Online Case Report

Prolonged postoperative altered mental status after methylene blue infusion during parathyroidectomy: a case report and review of the literature

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Methylene blue (5 mg/kg) is routinely given at our institution during parathyroidectomy. The dye stains the parathyroid glands and helps in better surgical visualisation. The technique is generally considered to be safe except for causing pseudo-cyanosis. We report a case of a patient who had confusion, agitation and altered mental status during the early postoperative course probably secondary to methylene blue infusion.

Keywords: Methylene blue – Parathyroidectomy – Confusion – Agitation

Methylene blue (5 mg/kg) is routinely given at our institution during parathyroidectomy. The dye stains the parathyroid glands and helps in better surgical visualisation. The technique is generally considered to be safe¹ except for causing pseudo-cyanosis. We report a case of a patient who had confusion, agitation and altered mental status during the early postoperative course probably secondary to methylene blue infusion.

Case report

A 66-year-old woman (weight 74 kg) underwent right inferior parathyroidectomy for sporadic primary hyperparathyroidism. She had previous general anaesthesia for carpal tunnel release and excision of benign breast lump without any undue consequences. There was no past history of hypertension, alcoholism nor diabetes mellitus. She had history of depression with anxiety and fibromyalgia. Her medication included clomipramine 50 mg at night and alverine citrate 60 mg three times a day.

She had no pre-medication. Anaesthetic induction was carried out with Fentanyl, Propofol and Vecuronium. Anaesthesia was maintained with nitrous oxide and Isoflurane. During the case, she received 1000 ml of normal saline. An intravenous infusion of methylene blue of 370 mg in 500 ml of glucose 5% was started 1 h before surgery and continued during surgery. At the end of the case, the patient was given neostigmine 2.5 mg, with glycopyrrolate 0.5 mg and dolagestron 12.5 mg. She was slow to awake and breathe and it was thought that she might be sensitive to opiates; therefore, naloxone was given and she was extubated in recovery. After extubation, she was confused but able to communicate. She was agitated and making inappropriate and jerky movement of all four limbs. Her vital signs were normal and there was no focal neurological deficit. She was maintaining her airway and O₂ saturation was 99%. Her blood glucose, urea, electrolytes, and serum calcium were normal. Arterial blood gas was normal with PO₂ of 11 kPa. The patient was transferred to the ward although she remained agitated and confused for 2 days

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and then gradually improved in the next 2 days to her pre-operative mental level. During her stay in the ward, her methaemoglobin level was 0.5% (normal < 7%). CT brain carried out 24 hours after surgery was normal. She was discharged without further complication. Her thyroid function tests (TFTs) were deranged TSH < 0.05 mU/l (normal, 0.4–5.5 mU/l), free T4 47.8 pmol/l (normal, 11–26 pmol/l) and free T3 13.4 pmol/l (normal, 3–6 pmol/l). TFTs were back to normal when she was seen in clinic a week later. Histology confirmed a parathyroid adenoma.

Discussion

There have been two other reports of mental toxicity of methylene blue after parathyroidectomy in the literature. Martindale *et al.*² reported a patient who had rotational nystagmus and dilated pupils unreactive to light in the recovery. Thirty minutes later, the patient displayed rigid, jerky movements of all four limbs and remained very agitated for the subsequent 2 h with fluctuating Glasgow Coma Scale (GCS) of 7–10. Arterial blood gases demonstrated respiratory acidosis and the patient was re-intubated. The speech and the neurological status returned to normal in 2 days.

Bach *et al.*³ reported that their patient had marked aphasia in the recovery. In the next few hours, the aphasia improved, but the patient's speech remained slow and he was not oriented to time and place. The patient remained calm and pleasant throughout his hospital course. His mentation returned to normal after 2 days.

Our patient was agitated and confused for 2 days. Her speech was slow. She also had inappropriate rigid, jerky movements of all four limbs similar to the patient reported by Martindale *et al.* She returned to normal mental status in 4 days.

In all three cases, the implication of methylene blue toxicity was made by exclusion and by the prolonged time course of its resolution. There was acute onset of symptoms noted in the recovery and the time course of altered mental state and recovery to normal mentation of 2–4 days was similar in all three cases, which are similar to the length of time of urinary excretion of methylene blue.

All three patients had history of anxiety and depression. Patients reported by Martindale *et al.*² and Bach *et al.*³ were on Fluoxetine and Paroxetine, respectively. Both of these medicines are selective serotonin re-uptake inhibitors (SSRIs). Siebert *et al.*⁴ raised the possibility that the altered mental status of the patient reported by Bach *et al.*³ might be due to the fact that the patient was given intra-operatively the serotonin antagonist ondansetron with the selective serotonin re-uptake inhibitor paroxetine. Paroxetine is known to inhibit CYP2D6 (cytochrome P450 system), which vice versa provides for ondansetron degradation. A similar case was published by Stanford⁵ of postoperative

disorientation in a patient who had received paroxetine pre-operatively and ondansetron, but not methylene blue, intra-operatively. Siebert *et al.*⁴ suggested that this patient's postoperative disorientation might have been induced subsequent to a significant impairment of serotonin regulation, including a history of other serotonin-associated mental disorders (*e.g.* anxiety, depression). Our patient was on Clomipramine, which has antimuscarinic activity. It is unlikely that there was impairment of serotonin regulation leading to disorientation.

Despite innocuous use of intravenous methylene blue, it has definite toxic effects. Nadler *et al.*⁶ found that intravenous methylene blue excited the individual, and by its rapid elimination into the stomach and urine produced transitory gastrointestinal and urinary irritation. The most frequent toxic symptoms observed were restlessness, paraesthesia, burning sensation and chest pain, all of which subsided in 24–48 h. A number of individuals also complained of dizziness, headache and mental confusion, all of which completely resolved.

The mechanism of neurotoxicity by methylene blue is unclear. The chemical structure of methylene blue (tetramethylthionine) resembles that of phenothiazines and there may be a direct central mechanism of methylene blue neurotoxicity. In the past few years, the use of Fluoxetine and Paroxetine antidepressants has increased. These are selective serotonin re-uptake inhibitors (SSRIs). An adverse drug interaction between methylene blue and SSRIs cannot, therefore, be excluded. Methylene blue inhibits guanylate cyclase thereby inhibiting nitric oxide (NO) production.⁷ In animal studies, methylene blue has direct inhibitory effect on both constitutive and inducible forms of nitric oxide synthase. NO plays an important neuroregulatory role in striatal dopaminergic function; therefore, methylene blue may cause symptoms due to tardive dyskinesia.⁸

We are more confident in reporting the altered mental state due to methylene blue toxicity as our patient was not diabetic and the methaemoglobin level was normal, while methaemoglobin level was not done in the Bach *et al.*³ report and their patient had diabetes mellitus and was on metformin. Methaemoglobin level was normal in the patient reported by Martindale *et al.*² Our patient had altered mental state despite receiving low dose (5 mg/kg) of methylene blue infusion as compare to 7.5 mg/kg by Bach *et al.*³ and Martindale *et al.*²

Our patient was noted to have biochemical thyrotoxicity 5 days after surgery. We cannot explain this finding. The surgery was very straightforward, with immediate identification of parathyroid adenoma and minimal dissection. There was no antecedent history of thyroid disease and pre-operative TSH was 2.2 mU/l (normal, 0.4–5.5 mU/l) and the toxicity resolved rapidly without treatment in a week. Handling of the thyroid might be implicated in rapid release of pre-formed

thyroid hormones, but any handling was minimal in this case. We do not routinely measure thyroid hormones after parathyroid surgery: We suppose it is possible that they routinely go up and we are unaware. It is unlikely that elevated TFTs could have caused confusion as the patient recovered and went home despite elevated TFTs and they returned to normal in a week. There is no mention of TFTs in the reports of Bach *et al.*³ and Martindale *et al.*²

The UK National Poison Information Service Centre recommended an intravenous dose of methylene blue not exceeding 4 mg/kg using a 1% solution. In the meantime, we had two other patients who received methylene blue during parathyroidectomy at a dose of 5 mg/kg and both manifested similar signs of neurotoxicity. One of these patients was on Fluoxetine. Diagnosis of methylene blue toxicity was made by exclusion and both patients recovered in 3–4 days. Following these cases, we have altered our practice and reduced the dose of methylene blue to 3 mg/kg. This low dose is still adequate to stain the parathyroid, though the intensity of staining is definitely less; however, results have not been affected.

Conclusions

The use of methylene blue is considered safe and innocuous during parathyroidectomy but there are case reports of its effect on mental status and this should be considered in patients who subsequently manifest an unusual emergence from anaesthesia. Methylene blue neurotoxicity was reported previously with high dose of

7.5 mg/kg. It can happen at low dose of 5 mg/kg as well. The dose should not exceed 4 mg/kg as recommended by UK National Poisons Information Service Centre. The altered mental status due to methylene blue is reversible within 2–4 days. There is no case report so far indicating permanent neurological damage.

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