Perioperative challenges in a primary hyperparathyroid patient with osteitis fibrosa cystic and borderline QTc: a case-based review and practice analysis

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ABSTRACT

Introduction: Perioperative care of primary hyperparathyroidism patients is a significant challenge. The challenge increases when the preoperative optimization of the patient is suboptimal due to any reason. Concomitant complications like osteitis fibrosa cystic, renal involvement, and multiple electrolyte abnormalities predispose these patients towards multiple morbidities and even mortality during the perioperative period. It is known that the hypercalcemia causes shortened QT, and the inhalational and intravenous anesthesia drug-induced QT prolongation is likely to be buffered. On the other hand, prolonged QTc in primary hyperparathyroid patients in the presence of hypercalcemia is more uncommon, but an extremely challenging situation for anesthesiologists as these patients are more prone to torsadogenesity.

Materials and methods: A case-based review is presented in this paper. To review the current practice and opinions, we searched PubMed and Google Scholar using the advanced search engine with the combination index words of primary hyper-parathyroidism, anesthesia, anaesthesia, anesthesia management, and anaesthesia management with a time frame of January 1, 2000, to August 30, 2018.

Results: The results are enumerated in the text. Although anesthetic management of primary hyperparathyroid patients is available in the literature, anesthetic management of primary hyperparathyroid patients with prolonged or borderline QTc is not well described. In this paper, we present a case that was successfully managed using Desflurane based minimal flow anesthesia, which is probably also the first of such.

Conclusion: Balanced anesthesia with Propofol induction and modern inhalational agents for maintenance and non-depolarizing neuromuscular blockade appears to be safe method of anesthesia.

Keywords: Primary hyperparathyroid, severe hypercalcemia, torsade de pointes, Desflurane, anesthesia

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INTRODUCTION

Primary hyperparathyroidism (PHT) is relatively rare; parathyroid adenoma is one of the causes. Even with early diagnosis, PHT usually presents with multiple co-morbidities [1]. Mortality in PHT is also high i.e. 7.4% [2]. Hypercalcemia is invariably associated with PHT, and generally, the shortened QT interval is the reliable finding in hypercalcemia patients [3]. Prolonged QTc in patients with PHT, along with hypercalcemia, is far more uncommon and rarely described [4]. These facts make these rare patients even more challenging cases for anesthesiologists during the perioperative period. Preoperative optimization is always desirable before taking up such cases, [5] but may not always be possible. Although many cases are done under local anesthesia or regional blocks, the requirement of general anesthesia (GA) is still very much there. However, choosing anesthetic drugs and using inhalational anesthetic agents that can prolong QTc in already a hypercalcemic patient for such cases is a big dilemma [6]. Moreover, there are no data to suggest one technically superior to the other [7].

We present a context case which was successfully managed using Desflurane based minimal flow anesthesia, which is probably also the first of such. We have also searched and accessed the literature related to the current practice from PubMed and Google Scholar; reviewed and enumerated the techniques so that a better decision can be taken while managing such rare cases.

CASE REPORT

A 28 years-old female, 35 kg (body mass index 14.6 Kg/m^2), presented with complaints of pain in both upper and lower limbs for 6-month. Over the period, she also became weak, suffered spontaneous fractures of the left tibia and right humerus, which disabled her from standing and walking. Her laboratory investigation reported parathyroid hormone (PTH) 742.6 pg/ml, calcium 18.1 mg/dl, and ALP 913 IU/L. Fractures were treated with immobilization with Plaster of Paris cast application and were shifted to our hospital for further management. Her heart rate was 119/min, blood pressure 110/78 mmHg, and respiratory rate 20 / min at rest. She was also diagnosed as hypothyroidism and was started on 50 mcg thyroxine once daily. She was also on tab metoprolol 12.5 mg once daily. The modified Mallapati grading was 2, and there was having slight neck pain with unknown levels of neck movement. A nodule, measuring approx. 1.5 x 2 cm^2 in size was present on the right side of the neck without any sign and symptoms of tracheal involvement. A subsequent parathyroid scan revealed to have a right inferior parathyroid adenoma, and the USG neck reported a well-defined hypoechoic lesion in the right inferior parathyroid without any calcification. She was also found to have bilateral medical renal disease grade III with serum albumin and urine creatinine ratio 543.57 and positive urine microalbuminuria. A diagnosis of primary hyperparathyroidism with osteitis fibrosa cystica was made and planned for right parathyroidectomy.

Preoperatively, she was having serum phosphate of 5.8 mg/dl, magnesium 1.2 mg/dl, T4 - 2.19 ug/dl and TSH and T3 within normal limits. Her s. creatinine was 0.78; eGFR 59.33 ml/min/1.73m^2. She was also anemic (Hb 10.7 gm%). Preoperative treatment with diuretic, saline, zoledronic acid 40 mg, tab. $MgSO_4$ 200 mg twice daily, cholecalciferol 2000 units daily was started, but calcium level only reduced to 15.3 mg/dl over the next ten days. Meanwhile, she also developed a spontaneous fracture of the right clavicle and a hairline fracture of the mandible. So, she was taken up for surgery with an American Society of Anesthesiologists physical status IV on an urgent basis.

Along with pulse oximetry, non-invasive BP, five lead ECG, temperature; neuromuscular block, and anesthesia gas monitoring were used. She was premedicated with Inj. Midazolam 1mg and Inj. Nalbuphine 4 mg. GA was induced with inj. Propofol 60 mg and Desflurane in O2 + N_2O. Inj. Vecuronium 3 mg was used as a muscle relaxant, and the trachea was intubated by the experienced anesthesiologist using conventional direct laryngoscopy without extension of the neck. The anesthesia was maintained Desflurane in O_2 + N_2O with titrated MACage of 1.1 to 1.2 using Mindray A7 anesthetic workstation. Intraoperatively injection Vecuronium 1 mg was repeated with TOF count 2, and Paracetamol infusion 550 mg was given. Patients' hemodynamics and electro cardiac activity were very stable throughout. At the end of the uneventful three-hour intraoperative period, bilateral superficial cervical plexus block was performed using 0.2 % Ropivacaine with 30 mg total dose; the neuromuscular blockade was reversed, and the trachea was extubated. The patient was shifted to surgical intensive care for close further monitoring and management.

Postoperatively, she developed hypo-calcemic features on the very first post-op day despite a serum calcium level of 11.0 mg/dl. Oral Calcium with Vit D was supplemented; her serum calcium level reached normal by the fourth postoperative day.

She was pain-free for the first 24 hours, followed by pain was under control (NRS 2/10) with paracetamol only.

Perioperative anesthetic challenges

Surgical resection as a treatment for parathyroid adenoma causing PHT is nearly a century old [8]. Yet, the perioperative management of such patients, especially anesthetic management, has remained a big challenge. This is because of the involvement of multiple organ systems, including cardiovascular and renal, multiple electrolyte abnormalities, etc. [9]. In the present context case, preoperative optimization was not achieved even with in-patient treatment for ten days, and the numbers of pathological fractures were increasing day after day. She was even bedridden, which also was increasing the chance of bedsore, thromboembolism, etc.

The challenges in this context case were multitudinous. Multiple pathological bony fractures, including clavicle, made the patient transfer from bed to OR table and back challenging. She was also complaining of neck pain with an unknown level of permitted flexion-extension, which made again positioning and airway management a concern.

She was grossly malnourished.

Another study found prolonged and significantly higher QT interval (mean $\pm$ standard deviation 451 ± 38.6 ms vs. 435 ± 29.8 ms; $p < 0.001$) in patients with elevated PTH levels. The authors found elevated PTH is associated with longer corrected QT intervals independent of serum calcium concentration in acute coronary syndrome survivors [11]. Therefore, although the context patient had shortened QT (322 mSec), the QTc of 448 mSec was also a concern in choosing the induction and maintenance agent.

Although unusual, prolonged QT/QTc interval is reported in severe hypercalcemia in patients with primary hyperparathyroidism [4]. The authors concluded that the concomitant hypokalemia and hypomagnesemia might be the contributing factors. The context case was also having concomitant hypokalemia and hypomagnesemia. Abnormal calcium and magnesium homeostasis are also concern about neuromuscular drug use and reversal. Opioid analgesia is also a concern for postoperative respiratory status as such patients are often bedridden and weak. All these challenges were present in the context case too.

Multiple dyselectrolytemia (hypercalcemia, hypomagnesemia, hyperphosphatemia, mild hypokalemia, and hyponatremia) were also present, which made anesthetic management challenging.

Hypercalcemia is generally associated with shortened QT and QTc, and this electrocardiogram feature has been shown as highly specific and reliable [3]. Many anesthetic drugs, including commonly used modern inhalational anesthetic agents, cause prolongation of QT. So, from a general viewpoint, it appears that the effect of anesthetic agents may be buffering.

However, the scenario is not always the same. Patients with PHT have been shown to have prolonged QT interval as compared to age, body weight, and cardiovascular risk-matched controls. [10].

Literature search

To review the current practice and opinions, we first searched PubMed using the advanced search engine with the following index words and combinations in the title:

a. ("primary hyperparathyroidism"[Title]) AND "anaesthetic management" - 2 results, both case report [12,13].
b. ("primary hyperparathyroidism"[Title]) AND "anesthetic management" – 2 articles; one case and one review [5,14].
c. ("primary hyperparathyroidism"[Title]) AND "anaesthesia" – resulted in three relevant original articles [15,16,17].
d. As there was limited literature yield from our search, we also search in Google with "Anaesthetic management of primary hyperparathyroid patient", "Anesthetic management of primary hyperparathyroid patient" and found four more suitable articles; three case reports and one retrospective study [18- 21].

The combined results are enumerated in table 1. The searches were done on August 30, 2018, and only recent literature (literature of 2000 and afterward), published in English were considered.

Table 1. Systematic search results and their description

Authors (year)	Article	Induction	Maintenance	Muscle relaxant	Reversal	Others
Anwar-ul-Huda et al (2012) [8]	Case report	Sevoflurane + Fentanyl	Isoflurane + N_2O + O_2	Atracurium	Neostigmine + Atropine	
Chopra P et al (2009) [9]	Case report	Morphine + Thiopentone	Isoflurane + N_2O + O_2	Vecuronium		
Zeng H et al (2017) [10]	Case report	Propofol + Sufentanil	Sevoflurane + Remifentanil+ O_2	Atracurium	Not available	Incision site Ropivacaine infiltration
Baswa SJ, et al. (2013) [3]	Review	Not described in exact points. But indicates towards TIVA as a better option				
Melfa GI, et al. (2016) [11]	Original article	Did not mention anesthetic procedure in details. The paper just mentioned that cases were done under local anesthesia and General anesthesia				
Bergenfelz A, et al. (2005) [12]	Original article	Did not mention anesthetic procedure in details. The paper just mentioned that cases were done under local anesthesia and General anesthesia				
Rubello D, et al (2004) [13]	Original article	Did not mention anesthetic procedure in details. The paper just mentioned that cases were done under local anesthesia and General anesthesia				
Gupta B et al (2017) [14]	Case report	TIVA (Fentanyl, Propofol, Atracurium			Neostigmine + Glycopyrrolate	Dexmedeto-medine
Kumar V et al (2016) [15]	Case report (3 cases)	Fentanyl + Propofol /	Isoflurane + N_2O + O_2	Vecuronium	Neostigmine + Glycopyrrolate	
Koirala S et al (2015) [16]	Case report	Fentanyl + Propofol /	Isoflurane + O_2	Rocuronium	? Neostigmine + Glycopyrrolate	Dexmedetomedi ne
Corneci M, et al. (2012) [17]	Retrospe ctive study	Midazolam, Ketamine, Thiopentone, Propofol, Fentanyl, TIVA as well as Isoflurane / Sevoflurane		Rocuronium	Information not available	Regional anesthesia

DISCUSSION

Literature indicates that thiopentone and modern inhalational anesthetic agents are associated with prolongation of QTc, which may lead to ventricular arrhythmia or even torsades de pointes in such patients [22]. Many of the cases are done with total intravenous anesthesia (TIVA), and review literature also indicate so [1,18]. But, TIVA may not be well always available. Moreover, in patients with gross pan dyselectrolytemia and malnutrition, how the anesthetic agents, especially intravenous agents, will behave is uncertain. Accurate plasma concentration may not be represented by the TIVA, and therefore depth monitoring will require some additional monitoring like BIS or Entropy. Opioid use in such patients, even for short-acting opioids for longer duration can also be problematic as it can accumulate to give prolonged half-life (e.g., Fentanyl and context-sensitive halftime) and postoperative respiratory depression as well as nausea and vomiting. A patient with neck pain with fragile bones

is not a good candidate to take a chance for nausea and vomiting. Whereas drugs like Alfentanil, sufentanil are not widely available. Sufentanil is also implicated in torsadogenesity [22]. Although Sevoflurane and Desflurane are equally implicated in prolonged QTc, it is believed that Sevoflurane will be relatively safe as it is not associated with QT dispersion [22,23]. Sevoflurane use is also not without concern as Sevoflurane is implicated as causative of acute kidney injury [24]. In the context case, too, therefore, was planned to manage with low dose Nalbuphine (with the intention to have a relatively longer effect yet with less respiratory depression), Propofol and Desflurane based minimal flow anesthesia where MACage was monitored closely. Succinyl Choline was avoided to avoid fasciculation; it is also implicated to prolong QTc [22]. The neuromuscular blockade was maintained using Vecuronium guided by TOF monitoring. Interestingly, the patient required vecuronium top up every 40 – 45 minutes. The minimization of shifting was done by shifting the patient from ICU bed to OR table and back directly. The intraoperative period was absolutely stable, with no changes in QT, ST segments, and postoperatively too. Although both Sevoflurane and Desflurane is implicated with prolonged QTc, Propofol is shown to counteract this effect at induction [25,26]. The analgesia planed was also multimodal with paracetamol and bilateral superficial cervical plexus block with Ropivacaine 0.2%; the patient was having NRS pain of < 3 till 36 hours postoperative. Commonly used local anesthetics; Lignocaine, Bupivacaine, Ropivacaine, Levobupivacaine has been found to be safe to be used in such patients as well as the effect on QTc. [22,27,28]

Postoperative complications like hypocalcemia and associated symptoms, hungry bone syndrome (HBS), etc. also need special attention and management. In patients with severe primary hyperparathyroidism and preoperative high bone turnover, the development of profound, rapid, and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesemia is referred to as HBS. Following parathyroidectomy, this gets exacerbated by suppressing PTH levels [29]. A study has shown that these patients can be predicted to some extent in the preoperative period. The postoperative hypocalcemia was found to be higher in patients who underwent parathyroidectomy for primary hyperparathyroidism, had parathyroid hyperplasia, and osteoporosis. Patients with higher preoperative PTH, ALP, and blood urea nitrogen values, osteoporosis, and parathyroid hyperplasia had more HBS. Simultaneously thyroidectomy with parathyroidectomy also predisposes such patients to HBS [30]. Therefore preoperative assessment and risk stratification should take these into considerations.

The context case was successfully managed, and such a case can even be managed by other methods. Although Propofol and TIVA are considered better, the successful use of inhalational agents like Isoflurane and thiopentone group of drugs are also reported [13,19]. Minimally invasive parathyroidectomy and minimally invasive video-assisted parathyroidectomy are done under local anesthesia, too, but need a strict selection of patients [15-17]. The conversion rate to GA is also high (i.e., 11%) [31,32]. However, we believe the successful use of Desflurane based minimal flow anesthesia with absolute hemodynamic stability, better recovery, and no evidence of QTc prolongation even in patients with uncontrolled hypercalcemia with borderline preoperative QTc is a notable finding. As the depth (MAC) monitoring of inhalational anesthesia is relatively widely available, the safer desflurane anesthesia may be a better method in many such patients. However, multiple reports/series of such cases or even comparisons will be required in the future to recommend this as the better / alternative method.

Summary of the current practice and opinion

Perioperative management of primary hyperparathyroid patients is still challenging, and the dilemma still persists on choosing anesthetic drugs and techniques. Local or regional anesthesia, TIVA, and even modern volatile agent-based balanced anesthesia can be safely used. From the above search and literature review, the following anesthetic management plan can be considered.

- A properly selected and localized case planned for minimally invasive parathyroidectomy can be done under local anesthesia (e.g., bilateral cervical plexus block). Commonly used local anesthetics are safe
- Conventional surgeries or surgeries, along with thyroidectomy, usually need general anesthesia.
- Propofol induction appears to be safer. Thiopentone is better avoided
- Although all modern volatile anesthetics have been implicated in increasing QTc; they can be safely used in the therapeutic range. However, Propofol induction before inhalational agent use appears to be an essential step.
- Atracurium, Vecuronium, Rocuronium appears to be safe. Succinyl Choline is better avoided.

- Neuromuscular monitoring is essential in such patients, along with judicious use and choice of drugs.
- Reversal with Neostigmine has not been reported to be unsafe.
- Multimodal analgesia, preferably opioid-free anesthesia and analgesia, is a better option, although opioids are not found to be torsadogenic.
- Both TIVA and Balanced anesthesia can be used. Depth of anesthesia monitoring (i.e., MACage, BIS, etc.) can supplement in decision making and thereby better patient care.

The present practice review is, however, limited by the literature search only limited to PubMed and Google Scholar; other databases like Embase, Cochrane, Web of Sciences were not searched. Moreover, we included only the literature available to us in the English language. The practice opinion statements provided are also based mostly on the case reports and observational findings, which limits the quality of evidence.

CONCLUSIONS

Case management differs from person to person. Literature indicates that both TIVA and balanced GA can be used safely, but needs to be tailored. The management of such patients should be multidisciplinary and to be carried out in setup, with better perioperative monitoring and management facilities.

Conflicts of interest

The authors declare no competing and conflicts of interests.

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