Evidence-Based Case Report

Effect of Bisphosphonate in Preventing Hungry Bone Syndrome in Patients with Primary Hyperparathyroidism Undergoing Parathyroidectomy

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Abstract

Primary hyperparathyroidism is a common endocrine disorder that often requires parathyroid-dectomy as a curative measure. However, post-operatively, patients are susceptible to severe and prolonged hypocalcemia, known as post-parathyroidectomy hypocalcemia syndrome (HBS), which can prolong the length of stay and increase the cost of care. Preoperative use of bisphosphonates has been proposed as a potential therapy to reduce the incidence of HBS. This EBCR aims to determine the effectiveness of preoperative bisphosphonate administration in reducing the risk of HBS in patients with primary hyperparathyroidism undergoing parathyroidectomy. A systematic literature review conducted through three electronic databases and critical analysis using FAITH tools from the Central of Evidence-based Medicine, University of Oxford, showed that pre-operative administration of bisphosphonates significantly reduces the occurrence of HBS with an overall NNT (Number Needed to Treat) of three. However, further research is needed to validate bisphosphonates' effectiveness and safety in this context. Overall, these EBCR suggest that bisphosphonates can be considered as part of a preventive strategy for HBS in patients with primary hyperparathyroidism undergoing parathyroidectomy.
Keywords: *hungry bone syndrome, primary hyperparathyroidism, bisphosphonate.*

Efek Pemberian Bisfosfonat Pra-Operasi dalam Mencegah *Hungry Bone Syndrome* pada Pasien Hiperparatiroidisme Primer yang Menjalani Paratiroidektomi

Abstrak

Hiperparatiroidisme primer adalah kelainan endokrin yang sering memerlukan paratiroidektomi sebagai tindakan kuratif. Namun, pasca-operasi, pasien rentan mengalami hipokalsemia berat dan berkepanjangan, yang dikenal sebagai sindrom hipokalsemia pasca-paratiroidektomi (hungry bone syndrome/HBS), yang dapat memperpanjang masa rawat inap dan meningkatkan biaya perawatan. Penggunaan bisfosfonat sebelum operasi telah diusulkan sebagai terapi potensial untuk mengurangi kejadian HBS. EBCR ini bertujuan untuk menentukan efektivitas pemberian bisfosfonat pra-operasi dalam mengurangi risiko HBS pada pasien hiperparatiroidisme primer yang menjalani paratiroidektomi.Tinjauan literatur sistematis yang dilakukan melalui tiga database elektronik dan analisis kritis menggunakan FAITH tools dari Central of Evidence-based Medicine, University of Oxford, menunjukkan bahwa pemberian bisfosfonat pra-operasi mengurangi terjadinya HBS dengan NNT secara signifikan (keseluruhan sebesar 3). Meskipun demikian, diperlukan penelitian lebih lanjut untuk memvalidasi efektivitas dan keamanan bisfosfonat dalam konteks ini. Secara keseluruhan, hasil EBCR ini menunjukkan bahwa bisfosfonat dapat dipertimbangkan sebagai bagian dari strategi pencegahan HBS pada pasien dengan hiperparatiroidisme primer yang menjalani paratiroidektomi.
Kata kunci: *hungry bone syndrome, hiperparatiroidisme primer, bisfosfonat.*

Introduction

Primary hyperparathyroidism ranks as the third most prevalent endocrine disorder, following diabetes mellitus and thyroid conditions, which affects up to 1% of the adult population.[1] Primary hyperparathyroidism (PHPT) arises from the excessive secretion of parathyroid hormone independently, primarily attributed to adenoma (80% single, 4% double), hyperplasia (15%), and exceptionally malignancy (1%).[2] The incidence of PHPT, in general, is rising globally. Prevalence has risen from 1.8 to 6.7/1000 between 1997 and 2006. Additionally, the worldwide incidence rate of PHPT is approximately 20 per 100,000 people under 50 years old, with variations in incidence rates among different racial groups.[3,4]

Parathyroidectomy is the sole curative option for PHPT. However, parathyroidectomy is not a complication-free procedure.[5] Following a parathyroidectomy, the occurrence of low calcium levels in the blood, known as postoperative hypocalcemia, is a widely recognized complication. Patients with primary hyperparathyroidism who undergo parathyroidectomy experience a swift reduction in serum calcium levels following the removal of overactive glands. This decline in serum calcium levels typically peaks within 2 to 4 days post-surgery; however, in patients with hungry bone syndrome (HBS), it may continue to decrease beyond the fourth day.[6,7] HBS is defined as rapid, profound, and prolonged hypocalcemia of less than 8.4 mg/dL that endures for over four days following surgery in the presence of normal or elevated parathyroid hormone (PTH) levels.[8,9] HBS commonly manifests in the postoperative phase following parathyroidectomy in individuals with PHPT.[9] The incidence of HBS in PHPT after parathyroidectomy varies, with reported prevalence rates ranging from 24% to 87%.[10]

Following parathyroidectomy, the sudden decrease in serum PTH levels is thought to alter the equilibrium between bone formation and resorption, promoting bone formation and leading to a substantial increase in skeletal calcium uptake, ultimately causing severe hypocalcemia.[11] HBS extends hospital stays and increases disease expenses, as HBS can persist over an extended duration, necessitating prolonged calcium supplementation. Patients experiencing hypocalcemia had notably longer hospitalizations (5.7 days compared to 3.1 days) and incurred higher individual costs ($8,367.35 versus $2,534.44) than those without hypocalcemia.[12] According to Nicholson et al[13] treatment expenses for hypocalcemia ranged from $329 to $4,955 per patient, primarily attributable to the monitoring and management of hypocalcemia. Meanwhile, there is no data on the cost of treatment of hypocalcemia in Indonesia. Therefore, it would be sensible to prevent the development of HBS to avoid prolonged hospital stays and to reduce healthcare costs of post-thyroidectomy hypocalcemia in the setting of limited resources in the healthcare system due to hypocalcemia.[14]

One of the strategies that can be applied to this circumstance is preventing the occurrence of HBS. Bisphosphonates have been studied for their potential to prevent HBS in patients with PHPT undergoing parathyroidectomy. Administering preoperative intravenous zoledronic acid has been shown to notably decrease the requirement for intravenous calcium supplementation and shorten the length of postoperative hospitalization, indicating its potential to reduce the incidence of HBS in patients with PHPT.[15] Bisphosphonates, including zoledronic acid, can inhibit osteoclast activity, which may help prevent excessive bone resorption and the subsequent release of calcium into the bloodstream, thereby reducing the risk of HBS.[16] Although some studies reported encouraging results, results on the protective role of bisphosphonates are conflicting.[17,18] Thus, this EBCR aims to determine the effectiveness of preoperative bisphosphonate administration in reducing the risk of HBS in patients with primary hyperparathyroidism undergoing parathyroidectomy.

Clinical Scenario

An 18-year-old man came to dr. Cipto Mangunkusumo National Hospital, Jakarta, with a chief complaint of weakness for two days. The patient was previously diagnosed with primary hyperparathyroidism and was referred from Moewardi Hospital for parathyroidectomy due to left parathyroid adenoma. Since his condition deteriorated abruptly, the patient came to the ER and was referred to internal medicine from the surgery department for evaluation and treatment of the PHPT and sudden weakness.

The patients denied having any syncope, seizure, or one-sided weakness—no vomiting or diarrhea preceding the complaints. Patients reported other symptoms, such as tingling on both feet and arms and knee pain after prolonged walking or doing sports activities. Complaints of a lump in

the neck were denied, and swallowing problems/ hoarseness were absent. There were no complaints about sweating or heart palpitations. His prior clinical history included nephrocalcinosis in 2021 and a fracture of the left femoral bone in 2022 due to minor trauma, elevation of intact PTH levels, and hypercalcemia. The patient denied the consumption of any medication. There was no history of alcohol consumption or smoking, no medication, and no history of undergoing radiotherapy. The history of malignancy was denied.

During the physical examination, the patient was alert and showed stable vital signs. A neck examination resulted in no remarkable finding. There were no signs of enlargement of the thyroid and lymph nodes. An examination of the extremities showed a shortening of the left inferior limb. We found no tremors or lateralization with normal motor and sensory function. On admission, moderate hypercalcemia (serum corrected Ca 12.5 mg/dL) and elevated intact PTH level (556.4 pg/mL) were found. We found low phosphate levels (1.37 mg/dL), vitamin D deficiency (7.4 ng/ml), and increased urinary Ca (325 mg/24 h). A Sestamibi parathyroid scan found a left parathyroid adenoma with 8.1 x 11.1 x 20 mm dimensions.

Various risk factors have been identified to correlate with an increased risk of HBS, including increased levels of PTH, pre-operative serum calcium, and vitamin D deficiency. Due to the increased risk of HBS in the patient, preventive treatment was needed to prevent HBS. Studies showed that bisphosphonate can be used as a preventive measure for HBS. We planned to initiate pre-operative treatment for patients with PHPT with bisphosphonates to prevent complications of HBS after parathyroidectomy.

Problem Formulation

In adult patients with PHPT undergoing parathyroidectomy, how is the effect of pre-operative bisphosphonates therapy on preventing HBS?

The PICO in this study was as follows: Population: adult patients with PHPT undergoing parathyroidectomy; Intervention: pre-operative zoledronic acid or bisphosphonates; Comparison: no pre-operative zoledronic acid or bisphosphonates; Outcome: HBS

Search Strategy

We systematically searched databases using three electronic databases, including Pubmed, ProQuest, and SCOPUS, from each database's inception to February 15, 2024, without language restriction to identify relevant studies. The following keywords were used: 'primary hyperparathyroidism,' 'parathyroidectomy,' 'hungry bone syndrome,' 'bisphosphonates,' 'zoledronic acid' with various synonyms (Table 1). The "related articles" function in PubMed and citation screening for reference lists of retrieved articles were also used to identify additional articles.

Eligibility Criteria

Studies meeting the eligibility criteria were selected, with inclusion based on the following criteria: adult participants aged ≥18 years old with PHPT undergoing parathyroidectomy, comparison between patients with and without pre-operative zoledronic acid therapy, and the outcome of interest was HBS. HBS is defined as prolonged hypocalcemia for more than four days after parathyroidectomy. The types of studies included are meta-analysis/systematic reviews of RCTs or cohort studies, RCTs, and cohort studies. Restrictions by language, sample size, and year of publication were not applied. The exclusion criteria were abstracts, books, correspondences, case series, and case reports.

Study Selection and Data Extraction

Publications from systematic searches were screened for duplicates, then assessed by title and abstract for inclusion. Full-text evaluation based on PICO followed, with discrepancies resolved through discussion. One meta-analysis was selected for appraisal, and data extracted included author, year, country, study design, population traits, and summary of results.

Table 1. Keywords for Search Strategies

Database	Search Strategies	Hit
Pubmed	((Primary hyperparathyroidism[Title/Abstract]) OR (Primary hyperparathyroidism[MeSH Terms]) OR (hyperparathyroidism[TitSle/Abstract]) OR (hyperparathyroidism[MeSH Terms])) AND (parathyroidectomy[Title/Abstract] OR (parathyroidectomy[MeSH Terms])) AND ((Postoperative[Title/Abstract]) OR (Postoperative[MeSH Terms]) OR (Post-operative[Title/Abstract]) OR (Post-operative[MeSH Terms])) AND ((hungry bone syndrome[Title/Abstract]) OR (hungry bone syndrome[MeSH Terms])) AND ((Bisphosphonates[Title/Abstract]) OR (Bisphosphonates[MeSH Terms]) OR (Zoledronic acid[Title/Abstract]) OR (Zoledronic acid[MeSH Terms]))	10
ProQuest	#S1 abstract(Primary hyperparathyroidism) OR title(Primary hyperparathyroidism) #S2 abstract(hyperparathyroidism) OR title(hyperparathyroidism) #S3 [S1] OR [S2] #S4 abstract(parathyroidectomy) OR title(parathyroidectomy) #S5 abstract(Postoperative) OR title(Postoperative) #S6 abstract(Post-operative) OR title(Post-operative) #S7 [S5] OR [S6] #S8 abstract(hungry bone syndrome) OR title(hungry bone syndrome) #S9 abstract(Bisphosphonates) OR title(Bisphosphonates) #S10 abstract(Zoledronic acid) OR title(Zoledronic acid) #S11 [S9] OR [S10] #S12 [S3] AND [S4] AND [S7] AND [S8] AND [S11]	5
SCOPUS	TITLE-ABS-KEY (primary AND hyperparathyroidism OR hyperparathyroidism) AND TITLE-ABS-KEY (postoperative OR parathyroidectomy) AND TITLE-ABS-KEY (hungry AND bone AND syndrome) AND TITLE-ABS-KEY (bisphosphonates OR zoledronic AND acid)	21

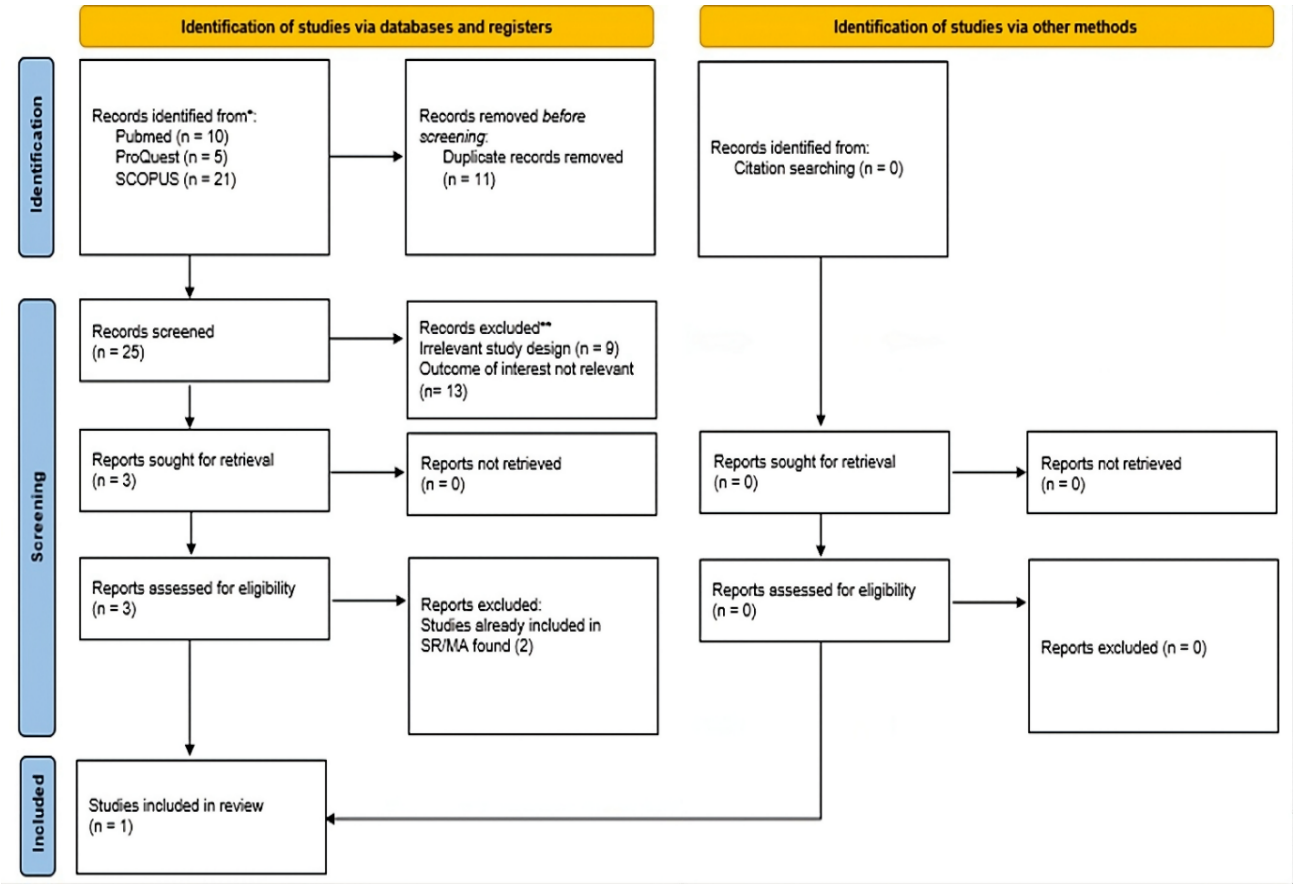

Figure 1. PRISMA Flow Diagram of Systematic Article Searches

Critical Appraisal

Selected studies were critically appraised using FAITH tools for systematic review/meta-analysis studies developed by the Center for Evidence-Based Medicine (CEBM) at the University of Oxford. Critical appraisal was conducted by authors independently. A critical appraisal was carried out regarding validity, importance, and applicability. Differences in critical appraisal were discussed until a consensus was made.

Table 2. List of Articles Included in the Meta-Analysis

Author	Year	Country	Study design	Intervention	Control	Sample size
Lee et al[34]	2006	Taiwan	Retrospective cohort study	IV plus oral clodronate, intravenous pamidronate, and oral clodronate alone.	No preoperative bisphosphonate treatment	23
Mayilvaganan et al[35]	2017	India	Retrospective cohort study	IV zoledronic acid	No preoperative bisphosphonate treatment	19

Results

The study selection process included one study, as depicted in Figure 1. No articles were discovered through screening. Included study for this analysis is a meta-analysis conducted by Pal et al[27] evaluated the risk of hungry bone syndrome (HBS) following parathyroidectomy in patients with primary hyperparathyroidism (PHPT) who received preoperative bisphosphonate therapy. This study included two retrospective cohort studies involving a total of 42 participants with PHPT who underwent parathyroidectomy. The analysis found that the risk of developing HBS was significantly lower in patients who had received bisphosphonates preoperatively compared to those who had not, with a relative risk (RR) of 0.12 (95% confidence interval [CI] 0.02–0.89; $p = 0.04$; $I^2 = 0\%$). The study included a meta-analysis, which was the conclusion of two studies that had been conducted previously. The following is a list of articles included in the meta-analysis (Table 2). The included article was critically appraised using FAITH tools, and the result of the critical appraisal of the included meta-analysis and its validity is shown in Table 3.

A critical review of the study by Pal et al[27] assessed its validity, importance, and applicability in evaluating the role of bisphosphonates in preventing hungry bone syndrome (HBS) following parathyroidectomy in patients with primary hyperparathyroidism (PHPT). The study demonstrated high validity, with positive responses to six out of seven critical appraisal questions. The findings were considered significant, as they indicated a reduction in the occurrence of HBS postoperatively in patients who received bisphosphonates. While the study suggested that bisphosphonates might be beneficial in preventing HBS, the authors emphasized the need for further high-quality research to evaluate their efficacy and safety profile. Based on the evidence hierarchy, the study was classified as Level 2A.

Discussion

Parathyroidectomy is widely considered the best treatment for PHPT due to its curative potential and effectiveness in managing the condition. The efficacy of parathyroidectomy in treating PHPT is well-established, with studies highlighting its role as the gold standard procedure for surgical management of the condition and the only curative option providing a permanent solution for the underlying cause of the disease for patients with PHPT and offering a definitive resolution of the disease and its associated symptoms.[19,20] Parathyroidectomy is effective in restoring calcium homeostasis in patients with primary hyperparathyroidism.[21]

Hypocalcemia is a frequent complication post-parathyroidectomy, where, in some cases, the condition is prolonged and results in HBS. It enhances skeletal calcium usage, leading to an immediate halt in bone resorption despite ongoing bone formation,

resulting in a profound and sometimes long-lasting decrease in serum calcium levels.[22]

The pathophysiology of HBS involves an accelerated bone formation rate and a sudden reduction in the expanded resorption space, resulting in heightened skeletal calcium utilization once the impact of elevated circulating PTH diminishes.[23] After parathyroidectomy, the sudden drop in serum PTH levels triggers a hyperdynamic process of calcium reabsorption into bones, resulting in severe and prolonged hypocalcemia, which characterizes HBS.[21] This phenomenon is due to the rapid remineralization of bone tissue following the removal of the parathyroid glands, leading to a state of "hungry bones" that avidly absorb calcium from the bloodstream.[24]

Table 3. Result of Critical Appraisal Based on Validity

Item of Appraisal	Description
Critical appraisal	
Title	Role of Bisphosphonates in The Prevention of Postoperative Hungry Bone Syndrome in Primary Hyperparathyroidism: A Meta-Analysis and Need for Randomized Controlled Trials
Study design	Meta-analysis of cohort studies
Level of evidence	2A
Validity	
Question – Does the systematic review address a focused question (PICO)?	Yes – in this article, the PICO, which the author asked about, was clearly stated in the title and abstract.
… and use it to direct the search and select articles for inclusion?	Yes – this article's inclusion and exclusion criteria were clearly stated in the methods section. Inclusion criteria consisted of observational studies that examined administering at least one dose of any bisphosphonate pre-operatively in PHPT patients and compared the incidence of HBS in the postoperative period between those who received it and those who did not. Meanwhile, the exclusion criteria for this meta-analysis include case reports and case series.
Find – Did the search find all the relevant evidence?	Yes – A literature search for this article was conducted in two databases, PubMed and Google Scholar. This literature search was not limited by language and time. In a literature search in two databases, 533 articles were obtained, which were then carried out by eliminating duplicates, screening titles and abstracts, and assessing eligibility criteria, leaving two articles that met the eligibility criteria to be reviewed and included in this meta-analysis. The keywords used in the literature search have also been mentioned. Keywords used included 'Primary hyperparathyroidism' OR 'Hyperparathyroidism' AND 'Hungry bone syndrome' AND 'Bisphosphonates' OR 'Zoledronic acid.'
Appraise – Have the studies been critically appraised?	Yes – Two reviewers critically reviewed the articles selected for this meta-analysis. The assessment of the chosen articles' quality was conducted utilizing the Methodological Index for Non-Randomized Studies (MINORS) scale, consisting of 12 criteria rated as 0 (not documented), 1 (documented but insufficient), or 2 (documented and sufficient). The highest achievable score for non-comparative studies is 16, while for comparative studies is 24. The MINORS scores of 14 and 15 for the included studies indicate suboptimal quality.
Include – Did they only include high-quality studies?	No – The selected articles in this meta-analysis were all retrospective cohorts, which are not the best for intervention study designs. The quality of the selected articles was still sub-optimal because they had moderate quality based on their MINORS scale.
Total up – Have the results been totaled with appropriate summary tables and plots?	Yes – A summary table of the selected articles is presented in supplemental articles. Apart from that, this article also displayed a pooled effect as a forest plot.
Heterogeneity - … and heterogeneity between studies assessed and explained?	Yes – In each forest plot for each outcome, the Chi^2 and I^2 values are included, which indicate heterogeneity. For the outcome of preventing HBS, the value of I^2 = 0% was obtained, which means that the results of the selected articles on the outcome of preventing hungry bone syndrome were homogeneous.

Table 4. Result of Critical Appraisal Based on Importance, and Applicability

Item of Appraisal	Description
Importance	
What measure was used, and how significant was the effect (could it have been due to chance)?	The meta-analysis results in this article were presented as a forest plot to determine the role of pre-operative bisphosphonates in preventing HBS in PHPT patients undergoing parathyroidectomy. The study showed that pre-operative biphosphonate therapy could prevent hungry bone syndrome (RR: 0.12; 95% CI: 0.02-0.89; P: 0.04). Apart from that, in the forest plot, the value of I^2 = 0% was obtained, which means that the results from the selected articles on the outcome of preventing HBS were homogeneous. The calculated NNT was 3, implying that the intervention substantially reduces the risk of hungry bone syndrome occurrence.
Applicability	
Is my patient so different from those in the study that the results cannot apply?	No – Patient characteristics in this meta-analysis were similar to those in clinical scenarios.
Is the treatment feasible in my setting?	Yes – Bisphosphonate is now widely available in Indonesia and is included in the National Health Insurance Forum (JKN). Thus, it can be used under appropriate indications.
Will the potential benefits of treatment outweigh the potential harms of treatments for my patient?	Yes – The results show that pre-operative bisphosphonates can reduce the risk of HBS by 88% compared to those without therapy with an NTT of 3. A lower NNT generally indicates a more significant benefit of treatment. In this case, an NNT of 3 suggests that the benefit of pre-operative bisphosphonates in preventing hungry bone syndrome is relatively substantial. However, the robustness of the result is questionable because it was synthesized from studies with low levels of evidence and did not include RCTs in the analysis. Thus, bisphosphonates may be considered while further studies with a higher level of evidence are being conducted.

Studies have indicated varying rates of occurrence of HBS in PHPT.[25,26] The severity of HBS is highlighted by its classification as a severe and underdiagnosed complication of parathyroidectomy in the treatment of primary hyperparathyroidism. It can be life-threatening if not managed appropriately.[27,28] The condition necessitates long-term calcium supplementation to address the hypocalcemic state resulting from the remineralization of various minerals in the bones.[29]

Various factors contribute to the development of HBS including elevated levels of PTH, alkaline phosphatase (ALP), blood urea nitrogen (BUN), higher BMI, and larger removed glands.[22,30] Deficiency in vitamin D, lower dietary calcium intake, and younger age at surgery may also increase the risk of HBS.[22,31] Patients with HBS often exhibit larger volumes and weights of removed glands, along with higher pre-operative levels of serum calcium, PTH, and alkaline phosphate compared to those who undergo uncomplicated parathyroidectomy.[22,32] Additionally, radiological evidence of bone diseases such as brown tumors, fractures, and osteitis fibrosa cystica, along with higher osteoclast numbers on bone biopsy, are associated with an increased risk of HBS.[22,33]

Prevention strategies for HBS have been explored, such as the pre-operative use of pamidronate to prevent the risk of severe and prolonged hypocalcemia post-parathyroidectomy.[34] Additionally, treatments like zoledronic acid have been investigated in preventing HBS in PHPT patients. These interventions aim to reduce the likelihood of developing this challenging complication, which can lead to prolonged hospitalization and require careful management.

Bisphosphonates are commonly utilized as antiresorptive medications for managing osteoporosis and bone conditions linked to heightened bone turnover. In primary hyperparathyroidism, bisphosphonates act by inhibiting osteoclastic bone resorption and reducing the frequency of remodeling site activation, thereby aiding in replenishing remodeling spaces. When used before parathyroidectomy in the context of PHPT, bisphosphonates may prevent the

intensity and duration of HBS by decreasing bone turnover levels or even normalizing them before surgery.[35,26] This proactive approach could have a postoperative impact by moderating the rate of calcium influx into the bone, thereby averting a sudden decline in calcium levels and the onset of severe hypocalcemia.

The available evidence based on included studies in the meta-analysis showed various dosages, drug forms, and initiation times of bisphosphonate therapy were applied. Lee et al[34] analyzed patients with primary hyperparathyroidism who had been given either oral clodronate 400–1,600 mg/day or intravenous pamidronate 60 mg/day within 1 to 17 days before their parathyroidectomy. Mayilvaganan et al[35] analyzed 19 patients with PHPT who had been given 4 mg of intravenous zoledronate 24 to 48 hours before parathyroidectomy. These studies showed that all bisphosphonate was administrated pre-operatively with various days of initiation, dosage, and forms of bisphosphonate.

Bisphosphonates have several severe adverse effects, including upper GI discomfort, worsening renal function, hypocalcemia, musculoskeletal pain, flu-like symptoms, reduced bone mineralization, and osteomalacia.[36] Adverse effects in the upper gastrointestinal tract are frequently observed with oral bisphosphonates, particularly in individuals with gastroesophageal reflux issues. Bisphosphonates are eliminated from the bloodstream through renal filtration, and patients with a creatinine clearance below 30 to 35 ml should avoid all types of bisphosphonates. Due to their action as inhibitors of bone resorption, bisphosphonates can lead to a drop in circulating calcium levels, mainly if high concentrations are rapidly achieved, as is the case with intravenous administration.

Symptomatic hypocalcemia is more common in patients treated with intravenous zoledronate compared to those treated with oral bisphosphonates.[36,37,38] Musculoskeletal pain is frequent, particularly following intravenous bisphosphonate therapy, where pain may manifest alone or alongside flu-like symptoms such as fever. In the initial study of zoledronic acid, 16% experienced fever, 9.5% reported muscle pain, and 6.3% complained of joint pain. Musculoskeletal pain is less prevalent with oral bisphosphonates.[38]

The study by Pal et al[27] indicates that preoperative bisphosphonate administration significantly reduces the risk of hungry bone syndrome in patients with PHPT undergoing parathyroidectomy (RR 0.12; 95% CI 0.02–0.89; p-value 0.04; I^2 = 0%). The meta-analysis demonstrates a significant reduction in HBS with bisphosphonate administration, showing an 88% decrease in the risk of developing HBS. This risk reduction is statistically significant with a p-value of less than 0.005 and confidence intervals that do not cross 1. Also, the calculated NNT was 3, which signifies a clinically meaningful benefit of pre-operative bisphosphonates in reducing the incidence of HBS among patients undergoing parathyroidectomy. However, the studies included in this meta-analysis lack high-quality levels of evidence. All studies included in this meta-analysis are retrospective cohort studies, and none are randomized controlled trials (RCTs). RCTs are considered the gold standard in interventional studies, while non-RCTs have lower levels of evidence due to various limitations, such as a high risk of bias. Additionally, the population sizes in each study included in this meta-analysis were also small, which may affect the robustness of the results.

In terms of applicability, bisphosphonates may be recommended for use to prevent HBS in patients with PHPT due to its substantial effect on preventing HBS. Given the limited data on the efficacy and safety of bisphosphonates, further studies with higher levels of evidence are awaited. Bisphosphonate drugs are widely available in Indonesia. This medication is sold at a high price in the market, costing around 1.5 to 3 million Indonesian Rupiah per bottle. However, it remains affordable for some segments of the population and is already included in the list of drugs covered by the National Health Insurance (JKN). With an overall NNT of 3, one additional case of hypocalcemia is expected to be prevented for every three patients treated. Further economic analysis needs to be carried out regarding the costs of administering bisphosphonates and prolonged hospital stays due to hypocalcemia.

This article has limitations which may affect the robustness of the result. First, it was a meta-analysis of a retrospective observational study with a limited number of included studies and participants. Second, the suboptimal study quality in the meta-analysis may suggest moderate quality, a less-than-ideal study. Third, most of the population has yet to receive standardized types, dosages, and duration of bisphosphonate therapy. It is critical to ensure consistency, comparability, and replicability, establish causal relationships, and promote patient safety in interventional studies.

While the use of bisphosphonates to prevent HBS in PHPT shows promise and has been suggested in some studies, further research,

including prospective studies and RCTs, preferably using a standardized regiment with a larger sample size and appropriate blinding and randomization, is needed to establish the efficacy and optimal protocols for the use of preoperative bisphosphonates in preventing this challenging complication following parathyroidectomy. Drawing conclusions and making decisions based on such studies should be done judiciously.

Conclusion

Based on a critical review of meta-analysis that has been carried out, the pre-operative use of bisphosphonate in patients with PHPT undergoing parathyroidectomy can reduce the risk of HBS compared to those who have not received the treatment. Based on the evaluated data, bisphosphonates may be considered for clinical use, as the study results indicate a substantial impact on reducing the risk of HBS. However, further studies with stronger evidence are needed to confirm their efficacy and safety.

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