her thoracotomy site and her paravertebral catheter was bloused with 10 ml of bupivacaine 0.25%. Following immediate pain relief, she became unresponsive with fixed dilated pupils and apneic requiring endotracheal intubation again. This case highlights the difficulty of diagnosing a definite reason for delayed emergence in the immediate postoperative period. While the diagnosis was clear after the second incident it was less so in an anesthetized patient just waking up from anesthesia and the disturbing environment at the conclusion of surgery.

It is important to notice that the clinical symptoms that all of these cases had in common were severe hypotension and dilated pupils.

In conclusion, we have outlined the many factors, some known and some less known that may lead to a delayed emergence. This is by no means a complete list of all potential reasons for delayed emergence but will hopefully help anesthesiologists in making better informed clinical decisions as to why their patient might be slow to wake up. In any case, a high clinical suspicion is necessary and presentations are usually not textbook-like which makes it all the more difficult to diagnose potential reasons. Table 2 summarizes risk factors, clinical features and treatment options for the discussed causes for delayed emergence.

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