

# Preoperative zoledronic acid therapy prevent hungry bone syndrome in patients with primary hyperparathyroidism

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## ABSTRACT

**Background:** Hungry bone syndrome is a common complication of surgery for primary hyperparathyroidism in India which often leads to prolonged hospitalization. There are varying reports on the use and efficacy of bisphosphonates in the prevention of hungry bone syndrome. **Methods:** We retrospectively analyzed the effect of preoperative bisphosphonate therapy on rates of hungry bone syndrome in our patients with primary hyperparathyroidism. A total of 19 patients underwent surgery for primary hyperparathyroidism at our institute between January 2013 and June 2015 among whom eight did not receive preoperative bisphosphonates and 11 received intravenous zoledronic acid 4 mg, 24–48 h preoperatively. **Results:** There was no significant difference between the two groups with respect to age, gender, duration of symptoms, preoperative serum calcium, phosphorus, parathyroid hormone, alkaline phosphatase, and the presence of radiological evidence of hyperparathyroid bone disease also did not differ between the groups. Three out of the eight patients who did not receive preoperative zoledronic acid therapy had hungry bone syndrome but none in the zoledronic acid group. The prevalence of hungry bone syndrome tended to be lower in the zoledronic acid group ( $P = 0.058$ ). The need for intravenous calcium and duration of postoperative hospital stay were significantly lesser in the zoledronic acid group. **Conclusion:** Preoperative intravenous zoledronic acid significantly reduces the need for intravenous calcium therapy and duration of postoperative hospital stay and seems a promising option to reduce the rate of hungry bone syndrome in patients with primary hyperparathyroidism.

**Key words:** Hungry bone syndrome, primary hyperparathyroidism, zoledronic acid

## INTRODUCTION

A rapid decrease in serum calcium levels occurs after successful removal of one or more hyperactive parathyroid gland(s) in patients with primary hyperparathyroidism. This decrease in serum calcium levels is usually mild and transient (<4 days).<sup>[1-3]</sup> Prolonged hypocalcemia after

parathyroidectomy may be due to intentional or accidental removal of all parathyroid glands, devascularization or trauma to residual parathyroid glands, long-term suppression of residual nonpathological parathyroid glands, or hungry bone syndrome.<sup>[1-3]</sup>

Hungry bone syndrome is a condition characterized by rapid, profound, and prolonged (>4 days) hypocalcemia associated with hypophosphatemia and hypomagnesemia which follows successful parathyroidectomy in patients with severe primary hyperparathyroidism.<sup>[4]</sup> This condition

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occurs due to the greatly increased skeletal utilization of calcium in the postoperative period. Older age, larger weight of the parathyroid adenomas, radiological evidence of bone disease, and Vitamin D deficiency are associated with increased prevalence of hungry bone syndrome.<sup>[5-7]</sup> Among the biochemical parameters, higher preoperative serum calcium level, parathyroid hormone (PTH) level, and alkaline phosphatase levels are associated with higher rates of hungry bone syndrome.<sup>[1,8,9]</sup>

In contrast to rest of the world,<sup>[10]</sup> hungry bone syndrome is a common complication of surgery for primary hyperparathyroidism in India and is observed in 24–87% of patients.<sup>[11-15]</sup> This is probably because of severe hyperparathyroidism due to late diagnosis and/or concomitant Vitamin D deficiency. In recent years, parathyroid surgery has undergone a paradigm shift and most patients are discharged 24–48 h following surgery. Occurrence of hungry bone syndrome leading to severe hypocalcemia in the postoperative period often increases the duration of hospital stay. Hence, it is important for both the treating endocrinologist and the operating endocrine surgeon to recognize the patients at risk for hungry bone syndrome and implement some measures to prevent or decrease the severity of hungry bone syndrome in these patients.

There are varying reports on the use and efficacy of bisphosphonates in the prevention of hungry bone syndrome. Few studies have documented the benefit of bisphosphonates in preventing hungry bone syndrome after surgery for primary hyperparathyroidism, whereas although rarely, some also report worsening of postoperative hypocalcemia with preoperative bisphosphonate therapy.<sup>[16-21]</sup> Hence, we have analyzed the efficacy of zoledronic acid to prevent hungry bone syndrome in our patients with primary hyperparathyroidism.

## METHODS

This retrospective study was conducted at Vydehi Institute of Medical Sciences and Research Centre. A written informed consent was obtained from each participant and study approval was obtained by the Institutional Ethics Committee.

A total of 19 patients were operated for primary hyperparathyroidism at our institute between January 2013 and June 2015. Between January 2013 and December 2013, eight patients underwent surgery for primary hyperparathyroidism, but they did not receive preoperative bisphosphonates. Between January 2014 and

June 2015, 11 patients underwent surgery for primary hyperparathyroidism and received zoledronic acid 4 mg, 24–48 h preoperatively.

All patients with primary hyperparathyroidism have undergone baseline serum calcium, phosphorus, alkaline phosphatase, creatinine, albumin, urinary calcium-to-creatinine ratio, skeletal radiographs, and ultrasound neck and sestamibi scintigraphy. Computerized tomography of the neck was performed in four patients where there were discordant results between ultrasound neck and sestamibi parathyroid scintigraphy. Postoperatively, all patients were tested for serum calcium and serum phosphorus levels at 6 h and 24 h, every day till discharge and then every 1–2 weekly till normalization of serum calcium and serum phosphorus. All patients with symptomatic hypocalcemia were managed initially with intravenous calcium followed by high doses oral calcium and calcitriol.

## Statistical analysis

The data were represented as mean  $\pm$  standard deviation or percentages as appropriate. Continuous variables between the two groups were analyzed using independent *t*-test and categorical variables were analyzed using Fisher's exact test. *P* < 0.05 was considered statistically significant.

## RESULTS

Among the 19 patients with primary hyperparathyroidism, 15 patients had single parathyroid adenoma, one had parathyroid carcinoma, one had triple adenoma (hyperparathyroidism-jaw tumor syndrome), two had double adenoma, and one had hyperplasia of all four glands (multiple endocrine neoplasia-1). The ultrasound neck and sestamibi scintigraphy were concordant in all patients with single adenoma and the one patient with parathyroid carcinoma. Preoperative and postoperative characteristics of the two groups with and without preoperative zoledronic acid therapy are summarized in Table 1. There was no significant difference between the two groups with respect to age, gender, duration of symptoms, preoperative serum calcium level, phosphorus level, PTH level, and alkaline phosphatase level. Even the presence of radiological evidence of hyperparathyroid bone disease also did not differ between the groups. Three out of the eight patients who did not receive preoperative zoledronic acid therapy had hungry bone syndrome, whereas none in the zoledronic acid group had hungry bone syndrome. The prevalence of hungry bone syndrome tended to be lower in the zoledronic acid group (*P* = 0.058). The need for intravenous calcium and duration of postoperative hospital stay were significantly lesser in the zoledronic acid group.

**Table 1: Comparison of baseline parameters and prevalence of hungry bone syndrome between the two groups with and without zoledronic acid therapy**

Variables	No zoledronic acid group (n=8)	Zoledronic acid group (n=11)	P
Serum calcium	13.87±2.05	14.72±3.56	0.557
Serum phosphorus	2.12±0.34	2.19±0.33	0.675
Serum parathyroid hormone	572.37±292.33	541.3636±415.27034	0.859
Serum alkaline phosphatase	731.75±341.90	673.4545±517.95	0.786
Radiological signs of hyperparathyroidism	6	8	0.664
Hungry bone syndrome	3	0	0.058
Postoperative calcium	7.77±1.065	8.3182±0.467	0.147
Postoperative phosphorus	2.9000±0.89	3.3000±0.662	0.209
Need for intravenous calcium (days)	3.5±3.46	1.09±0.9	0.04
Duration of postoperative hospitalization (days)	6.25±3.32	3.63±0.8	0.022

## DISCUSSION

Our study demonstrates that preoperative zoledronic acid therapy significantly reduces the need for intravenous calcium and duration of postoperative hospital stay. Although the difference between the prevalence of hungry bone syndrome between the two groups was not statistically significant, it tended to be lower in the zoledronic acid group. Lack of this statistical difference is most likely due to a small number of participants in the study. Few case reports initially demonstrated that preoperative treatment with pamidronate or alendronate ameliorates hungry bone syndrome in severe, prolonged primary hyperparathyroidism.<sup>[16,17]</sup> The first comparative study was reported by Lee *et al.* In this study, despite the similar baseline serum calcium, PTH, and alkaline phosphatase levels between the two groups, none of the patients who received preoperative oral clodronate 400–1600 mg/day or intravenous pamidronate 60 mg/day developed hungry bone syndrome compared nine of 17 patients who did not receive bisphosphonates.<sup>[18]</sup> The efficacy of bisphosphonates in preventing hungry bone syndrome was also supported by other retrospective studies. In a study by Malabu and Founda including 46 patients with severe bone disease, who were treated with intravenous zoledronate preoperatively where the rate of hungry bone syndrome of only 4%.<sup>[19]</sup> Another retrospective study by França *et al.* including six patients with radiological features of osteitis fibrosa cystica, who were preoperatively treated with bisphosphonates (oral alendronate 20–30 mg/day for 4–6 weeks or 25 a single dose of pamidronate 90 mg or ibandronate 150 mg intravenously), reported that none of the patients needed postoperative intravenous calcium supplementation.<sup>[20]</sup> However, bisphosphonate therapy may not be completely effective in preventing hungry bone syndrome in all participants as reported by few authors.<sup>[21–24]</sup>

The first limitation of the study is its retrospective nature. Second, the study includes a small number of participants in either group. Third, Vitamin D deficiency which is

a well-known risk factor for hungry bone syndrome is not studied. Fourth, benefits of preoperative zoledronic acid to reduce the rates of hungry bone syndrome in our study group may be due to a larger proportion of severe hyperparathyroidism having radiological evidence of primary hyperparathyroidism; hence, these benefits may not be applicable to patients with mild primary hyperparathyroidism.

## CONCLUSION

Preoperative intravenous zoledronic acid significantly reduces the need for intravenous calcium therapy and duration of postoperative hospital stay and seems a promising option to reduce the rate of hungry bone syndrome in patients with primary hyperparathyroidism.

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### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Brasier AR, Nussbaum SR. Hungry bone syndrome: Clinical and biochemical predictors of its occurrence after parathyroid surgery. *Am J Med* 1988;84:654-60.
2. Kaplan EL, Bartlett S, Sugimoto J, Fredland A. Relation of postoperative hypocalcemia to operative techniques: Deleterious effect of excessive use of parathyroid biopsy. *Surgery* 1982;92:827-34.
3. Norman JG, Politz DE. Safety of immediate discharge after parathyroidectomy: A prospective study of 3,000 consecutive patients. *Endocr Pract* 2007;13:105-13.
4. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: Still a challenge in the post-operative management of primary hyperparathyroidism: A systematic review of the literature. *Eur J Endocrinol* 2013;168:R45-53.
5. Zamboni WA, Folse R. Adenoma weight: A predictor of transient hypocalcemia after parathyroidectomy. *Am J Surg* 1986;152:611-5.
6. Raef H, Ingemansson S, Sobhi S, Sultan A, Ahmed M, Chaudhry M. The effect of Vitamin D status on the severity of bone disease and on the other features of primary hyperparathyroidism (pHPT) in a Vitamin D deficient region. *J Endocrinol Invest* 2004;27:807-12.

7. Agarwal G, Mishra SK, Kar DK, Singh AK, Arya V, Gupta SK, *et al.* Recovery pattern of patients with osteitis fibrosa cystica in primary hyperparathyroidism after successful parathyroidectomy. *Surgery* 2002;132:1075-83.
8. Heath DA, Van't Hoff W, Barnes AD, Gray JG. Value of 1-alpha-hydroxy Vitamin D3 in treatment of primary hyperparathyroidism before parathyroidectomy. *Br Med J* 1979;1:450-2.
9. Spiegel AM, Marx SJ, Brennan MF, Brown EM, Downs RW Jr., Gardner DG, *et al.* Parathyroid function after parathyroidectomy: Evaluation by measurement of urinary cAMP. *Clin Endocrinol (Oxf)* 1981;15:65-73.
10. Gopal RA, Acharya SV, Bandgar T, Menon PS, Dalvi AN, Shah NS. Clinical profile of primary hyperparathyroidism from western India: A single center experience. *J Postgrad Med* 2010;56:79-84.
11. Al-Jawad M, Rashid AK, Narayan KA. Primary hyperparathyroidism in Saudi Arabia: A review of 46 cases. *Med J Malaysia* 2007;62:282-5.
12. Bhansali A, Masoodi SR, Reddy KS, Behera A, das Radotra B, Mittal BR, *et al.* Primary hyperparathyroidism in north India: A description of 52 cases. *Ann Saudi Med* 2005;25:29-35.
13. Pradeep PV, Jayashree B, Mishra A, Mishra SK. Systematic review of primary hyperparathyroidism in India: The past, present, and the future trends. *Int J Endocrinol* 2011;2011:921814.
14. George J, Acharya SV, Bandgar TR, Menon PS, Shah NS. Primary hyperparathyroidism in children and adolescents. *Indian J Pediatr* 2010;77:175-8.
15. Shah VN, Bhadada S, Bhansali A, Behera A, Mittal BR. Changes in clinical and biochemical presentations of primary hyperparathyroidism in India over a period of 20 years. *Indian J Med Res* 2014;139:694-9.
16. Brossard JH, Garon J, Lepage R, Gascon-Barré M, D'Amour P. Inhibition of 1,25(OH)2D production by hypercalcemia in osteitis fibrosa cystica: Influence on parathyroid hormone secretion and hungry bone disease. *Bone Miner* 1993;23:15-26.
17. Gurevich Y, Poretsky L. Possible prevention of hungry bone syndrome following 31 parathyroidectomy by preoperative use of Zolendronic acid. *Otolaryngol Head Neck Surg* 2008;138:403-4.
18. Lee IT, Sheu WH, Tu ST, Kuo SW, Pei D. Bisphosphonate pretreatment attenuates hungry bone syndrome postoperatively in subjects with primary hyperparathyroidism. *J Bone Miner Metab* 2006;24:255-8.
19. Malabu UH, Founda MA. Primary hyperparathyroidism in Saudi Arabia: A review of 46 cases. *Med J Malaysia* 2007;62:394-7.
20. França TC, Griz L, Pinho J, Diniz ET, Andrade LD, Lucena CS, *et al.* Bisphosphonates can reduce bone hunger after parathyroidectomy in patients with primary hyperparathyroidism and osteitis fibrosa cystica. *Rev Bras Reumatol* 2011;51:131-7.
21. Corsello SM, Paragliola RM, Locantore P, Ingraudo F, Ricciato MP, Rota CA, *et al.* Post-surgery severe hypocalcemia in primary hyperparathyroidism preoperatively treated with zoledronic acid. *Hormones (Athens)* 2010;9:338-42.
22. Demirci H, Suyani E, Karakoc A, Toruner FB, Yetkin I, Ayvaz G, *et al.* A longstanding hungry bone syndrome. *Endocrinologist* 2007;17:10-2.
23. Hisham AN, Aina EN, Zanariah H. Recognition and management of hungry bone syndrome – A case report. *Med J Malaysia* 2000;55:132-4.
24. Yong TY, Li JY. Mediastinal parathyroid carcinoma presenting with severe skeletal manifestations. *J Bone Miner Metab* 2010;28:591-4.