CASE REPORT

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Mitigating Hungry Bone Syndrome: Case Reports on Best Practices After Parathyroidectomy

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ABSTRACT

Severe hyperparathyroidism caused by prolonged high levels of parathyroid hormone (PTH) can be managed by removing the gland. One of the critical complications related to parathyroidectomy is hungry bone syndrome (HBS), an emergency morbidity which may be fatal if not promptly and adequately managed. HBS is defined by a rapid and profound decline in serum calcium levels following surgery, as the bones avidly uptake calcium and phosphate in the absence of high PTH levels. It may present as worsened bone pain, carpopedal spasm, severe hypocalcemia, hypophosphatemia, and hypomagnesemia. This report highlights two patients who underwent parathyroidectomy and had different postoperative outcomes for HBS. The first case involves a 19-year-old male who had a history of recurrent fractures and bone pain. In 2019, he got a fracture from a fall, and in 2020, he experienced another fall leading to shoulder dislocation and further fractures. By late 2021, he was diagnosed with severe hyperparathyroidism due to parathyroid adenoma and the gland was removed. Two days after post-parathyroidectomy, he developed HBS. He was treated with calcium and vitamin D supplementation. Over two years of follow-ups, his bone density and mobility improved significantly. The second case involves a 46-year-old male with uncontrolled hypertension and chronic kidney disease stage 5 on hemodialysis, presenting with bone pain and deformities. This patient had a long history of bone pain and fractures. He underwent a similar surgical intervention for tertiary hyperparathyroidism but did not develop HBS postoperatively. Careful perioperative monitoring of electrolytes, vigorous supplementation of calcium and vitamin D, and the use of antiresorptive therapies before surgery had been employed. These cases underline the variety of postoperative outcomes and the importance of tailored management strategies. Early intervention, appropriate surgical management, and aggressive postoperative supplementation are crucial to prevent and manage HBS in patients with severe hyperparathyroidism. Multidisciplinary approach and the utilization of various imaging modalities and intraoperative PTH monitoring are mandatory in managing such complex cases. Applying these approaches will reduce the risk of HBS while guaranteeing excellent postoperative care for individuals following parathyroidectomy.

Keywords: Primary hyperparathyroidism, tertiary hyperparathyroidism, chronic kidney disease, osteoporosis, haemodialysis

INTRODUCTION

Parathyroidectomy is the definitive treatment for severe hyperparathyroidism, particularly in cases of primary caused by parathyroid adenomas or tertiary hyperparathyroidism caused by chronic kidney disease (CKD).[1] However, one of the critical challenges post-parathyroidectomy is managing hungry bone syndrome, a condition that can significantly complicate recovery. Hungry bone syndrome (HBS) is a potentially life-threatening condition characterized by a rapid decrease in serum calcium levels as the bones, which have been under-mineralized due to prolonged high levels of parathyroid hormone (PTH), suddenly absorb calcium and phosphate when PTH levels drop post-surgery.[2] This can result in severe hypocalcemia, hypophosphatemia, and hypomagnesemia, necessitating immediate medical intervention. The symptoms such as muscle cramps, tetany, and even cardiac complications can occur if not properly managed. The severity and onset of HBS can vary significantly between patients, making it crucial to adopt personalized management strategies.[3]

CASE ILLUSTRATION

Patient 1. Mr. SP, a 19-year-old man presented to the endocrinology clinic in November 2021, with multiple pathological fractures in all four extremities. His medical history revealed a series of untreated or inadequately treated fractures over the past 2 years, which had significantly impacted his quality of life. In 2019, he got fracture of ankle in a motorbike accident. The fracture was managed with traditional massage therapy, which was insufficient for proper healing. In 2020, he suffered a shoulder dislocation after falling out of bed. Again, he sought treatment from a traditional healer, leading to pain. Radiographs showed significant osteoporosis, indicative of severe underlying metabolic bone disease. His family history was unremarkable for metabolic bone disorders or endocrinopathies. He reported significant distress due to his progressive disability and dependency on caregivers. His inability to ambulate normally affected his education which forced him to halt the study in university.

Blood pressure was 137/94 mmHg, heart rate 91 bpm, respiratory rate 16/min, temperature 36°C. He was obese with a Body Mass Index (BMI) of 33 kg/m^2. Physical examination revealed disalignment of cruris dextra and sinistra due to multiple closed fractures. Laboratory findings preoperative showed hypercalcemia, hypophosphatemia, markedly elevated intact parathyroid hormone (iPTH) (576 pg/mL), and Vitamin D insufficiency (13.5 ng/mL). X-Rays showed multiple fractures with lytic lesions and sclerotic borders in the femur, pelvis, and humerus. Bone mineral density (BMD) revealed a Z-score of -3.0. Neck ultrasound revealed multiple heterogeneous lesions in the right and left parathyroid, suspected parathyroid adenoma. He was diagnosed with primary hyperparathyroidism (pHPT) caused by parathyroid adenoma, multiple pathological closed fractures on hip, cruris dextra and sinistra, and secondary osteoporosis.

Bisphosphonate therapy with 4 mg of zolendronat acid injection was initiated, followed by internal fixation of the fracture by the orthopedic. Subsequently, the parathyroid gland was removed by the oncologic surgeon. Intra-operative PTH level dropped to 20 pg/mL which marked the successful marker of the surgery. Two days post parathyroidectomy, he developed hungry bone syndrome, characterized by hypocalcemia, hypophosphatemia, and hypomagnesemia. To manage this, high dose calcium (1 g of calcium gluconate thrice daily) and 5000 IU of vitamin D were delivered the event was resolved after 3 days later. Injection of acid was continued every 6 months for 2 years and was transitioned to oral bisphosphonate

(risedronate), as his condition stabilized. The BMD improved with a Z-score of -2.0 (from -3.0 the previous year). The patient also underwent extensive rehabilitation, leading to significant improvements in mobility.

By early 2023, he could walk with a walker and perform daily activities independently. By 2024, the patient had achieved significant functional recovery, with improved bone density and a more stable overall condition. His care plan included ongoing monitoring, calcium and vitamin D supplementation, and a tailored rehabilitation program to maintain mobility and prevent future fractures. The integration of psychiatric support helped address the emotional toll of his condition, contributing to a more holistic recovery.

Patient 2. Mr. AH, 46-year-old male with (CKD) stage V on haemodialysis (HD), presented with progressive skeletal deformities, multiple fractures, and severe bone pain. He experienced persistent right thigh pain for the past year, accompanied by skeletal deformities and difficulty walking. He was diagnosed with hypertension 15 years ago, with poorly controlled blood pressure, often reaching systolic levels of 230 mmHg due to poor compliance to antihypertensive medications. CKD Stage V was diagnosed 10 years ago and the patient started hemodialysis twice weekly, later increased too thrice weekly. Four years ago, he got a pelvic fracture for which a total hip replacement was performed. One year ago, he developed a facial mass over the upper jaw, leading to malocclusion, speech changes, and difficulty chewing. He also reported a shortened stature due to spinal curvature and shortened ribs, with finger and toe deformities. The appetite decreased and progressive weight loss occurred (from 68 kg to 45 kg). Physical examination revealed blood pressure 180/117 mmHg, heart rate 86 bpm, respiratory rate 16/min, temperature 36.1°C. He was normoweight with a BMI of 19.5 kg/m². Prominent maxillary bone with downward displacement of the soft palate was noticed in his head. The chest was barrel-shaped with thoracic kyphosis. He has limited range of motion in his low extremities due to pain. Laboratory findings revealed iPTH level >5000 pg/mL, serum calcium 9.8 mg/dL, phosphate 3.7 mg/dL, vitamin D (25-OH) 10.2 ng/mL (severely deficient) and The Estimated Glomerular Filtration Rate (eGFR) 13.6 mL/min/1.73 m². BMD showed severe osteoporosis with a T-score of -5.1 at the lumbar spine, -6.8 at the left hip, and -6.6 at the femoral neck. X-rays showed bilateral femoral deformities consistent with renal osteodystrophy, including a "Shepherd's crook" deformity in the right femur. Neck ultrasound showed hypoechoic lesions in the posteroinferior thyroid lobes, suggesting parathyroid adenomas. Neck Computed Tomography (CT scan) revealed suspicions for left inferior parathyroid adenoma and brown tumors in the mandibula and maxilla. He was diagnosed with tertiary hyperparathyroidism with suspected parathyroid adenoma, CKD Stage V on HD with mineral and bone disorder, severe osteoporosis with a history of multiple fractures, and uncontrolled hypertension.

Hewasplannedtoundergoparathyroidectomy. While waiting for this surgery, percutaneous ethanol injection was performed as a bridging therapy, and it successfully decreased the iPTH level from >5.000 pg/mL initially to 3.069 pg/mL. He also received clonidine, amlodipine, bisoprolol, irbesartan for hypertension, calcium carbonate and calcitriol for calcium and vitamin D supplementation, oral risedronate for osteoporosis, as well as HD thrice weekly, and was scheduled for parathyroidectomy. Due to renal function concerns, the surgery was postponed several times for oncological surgery clearance. With great concern on his renal status, a careful and well plan surgery was conducted. Parathyroidectomy was performed in July 2024 with intra-operative iPTH level

showed more than 50% decrement from 2.863 pg/mL to 870 pg/mL which marked a successful operation. Post operative, closed monitoring on calcium level was successfully prevent him from HBS. The next plan for this patient was to monitor calcium and phosphate every 3 months, iPTH level 6 months after surgery, and BMD 1 year after surgery to prevent recurrence of metabolic bone disease given his underlying CKD stage V. His osteoporosis remains severe, and fracture risk persists, necessitating long-term bisphosphonate therapy and calcium-vitamin D supplementation.

DISCUSSION

The two cases have a different outcome post-surgery. Mr. SP's case illustrates the challenges of managing a young patient with severe bone involvement and a high iPTH level, where postoperative supplementation alone was insufficient to prevent HBS. In contrast, Mr. AH's outcome was likely influenced by comprehensive preoperative management, including bisphosphonate therapy and careful monitoring.

Several risk factors have been identified that may predispose individuals to develop HBS after parathyroidectomy. Preoperative biochemical parameters, such as elevated alkaline phosphatase levels prior to surgery are more likely to experience postoperative hypocalcemia and HBS.[3, 4] Additionally, the presence of severe bone disease, as indicated by high turnover markers, has been shown to increase the likelihood of developing HBS, as these patients often have a greater demand for calcium postoperatively due to enhanced bone formation.[5] Age and the size of the parathyroid adenoma also plays a critical role in the risk of HBS. It was reported that older patients are at an increased risk, possibly due to the cumulative effects of prolonged hyperparathyroidism on bone metabolism.[1] Larger adenomas are associated with higher levels of PTH and calcium prior to surgery, which lead to a more significant drop in serum calcium levels after the adenoma is removed.[6] Furthermore, vitamin D deficiency has been associated with a higher incidence of HBS, as it exacerbates the hypocalcemic state following parathyroidectomy.[7] The preoperative levels of calcium and PTH are also significant; patients with low preoperative calcium levels and high PTH levels are more susceptible to HBS, as the sudden withdrawal of PTH disrupts the balance between bone formation and resorption, favoring the former.[8]

In the above cases, the one who develops HBS is younger than others which contradict the literature. The reason could be due to multiple factors. This age population tends to exhibit higher rates of bone turnover, which can lead to a more pronounced influx of calcium into the bones following the rapid decrease in PTH levels after surgery.[1] The increased osteoblastic activity in younger individuals can result in a more significant deposition of calcium in the bone matrix, exacerbating the hypocalcemic state that characterizes HBS.[8] Moreover, younger patients

Table 1. Risk factors for developing Hungry Bone Syndrome

Primary Hyperparathyroidism[9-11]	Secondary/tertiary Hyperparathyroidism[1, 12, 13]
- High pre-operative PTH - Elevated alkaline phosphatase - High blood urea nitrogen (BUN) - Older age - Skeletal involvement (brown tumors, osteitis fibrosa cystica) - Large parathyroid adenomas - Prolonged surgical time - Co-presence of osteoporosis	- High pre-operative PTH - Elevated alkaline phosphatase - Younger age at surgery - Normal or low pre-operative serum calcium - Long duration of pre-surgery dialysis - Obesity (inconsistent evidence)

PTH= Parathyroid hormone

often present with less severe pre-existing bone disease compared to older patients, which can result in a more dramatic response to the sudden cessation of PTH.[13]

The management of HBS after parathyroidectomy should involve a multidisciplinary approach, including endocrinologists, surgeons, and dietitians, to ensure optimal outcomes. The following strategies are recommended :[10]

1. Preoperative Management:

Calcium and Vitamin D Supplementation. Patients with evidence of preoperative vitamin D deficiency should receive adequate supplementation. Prophylactic administration of calcium and vitamin D is not universally recommended but is crucial in those with elevated iPTH or alkaline phosphatase levels, particularly in patients with Graves' disease or other high-risk conditions .[10] In this report, patient 1 (PHPT) received aggressive calcium and vitamin D supplementation before surgery due to profound vitamin D insufficiency and severe osteoporosis, as recommended, while patient 2 secondary hyperparathyroidism (SHPT), optimized calcium and vitamin D levels and controlled secondary complications of CKD, per guideline recommendations.

2. Intraoperative Management

A rapid decline in iPTH during surgery is predictive of postoperative hypocalcemia. Employ intraoperative iPTH monitoring to assess the adequacy of parathyroidectomy and predict the likelihood of postoperative HBS. Regular monitoring of serum calcium, phosphate, and magnesium levels during and after surgery is essential to detect and manage electrolyte imbalances early. [10] In both cases, intraoperative iPTH monitoring showed a rapid decline (more than 50% from baseline), allowing the surgical team to confirm parathyroidectomy, anticipate postoperative hypocalcemia, and immediately monitor and manage calcium.

3. Immediate Postoperative Care

Intensive monitoring of serum calcium, phosphate, and magnesium levels should be initiated immediately after surgery. Intravenous calcium may be required in severe cases, followed by oral calcium and vitamin D supplementation. [10] In this report, patient 1 developed hungry bone syndrome, which was detected early through close postoperative monitoring and promptly managed with intravenous calcium and ongoing supplementation to prevent severe complications, whereas patient 2, who was at high risk due to underlying CKD, received intensive monitoring and timely intravenous calcium administration, successfully preventing the development of hungry bone syndrome.

Steps for hypocalcemia management post parathyroidectomy:[14]

1. Assess whether the patient is symptomatic or asymptomatic.
2. For Symptomatic hypocalcemia, the first intervention is administering 1 ampoule of calcium intravenously (IV) over 5 minutes. Then reassessment, if symptoms persist after 15 minutes, administer another ampoule of calcium IV over 5 minutes. If symptoms continue, proceed with a calcium IV infusion (5 ampoules in 5% glucose solution over 8 hours) along with oral calcium (Ca 500mg in a 2-2-2 tablets dosing regimen) and calcitriol (0.25 µg per 24 hours).
3. Monitor and suspend the calcium IV infusion once the total calcium level exceeds 7.5 mg/dL.
4. For asymptomatic hypocalcemia with total ca < 7.5 mg/dL, the patient should be managed similarly to the symptomatic pathway, with calcium IV infusion, oral calcium, and calcitriol.
5. For asymptomatic hypocalcemia with total ca < 8 mg/dL, examine the presentation

of Chvostek's and Trousseau's sign, if it is positive, then start oral calcium 500 mg (2-2-2 tablets regimen) and calcitriol (0.25 µg per 24 hours). Reassess in 12 hours. If it is negative, then evaluate ionized calcium (Ca2+). If Ca2+ is low, then manage similarly with oral calcium and calcitriol. If it is normal, then reassess in 12 hours.

6. If there is no improvement after 24 hours of treatment, consider increasing the dose of calcium and assess for magnesium deficiency, which can complicate hypocalcemia management.
7. If total calcium > 8 mg/dL, continue with the current management and consider discharged the patient and adjusted to a less intensive outpatient management regimen, as their calcium levels have stabilized.

4. Long-term Follow-up

Regular monitoring of bone mineral density and serum calcium levels is essential to adjust supplementation and prevent recurrence of hypocalcemia or the development of hypercalciuria. The use of bisphosphonates, such as zoledronic acid, can be considered in patients with severe bone disease, although this should be tailored based on the patient's overall clinical status and risk of fractures.

CONCLUSION

Hungry Bone Syndrome remains a significant challenge in the postoperative management of patients undergoing parathyroidectomy for severe hyperparathyroidism. The cases presented illustrate the variability in HBS presentation and the importance of a personalized, evidence-based approach to postoperative care. By adopting best practices in preoperative planning, intraoperative monitoring, and postoperative management, healthcare providers can mitigate the risks associated with HBS and ensure better outcomes for their patients.

Effective management of tertiary hyperparathyroidism in CKD requires a comprehensive approach, including surgical intervention, medical management, and close monitoring of bone health. This case underscores the need for individualized treatment plans to prevent further complications and improve patient outcomes.

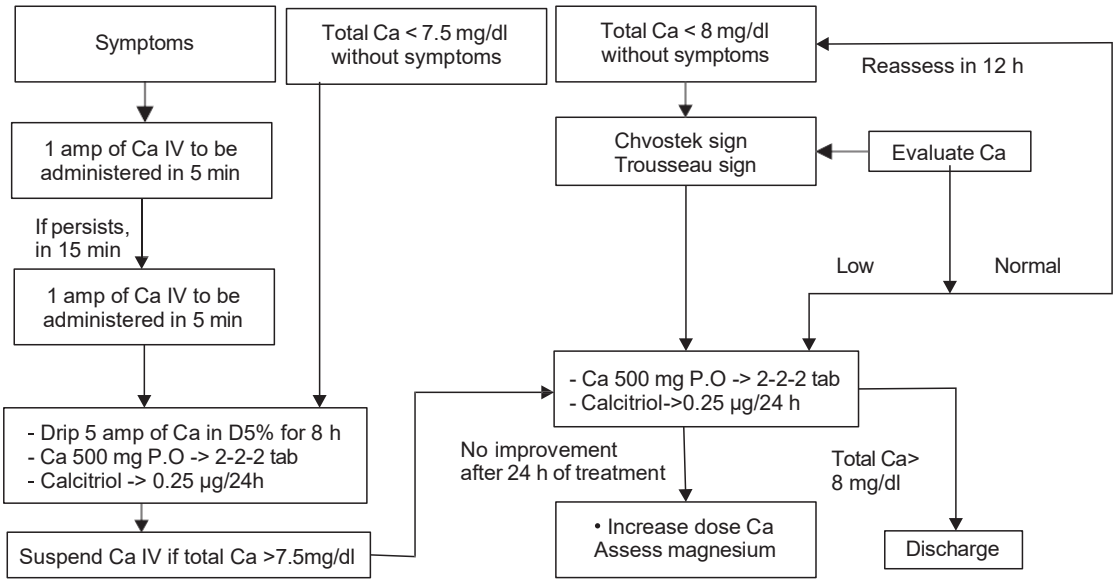

Figure 1 Algorithm for the acute management of hypocalcemia post parathyroidectomy.[14]

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