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The Efficacy of Paricalcitol Administration for Management of Pediatric Chronic Kidney Disease: A Systematic Review and Meta-analysis

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Abstract

Background

There is still controversy about the efficacy of paricalcitol in children with chronic kidney disease (CKD). Therefore, the present study was designed to assess current evidence on the efficacy of paricalcitol in CKD children.

Materials and Methods

In this systematic review, an extensive search was performed on the databases of Medline, Embase, Scopus and Web of Science up to the end of October 2019. The keywords related to CKD and paricalcitol were combined and searched. Two independent researchers reviewed the papers; data were analyzed in STATA 14.0 statistical program and the effect of paricalcitol administration on serum levels of intact parathyroid hormone (iPTH), calcium (Ca), phosphorous (P), and Ca × P product ratio were reported as odds ratio (OR), and 95% confidence interval (95%CI).

Results: Finally, data from three studies were included in the present study. Paricalcitol administration decreased iPTH levels in children with CKD (OR=0.12; 95%CI: 0.05 to 0.29; p<0.001). However, paricalcitol administration had no effect on serum calcium level (OR=1.16; 95%CI: 0.48 to 2.80; p=0.741), serum phosphorus level (OR=0.87; 95%CI: 0.38 to 1.99; p=0.735), and Ca × P ratio (OR=0.48; 95% CI: 0.15 to 1.50; p=0.208). No study has investigated the efficacy of paricalcitol on the control of proteinuria following CKD.

Conclusion

There is limited evidence on the efficacy and safety of paricalcitol in children with CKD. There are no studies in CKD children that have shown efficacy of Paricalcitol in controlling proteinuria.

Key Words: Chronic Kidney disease, Chronic, Paricalcitol, Renal Insufficiency, Vitamin D.

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1- INTRODUCTION

Chronic kidney disease (CKD) is a progressive kidney dysfunction that occurs over time. This progressive process occurs over a period of months to years and eventually leads to end-stage renal disease. CKD is defined as a decrease in renal function or a structural defect that results in a decrease in glomerular filtration below 60 mL/min/1.73 m^2 per body surface for more than 3 months (1). Epidemiological studies have shown that the average annual incidence of the disease varies in different populations of children. For example, the annual incidence of CKD in children in most European countries is more than 50 children per million in the general population (2); while in Italian children it is estimated at about 12.1 children per million (3). These studies suggest that although children comprise a small portion of the CKD patients, the incidence of the disease in children is of high importance because of its burden and the length of time a person lives with it (3). Studies suggest that the active form of vitamin D, such as paricalcitol, has potential effects on management of CKD (4). Vitamin D as a compound involved in homeostasis and regulation of the renin-angiotensin signaling pathway (5) has protective effects on the renal system (6). Studies considered paricalcitol as a potential agent to improve prognosis of CKD patients and a recent meta-analysis on adults suggests that this drug suppresses intact parathyroid hormone (iPTH), and decreases proteinuria in stages 2 to 5 of chronic renal failure, without increasing the side effects (7). However, there is still controversy about the efficacy of this drug in children with CKD. Therefore, the present study was designed to assess the current evidence on efficacy of paricalcitol in CKD in children.

2- MATERIALS AND METHODS

2-1. Study design

The present study is a systematic review with a meta-analysis in which we evaluated the role of paricalcitol administration in acute renal failure. PICO in the present study is as follows: P: patients with CKD in the age group of 1 to 19 years, I: oral or intravenous administration of paricalcitol, C: comparison with control group (standard treatment group), and O: serum iPTH levels, serum calcium and phosphate levels and calcium × phosphorus (Ca × P product) ratio.

2-2. Search strategy

Search was conducted in the databases of Medline, EMBASE, Scopus and Web of Science up to the end of October 2019. The search strategy is reported in the Medline database (via PubMed) at **Appendix.1**. To find additional articles, a manual search was carried out in the bibliography of relevant study and related journals. Finally, Google search engine and Google Scholar were searched to find additional articles.

Appendix 1: Medline search query.

1. "Renal Insufficiency, Chronic"[mh] OR "Chronic Kidney Disease"[mh] OR "Kidney Failure, Chronic"[mh] OR Chronic Renal Disease[tiab] OR Kidney Disease[tiab] OR Renal Disease[tiab] OR Kidney Dysfunction[tiab] OR Renal Dysfunction[tiab] OR Decreased Kidney Function[tiab] OR Decreased Renal Function[tiab] OR Kidney Insufficiency[tiab] OR Renal Insufficiency[tiab] OR Kidney Failure[tiab] OR Renal Failure[tiab] OR End-Stage Kidney Disease[tiab] OR Disease, End-Stage Kidney[tiab] OR End Stage Kidney Disease[tiab] OR Kidney Disease, End-Stage[tiab] OR Chronic Kidney Failure[tiab] OR End-Stage Renal Disease[tiab] OR Disease, End-Stage Renal[tiab] OR End Stage Renal Disease[tiab] OR Renal Disease, End-Stage[tiab] OR Renal Disease, End Stage[tiab] OR Renal Failure, End-Stage[tiab] OR End-Stage Renal Failure[tiab] OR Renal Failure, End Stage[tiab] OR Renal Failure, Chronic[tiab] OR Chronic Renal Failure[tiab] OR Esrd[tiab] OR Chronic Renal Insufficiencies[tiab] OR Renal Insufficiencies, Chronic[tiab] OR Chronic Renal Insufficiency[tiab] OR Kidney Insufficiency, Chronic[tiab] OR Chronic Kidney Insufficiency[tiab] OR Chronic Kidney Insufficiencies[tiab] OR Kidney Insufficiencies,

Chronic[tiab] OR Chronic Kidney Diseases[tiab] OR Chronic Kidney Disease[tiab] OR Disease, Chronic Kidney[tiab] OR Diseases, Chronic Kidney[tiab] OR Kidney Disease, Chronic[tiab] OR Kidney Diseases, Chronic[tiab] OR Chronic Renal Diseases[tiab] OR Chronic Renal Disease[tiab] OR Disease, Chronic Renal[tiab] OR Diseases, Chronic Renal[tiab] OR Renal Disease, Chronic[tiab] OR Renal Diseases, Chronic[tiab]

2. Paricalcitol[mh] OR "Vitamin D"[mh] OR 19-nor-1alpha,25-dihydroxyvitamin D2[tiab] OR 19-nor-1,25-(OH)2D2[tiab] OR paricalcitol-d6[tiab] OR Abbott brand of paricalcitol[tiab] OR Cholecalciferol[tiab] OR Hydroxycholecalciferol[tiab] OR Ergocalciferol[tiab] OR 25-Hydroxyvitamin D 2[tiab] OR Dihydrotachysterol[tiab] OR Zemplar[tiab] OR 1,25-dihydroxyergocalciferol[tiab]
3. (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))
4. #1 AND #2 AND #3.

2-3. Selection criteria

Clinical trials and observational studies evaluating the efficacy of paricalcitol in the treatment of pediatric CKD were included. Studies on adult population, without control group, and reviews were excluded.

2-4. Quality assessment and Data Extraction

The method of data collection, abstraction and quality control of articles has been reported in previous studies (8-17). In summary, the search results were combined and the duplicate studies were removed. After careful review and assessment of studies according to the predetermined inclusion and exclusion criteria, relevant articles were included. Data were extracted in a checklist containing data related to article characteristics (first author's name and year of publication), patients' characteristics (age, sex, etiology of CKD), sample size, follow-up duration, duration of drug administration, dosage, method of administration and outcomes. In case of disagreement between the two researchers, the third reviewer studied the findings and resolved the existing disagreement by discussion. The risk of bias among studies was assessed using Cochran's guidelines (18).

2-5. Outcomes

The assessed outcome of the present review was effect of paricalcitol on serum level of iPTH, calcium (Ca), phosphorus, calcium-phosphorus product (Ca × P) ratio, and proteinuria.

2-6. Statistical analysis

All analyses were performed using STATA 14.0 statistical software. Analyses were performed with the use of the "metan" command. Output was reported as overall odds ratio (OR) with 95% confidence interval (95% CI). Heterogeneity between studies was assessed based on I^2 test. Since the studies were homogenous (I^2 <50%), a fixed effect model was used for the analyses. Finally, publication bias was evaluated using Egger's test and Funnel Plot drawing (19).

3- RESULTS

The search resulted in 1,564 non-duplicate articles, of which 37 studies were selected for full text assessments. Of these, only three studies met the inclusion and exclusion criteria (20-22). The PRISMA flow diagram (**Figure.1**) illustrates the selection process. **Table.1** shows the details of the included articles. Two were randomized clinical trials and one retrospective review of patients. There were two studies on end-stage renal disease (ESRD) patients and one on CKD patients at stages 3 and 4. The age range was between 1.5 and 20 years. There were 50 patients in the untreated group (control group), and 53 patients in the paricalcitol group. The route of paricalcitol administration was oral in two and was

intravenous in one study. The administered doses ranged from 0.04 to 1.0 µg. Follow-up also varied between 12 and 28 weeks.

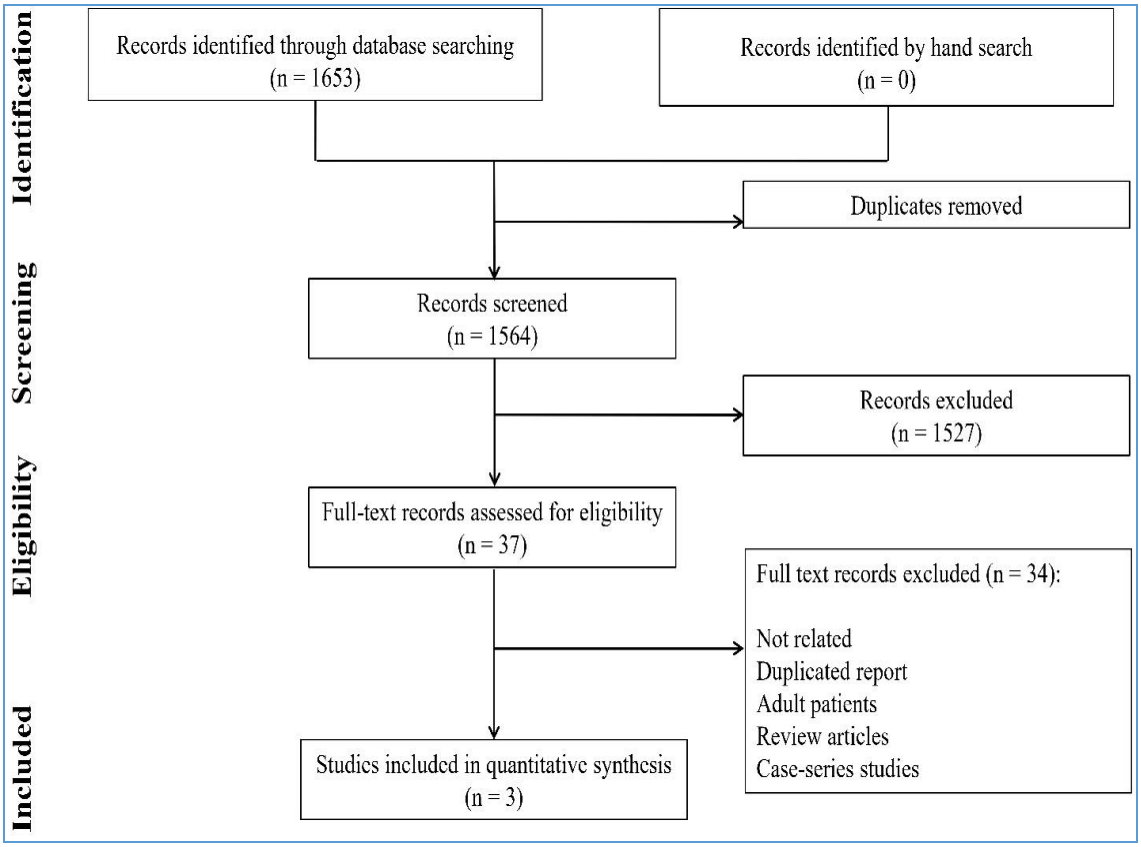

Fig1: PRISMA flow diagram of present study.

Table-1: General characteristics of included studies.

Author; Year; Country	Study design	Setting	Age, year	Control; Treated*	Male sex	Treatment strategy	Follow up (week)	Outcome
Greenbaum, 2007, USA	RCT	ESRD	5 - 19	14; 15	22	Daily oral paricalcitol (0.04 µg/kg) for 12 weeks	12	iPTH; Ca; P; Ca×P product
Seeherunvong, 2006, USA	Retrospecti ve review of patients	ESRD	1.5 -20	18; 20	8	IV paricalcitol three times weekly at dose of 0.04-0.1 µg/kg for average 26±8 weeks	28	iPTH; Ca; P; Ca×P product
Webb, 2017, UK	RCT	Stage 3 or 4 CKD	10–16	18; 18	30	Oral paricalcitol for 12 weeks three times per week for 12 weeks; initial dose of 1 µg; maximum dose 16 µg per week	24	iPTH; Ca; P; Ca×P product

*: Number, Ca: Calcium; CKD: Chronic kidney disease; ESRD: End stage renal disease; iPTH: Intact parathyroid hormone; P: Phosphorous, RCT: Randomized clinical trial.

3-1. Risk of bias assessment and publication bias

No publication bias was observed based on Egger's test and Funnel plot assessment as shown in **Figure.2** (iPTH: p = 0.577, Ca: p = 0.308, P: p = 0.800, Ca × P: p = 0.999). Risk of bias assessment showed risk of bias in random sequence generation, allocation concealment and blinding of patient and researchers was low in one study, unclear in another, while it was high in one study. Risk of incomplete outcome data and selective reporting was low in three studies (**Figure.3**).

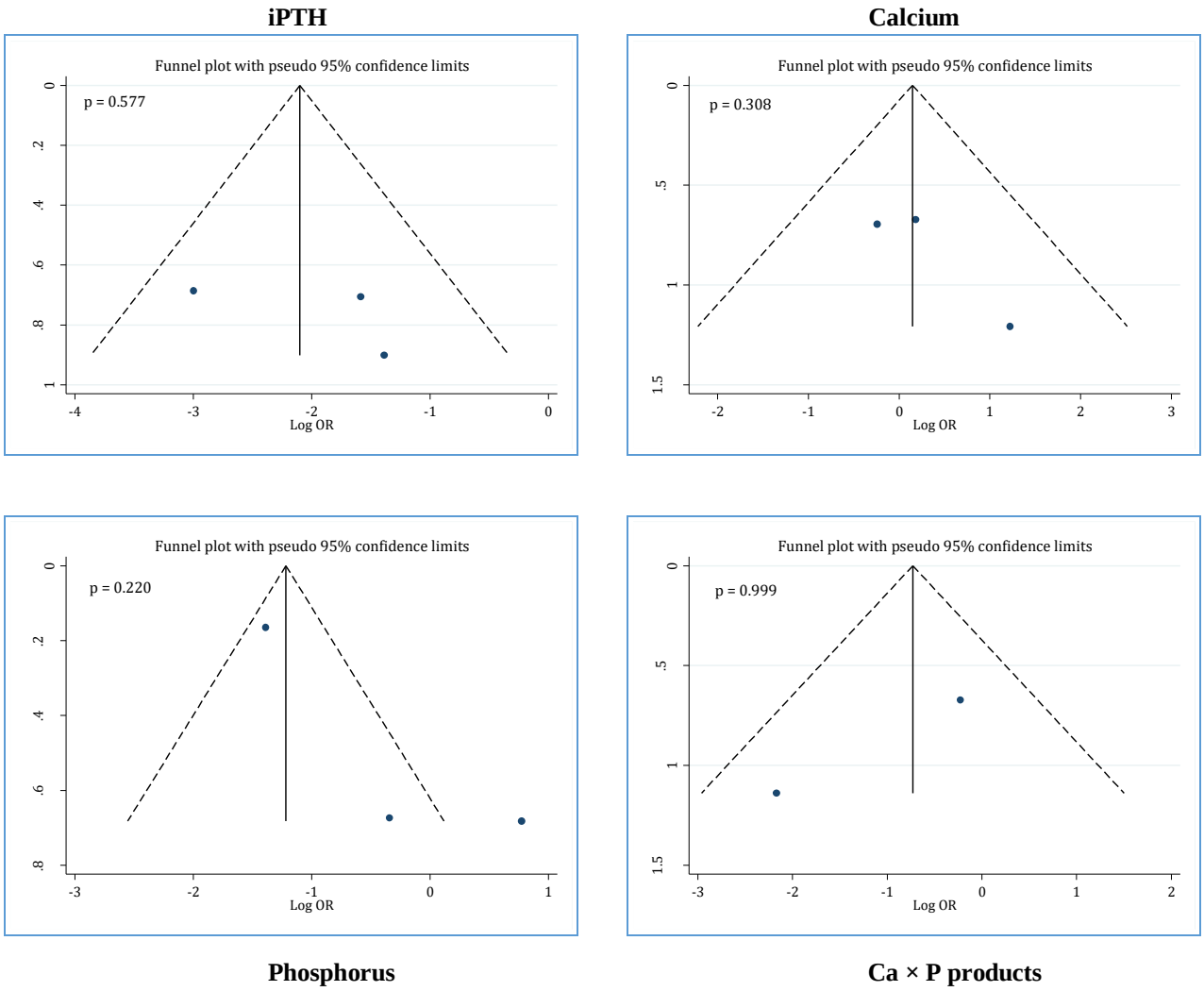

Fig.2: Funnel plot for assessment of publication bias according to outcomes. There was no publication bias. iPTH: Intact parathyroid hormone, Ca: Calcium, P: Phosphorous.

3-2. Meta-analysis

The role of paricalcitol administration on serum levels of iPTH was investigated in three studies. Findings of this section showed that paricalcitol administration reduced iPTH levels in children with CKD (OR = 0.12; 95% CI: 0.05 to 0.29; p <0.001). There was no significant heterogeneity in this section. Paricalcitol administration had no effect on serum calcium level. Pooled analysis performed on data from three studies showed that serum calcium (OR = 1.16; 95% CI: 0.48 to 2.80; p = 0.741), and phosphorus (OR = 0.87; 95% CI: 0.38 to 1.99; p = 0.735) levels did not change significantly after administration of paricalcitol in children with CKD. In addition, it was found that the Ca × P ratio after paricalcitol administration did not differ from those who did not receive the drug (OR = 0.48; 95% CI: 0.15 to 1.50; p = 0.208). It is noteworthy that no heterogeneity was observed among included studies in the efficacy of paricalcitol on serum level of iPTH (I^2=30.2%; p = 0.239, serum calcium level (I^2 = 0.0%; p = 0.574), phosphorous level (I^2 = 47.3%; p = 0.150), and Ca × p product (I^2 = 53.8; p = 0.141) (**Figure.4**).

Bias	Greenbaum, 2007	Seeherunvong, 2006	Webb, 2017
Random sequence generation	Low risk	High risk	Unclear
Allocation concealment	Low risk	High risk	Unclear
Blinding of patients and researchers	Low risk	High risk	Unclear
Blinding of outcome assessment	Low risk	High risk	Unclear
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other bias	Low risk	High risk	Low risk

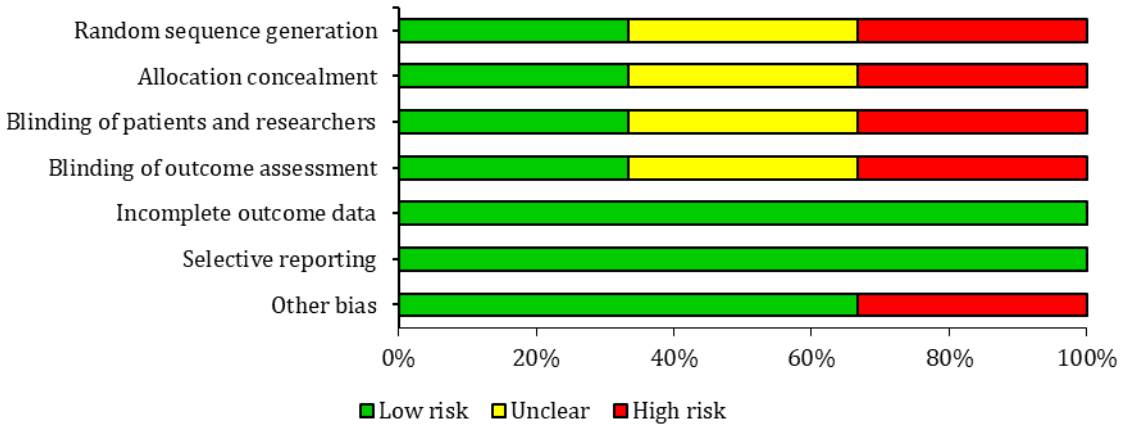

Fig.3: Quality control of included studies.

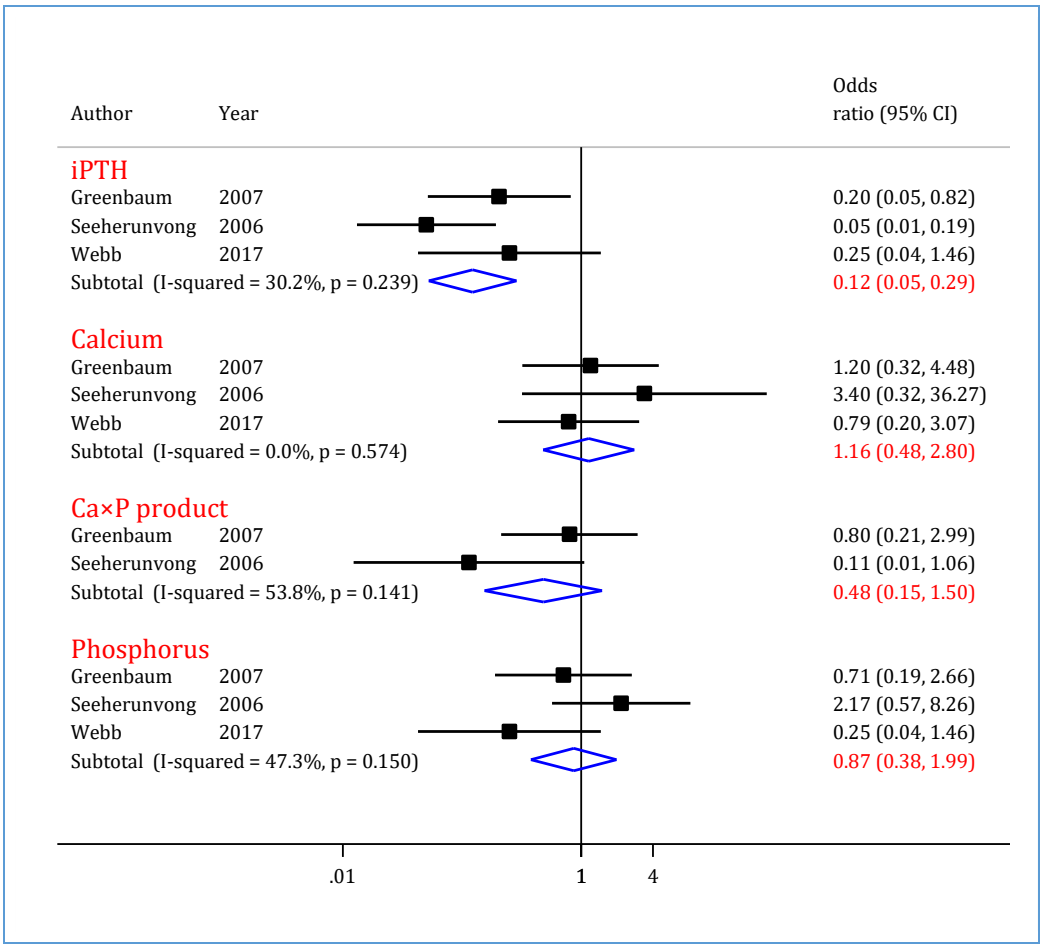

Fig.4: Forest plot for assessment of paricalcitol administration on intact parathyroid hormone (iPTH), calcium (Ca), phosphorous (P) and Ca×P product in pediatric chronic kidney disease.

4- DISCUSSION

The current systematic review found that there are only three studies, which investigated the efficacy of paricalcitol in the management of children with CKD and ESRD. Two of these studies were clinical trials and one was a retrospective review of patients. The findings of these three studies show that administration of paricalcitol in children with chronic renal failure decreased iPTH levels but did not affect serum calcium, phosphorus and Ca × P ratio. One of the main objectives of the present study was to evaluate the efficacy of paricalcitol in the control of proteinuria following CKD. Proteinuria is a major sign of kidney disease and an indicator of the progression of chronic kidney failure (23). Reduced proteinuria has been associated with improved renal outcome (24), and therefore any treatment strategy that reduces protein excretion may be useful in the treatment of CKD (24). Recent studies have suggested that the active form of vitamin D, such as paricalcitol, has potential effects on reducing proteinuria (4). Vitamin D as a compound involved in homeostasis and regulation of the renin-angiotensin signaling pathway (5), has protective effects on the renal system (6).

A meta-analysis on paricalcitol as a potential drug to reduce proteinuria in CKD in adults suggests that this drug inhibits parathyroid hormone secretion and decreases proteinuria in stages 2 to 5 of CKD without increasing the incidence of side effects (7). Secondary hyperthyroidism is a common problem in CKD patients. Elevated levels of iPTH are one of the most common symptoms of secondary hyperthyroidism resulting in decreased calcium levels, phosphate retention, and decreased calcitriol production (25). Increased levels of iPTH are associated with an increased risk of bone metabolism disorders, bone pain and fractures (26, 27). In line with adult studies (7), the findings of present meta-analysis showed that paricalcitol administration reduced iPTH levels without significant change in calcium, phosphorus and Ca × P ratio. Therefore, paricalcitol administration has no effect on the serum levels of calcium and serum compared to other vitamin D analogues such as calcitriol, which induces hypercalcemia and hyperphosphatemia (28-31). Therefore, it seems that paricalcitol is superior to other vitamin D derivatives. On the other hand, in a study on the complications of paricalcitol, Webb et al. reported that most of the effects observed after administration of paricalcitol were mild and the occurrence of dangerous complications was very rare. Therefore, it is also a safe medicine (22).

4-1. Study Limitations

There is no study on paricalcitol effect in reducing proteinuria. Therefore, we could not assess this outcome. In addition, only three studies were included. Although we performed an extra extensive manual search in grey literatures to achieve more articles, no additional studies were included.

5- CONCLUSION

The present study showed that administration of paricalcitol in children with chronic renal failure reduced iPTH levels without affecting on serum level of calcium, phosphorus and Ca × P ratio. However, evidence on the efficacy and safety of paricalcitol in CKD children is limited and further studies are needed. The findings also showed that there are no studies on efficacy of paricalcitol to manage proteinuria in CKD children.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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