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ORIGINAL RESEARCH

Efficacy and safety of paricalcitol in patients undergoing hemodialysis: a meta-analysis

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Background: The elevated calcium and phosphorus levels in patients undergoing hemodialysis may increase the risk of all-cause mortality. Paricalcitol, as a new vitamin D receptor activator (VDRA), seemed to be effective in reducing the calcium and phosphorus levels.

Objectives: The aim of this study was to compare the efficacy and safety of paricalcitol with other VDRAs in patients undergoing hemodialysis.

Methods: PubMed, Embase, and Web of Science database were systematically reviewed.

Selection criteria: Studies that focused on the use of paricalcitol for hemodialysis patients were eligible for inclusion.

Data collection and analysis: Two independent investigators performed the literature search, data extraction, and assessment of methodological quality. The outcomes were expressed with standard mean difference (SMD), HR, or risk ratio (RR) with 95% CI.

Results: Thirteen studies involving 112,695 patients were included in this meta-analysis. Among these studies, four studies were cohort studies and nine studies were randomized controlled trials (RCTs). For cohort studies, they were regarded as being of high quality; for RCTs, only one was classified as being at low risk of bias; and the remaining eight studies were at being unclear risk of bias. Compared with other VDRAs, paricalcitol significantly improved the overall survival (HR =0.86, 95% CI: 0.80, 0.92; $P<0.001$) and reduced the intact parathyroid hormone (iPTH) (SMD =–0.53, 95% CI: –0.90, –0.17; $P=0.004$). Paricalcitol offered similar effect with other VDRAs in the control of calcium (SMD =0.32, 95% CI: –0.04, 0.67; $P=0.078$) and phosphorus (SMD =0.06, 95% CI: –0.26, 0.37; $P=0.727$) levels. However, the serum change in calcium phosphate product was greater in the paricalcitol group than in the other VDRA group (SMD =2.13, 95% CI: 0.19, 4.07; $P=0.031$). There was no significant difference in the incidence of adverse events between the two groups (RR =1.02, 95% CI: 0.93, 1.12; $P=0.674$).

Conclusion: Paricalcitol was crucial in reducing the mortality in patients undergoing hemodialysis. Moreover, both paricalcitol and other VDRAs were effective in control of the serum iPTH, calcium, and phosphorus levels. Given the potential limitations in this study, more prospective large-scale, well-conducted RCTs are needed to confirm these findings.

Keywords: hemodialysis, paricalcitol, vitamin D receptor activator, meta-analysis

Introduction

Despite therapeutic advances have been introduced in the recent years, patients with stage 5 chronic kidney disease (CKD) maintained on hemodialysis still have a higher mortality rate.[1] Secondary hyperparathyroidism (SHPT), bone disorders, and cardiovascular disease are the common complications of CKD and are the main causes of dialysis-related mortality.[2–5] Several methods have been used to improve the survival of CKD patients, including increased doses of dialysis,[6,7] improved nutrition,[8]

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and management of anemia;[9] however, the mortality rates still remain high. In CKD patients, there is a lower level of 1α,25-dihydroxyvitamin D3,[10] which would result in a decrease in intestinal calcium absorption,[11] an increase in parathyroid hormone (PTH) production,[12] and the dysregulation of phosphorus metabolism.[13] Thus, maintaining sufficient levels of vitamin D is very important for CKD patients with SHPT. Parenteral vitamin D is the standard therapy for SHPT since it could effectively suppress PTH secretion.[14] However, the administration of such vitamin D is often associated with elevated calcium and phosphorus levels,[15,16] which may accelerate the vascular disease and hasten death.[17]

Paricalcitol (19-nor-1,25-dihydroxyvitamin D2) is approved in >60 countries for the treatment and prevention of hyperparathyroidism due to chronic renal failure. Previous study has demonstrated that paricalcitol could prolong the survival in patients undergoing chronic hemodialysis[18] and also suppress the intact parathyroid hormone (iPTH) levels in patients with substantially elevated phosphorus levels.[14] However, in another clinical trial conducted in Denmark, they did not observe any benefits of paricalcitol as compared to alfacalcidiol: both drugs had comparable impact on mineral metabolism and side effects.[19] Thus, we conducted this meta-analysis to compare the efficacy and safety of paricalcitol with other vitamin D receptor activators (VDRAs) in hemodialysis patients.

Methods

Literature search

We performed this meta-analysis according to the PRISMA statement guidelines (Table 1).[20] Since this study did not enroll a human or animal experiment, the ethical approval was not necessary.

Table 1 Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2–3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to PICOS	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number	None
Eligibility criteria	6	Specify study characteristics (eg, PICOS and length of follow-up) and report characteristics (eg, years considered, language, and publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (eg, databases with dates of coverage and contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and if applicable, included in the meta-analysis)	4–5
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, and in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (eg, PICOS and funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (eg, risk ratio and difference in means)	5

(*Continued*)

Table 1 (*Continued*)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias and selective reporting within studies)	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses and meta-regression), if done, indicating which were prespecified	5–6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, and follow-up period) and provide the citations	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (refer Item 12)	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and CIs, ideally with a forest plot	7–10
Synthesis of results	21	Present results of each meta-analysis done, including CIs and measures of consistency	7–10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (refer Item 15)	7
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses and meta-regression; refer Item 16)	10
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, health care providers, users, and policy makers)	10
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias) and at review level (eg, incomplete retrieval of identified research and reporting bias)	12–13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other supports (eg, supply of data) and role of funders for the systematic review	None

Abbreviation: PICOS, participants, interventions, comparisons, outcomes, and study design.

Relevant literatures were identified by searching PubMed, Embase, and Web of Science databases from their inception to April 15, 2018.

The structured search strategies were listed as follows: ("haemodialysis" [All Fields] OR "renal dialysis" [MeSH Terms] OR ("renal" [All Fields] AND "dialysis" [All Fields]) OR "renal dialysis" [All Fields] OR "hemodialysis" [All Fields]) AND ("paricalcitol" [Supplementary Concept] OR "paricalcitol" [All Fields]). We did not impose any language limitation in the search strategy. Moreover, we manually searched the reference lists of the included studies until no potential studies could be found.

Study selection

Studies satisfying the following inclusion criteria were as follows: 1) study design: randomized controlled trial (RCT), or case–control study, or cohort study; 2) population: CKD stage 5D adult patients (hemodialysis); 3) study intervention: patients in the study group received paricalcitol, whereas patients in the control group received other VDRAs; and 4) outcomes: overall survival (OS), the mean serum iPTH level change from baseline, mean calcium level change from baseline, mean phosphorus level change from baseline, calcium phosphate product, adverse event, and proportion of subjects with a ≥50% reduction in iPTH.

Data extraction

We constructed a data extraction sheet to extract the data of included studies. Two independent investigators extracted the following data: author's name, publication year, country, study design, number of patients in each group, age, gender, duration of follow-up, and the main outcomes (including OS, mean serum change in iPTH, calcium, and phosphate, and adverse events). Any disagreements between the two investigators were resolved by discussion and consensus.

Quality assessment

The quality of nonrandomized controlled study was assessed by using the modified Newcastle–Ottawa Scale (NOS).[21] This method consists of three items to evaluate the quality of a nonrandomized controlled study, including patient selection, comparability of the intervention/control group, and outcome assessment.[21] The score for each study ranges from 0 (lowest quality) to 9 points (highest quality). Any study with a score of >5 points is regarded as being high quality.[21]

The risk of bias in RCT was assessed by using the method recommended by Cochrane Collaboration.[22] This method used five items to evaluate the quality of study, including blinding, method of randomization, allocation concealment, follow-up, and intention-to-treat analysis.[22] Each study was considered to be high, low, or unclear risk of bias according to the abovementioned criteria.

Statistical analysis

For continuous outcome data (mean serum change in iPTH, calcium, and phosphorus levels), they were calculated with standard mean difference (SMD) with 95% CI; for time-to-event variables (OS), they were expressed as HR with 95% CI; for dichotomous outcome data (adverse events), they were expressed as risk ratio (RR) with 95% CI. Before the data were synthesized, the Cochran Q statistic and I^2 statistic[23] were conducted to test the heterogeneity across the included studies, in which P-value <0.1 or $I^2>50\%$ was considered to represent substantial heterogeneity.[23] Outcome data were pooled using a fixed-effect model[24] or random-effect model,[25] according to the heterogeneity among the included studies. When significant heterogeneity was identified, we performed sensitivity analysis by omitting one study at each turn to explore the potential sources of heterogeneity. The publication bias was assessed using Begg's[26] and Egger's tests.[27] A P-value of <0.05 was considered as statistically significant, except where otherwise specified. All analyses were performed by using STATA Version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Identification of eligible studies

A total of 1,032 potential records were identified by the initial search in the database, of which 658 studies were excluded because of duplicate records. In the process of title/abstracts screening, 354 studies were excluded because they were case reports, reviews, letters, or unrelated with our topics, leaving 20 studies for the full-text information review. Among these studies, seven studies were removed because four studies did not provide outcomes of our interest,[28–31] two studies used paricalcitol in both groups,[32,33] and one study was a study protocol.[34] Finally, 13 studies[18,19,35–45] with a total of 112,695 patients met the inclusion criteria and were included in this meta-analysis (Figure 1).

Study characteristics and quality assessment

The main characteristics of the included studies are presented in Table 2. These studies were published between 2001 and 2018. The total number of included patients was 112,695, ranging from 20 to 67,399 patients per study. Among these studies, four studies were cohorts,[18,35,37,38] whereas the remaining nine studies were RCTs.[19,36,39–45] Of the included studies, ten trials compared paricalcitol with calcitriol,[18,35–39,41–43,45] one study compared paricalcitol with maxacalcitol,[40] one study compared paricalcitol with cinacalcet,[44] and one study compared paricalcitol with alfacalcidol.[19] Tentori et al[37] conducted a three-arm cohort study to compare the survival outcomes among hemodialysis patients with different vitamin D analogs. In that trial, they provided the outcome data between the three groups (paricalcitol vs calcitriol, paricalcitol vs doxercalciferol, and calcitriol vs doxercalciferol); thus, we extracted these data for analysis.[37] In another RCT of Ketteler et al,[44] the authors analyzed the data according to the mode of paricalcitol administration (intravenous [IV] or oral). And they presented the outcome comparison between IV/oral paricalcitol vs cinacalcet, respectively. Therefore, we used all these data for meta-analysis. Ketteler et al[44] conducted an RCT to compare paricalcitol with cinacalcet for the treatment of SHPT in patients receiving hemodialysis. The baseline characteristics, including age, gender distribution, and duration of dialysis, were well-matched between the paricalcitol and cinacalcet groups. Whereas, for co-morbidities, type II diabetes was significantly more prevalent with oral paricalcitol (38.9%) than with oral cinacalcet (12.9%; $P<0.05$). The proportions of patients with cardiovascular co-morbidities were also higher among those in the paricalcitol group than those in the cinacalcet group.

The quality of non-RCT studies was assessed by NOS scale, and the scores ranged from 6 to 7, which indicated that these included studies were high quality (Table 1).

The quality of RCTs was evaluated by the risk of bias. Overall, only one study was regarded as being at low risk of bias[43] and the remaining eight studies were regarded as being at unclear risk of bias. The main reason for the unclear risk of bias was that these studies did not adequately report the blinding performance.[19,36,39–42,44,45]

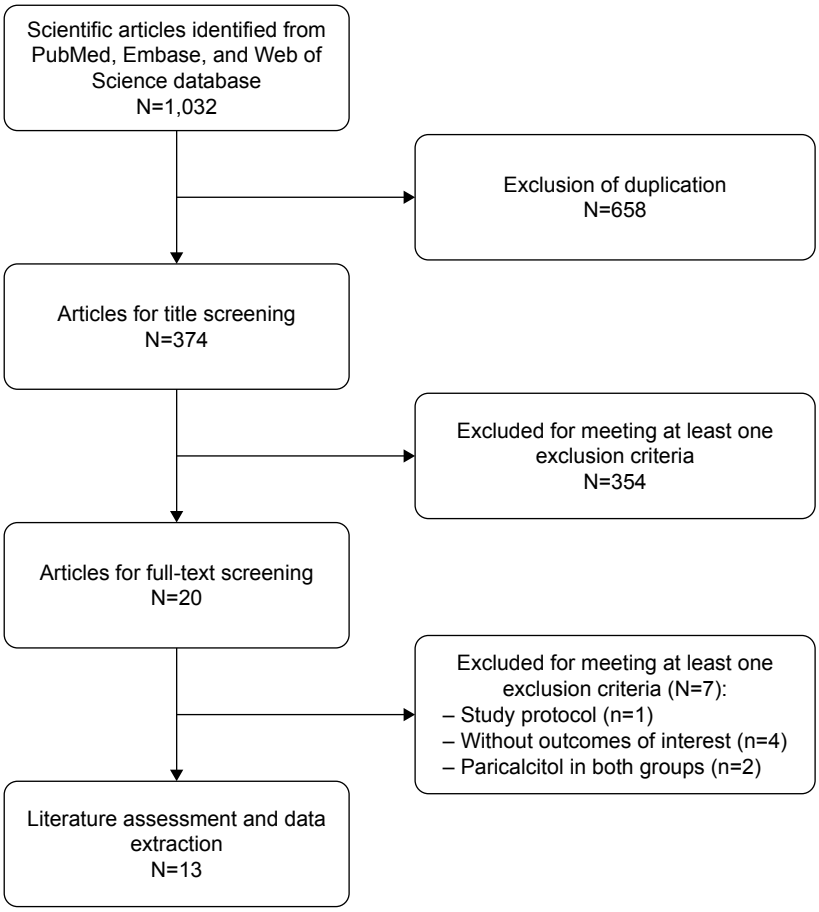

Figure 1 Eligibility of studies for inclusion in meta-analysis.

Overall survival

Four studies reported the data of OS.[18,35,37,38] The pooled estimate suggested that patients treated with paricalcitol had a prolonged OS than those with other VDRAs (HR =0.86, 95% CI: 0.80, 0.92; $P<0.001$) (Figure 2). There was a moderate heterogeneity among the included studies (I^2=51.0%, P=0.086).

Mean serum iPTH change from baseline

Eight studies reported the data of the serum iPTH change from baseline.[18,19,36,37,39,43–45] The serum iPTH level was significantly reduced in both the paricalcitol group and other VDRA group (131.89 vs 113.48 pmol/L). Pooled result showed that paricalcitol was associated with a greater serum iPTH change than other VDRAs (SMD =–0.53, 95% CI: –0.90, –0.17; P=0.004) (Figure 3). The test for heterogeneity was significant (I^2=99.1%, $P<0.001$). Thus, we conducted sensitivity analysis. When we excluded the study with outlier,[44] the overall estimate of remaining studies did not change substantially (SMD =–0.47, 95% CI: –0.48, –0.45; $P<0.001$), but the heterogeneity was still present (I^2=99.4%, $P<0.001$). When we excluded the studies with small sample size (N<100), the pooled result changed a little (SMD =–0.47, 95% CI: –0.49, –0.46; $P<0.001$) and the heterogeneity was still found. When we further excluded the study one by one, the overall estimate and heterogeneity did not alter substantially (data not shown).

Mean serum calcium level change from baseline

The data of serum calcium level were reported in eleven studies.[18,19,35–37,39,41–45] In the paricalcitol group, the serum calcium level increased in ten studies[18,19,35–37,39,42–45] and decreased in one study.[41] Whereas in other VDRA group, the serum calcium level increased in seven studies[18,19,35–37,39,42,43,45] and decreased in two studies.[41,44] The pooled estimate demonstrated that there was no significant difference in serum calcium level change between the two groups (SMD =0.32, 95% CI: –0.04, 0.67; P=0.078) (Figure 4). The test for heterogeneity was significant (I^2=99.0%, $P<0.001$).

We conducted sensitivity analysis to explore the potential sources of heterogeneity. When we excluded the trial with outlier,[44] the pooled result changed substantially, in which

Table 2 Baseline characteristics of patients in the trials included in the meta-analysis

Study	Country	Study design	Treatment regimen	Number of patients	Male/female	Age (years), mean ± SD	NOS score
Teng et al[18]	USA	Cohort	Paricalcitol	29,021	15,091/13,930	60.7	7
			Calcitriol	38,378	20,340/18,038	61.3	
Hansen et al[19]	Denmark	RCT	Paricalcitol	42	26/16	63.7±15.8	NA
			Alfacalcidol	38	25/13	63.7±14.0	
Cozzolino et al[35]	UK	Cohort	Paricalcitol	1,630	1,025/605	68 (56–75)	7
			Calcitriol	823	506/317	68 (58–77)	
Farhat et al[36]	the Netherlands	RCT	Paricalcitol	14	12/2	61.7±10.2	NA
			Calcitriol	13	11/2	62.3±15.4	
Tentori et al[37]	USA	Cohort	Paricalcitol	2,087	1,023/1,064	61 (32–83)	7
			Calcitriol	3,212	1,564/1,648	62 (32–83)	
			Doxercalciferol	2,432	1,267/1,165	62 (33–83)	
Shinaberger et al[38]	USA	Cohort	Paricalcitol	23,727	12,575/11,152	60.8±14.8	6
			Calcitriol	10,580	5,819/4,761	61.8±15.6	
Abdul Gafor et al[39]	Malaysia	RCT	Paricalcitol	13	6/7	48.2±14.1	NA
			Calcitriol	12	8/4	47.8±16.4	
Akizawa et al[40]	USA	RCT	Paricalcitol	127	82/45	61.5±11.2	NA
			Maxacalcitol	128	81/47	61.6±12.5	
Večerić-Haler et al[41]	Slovenia	RCT	Paricalcitol	10	8/2	56	NA
			Calcitriol	10	7/3	50	
Ong et al[42]	Malaysia	RCT	Paricalcitol	36	24/12	46.3±13.1	NA
			Calcitriol	30	17/13	45.4±17.9	
Jamaluddin et al[43]	Malaysia	RCT	Paricalcitol	12	7/5	48.33±12.05	NA
			Calcitriol	14	6/8	39.07±12.67	
Ketteler et al[44]	USA	RCT	Paricalcitol	134	87/47	61.2±12.7	NA
			Cinacalcet	134	81/53	59.9±12.0	
Sprague et al[45]	USA	RCT	Paricalcitol	19	NR	NR	NA
			Calcitriol	19	NR	NR	

Abbreviations: NA, not available; NOS, Newcastle–Ottawa Scale; NR, not reported; RCT, randomized controlled trial.

the mean serum calcium level in paricalcitol group reduced greatly than that in other VDRA group (SMD =–0.54, 95% CI: –0.88, –0.19; P=0.002); however, the heterogeneity was still present (I^2=99.1%, P<0.001). Exclusion of the study with small sample size[36,39,43] altered the overall estimate slightly (SMD =0.28, 95% CI: –0.15, 0.71; P=0.202), but significant heterogeneity was still observed among the remaining studies (I^2=99.4%, P<0.001).

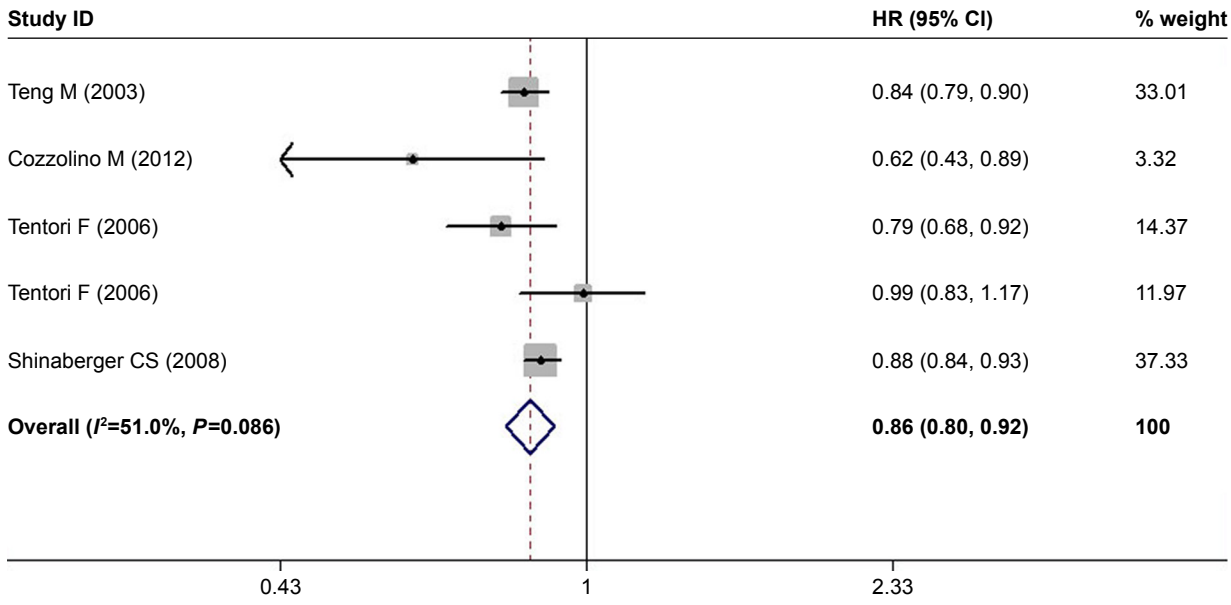

Figure 2 Forest plot showing the effect of paricalcitol on the overall survival.
Note: Weights are from random effects analysis.

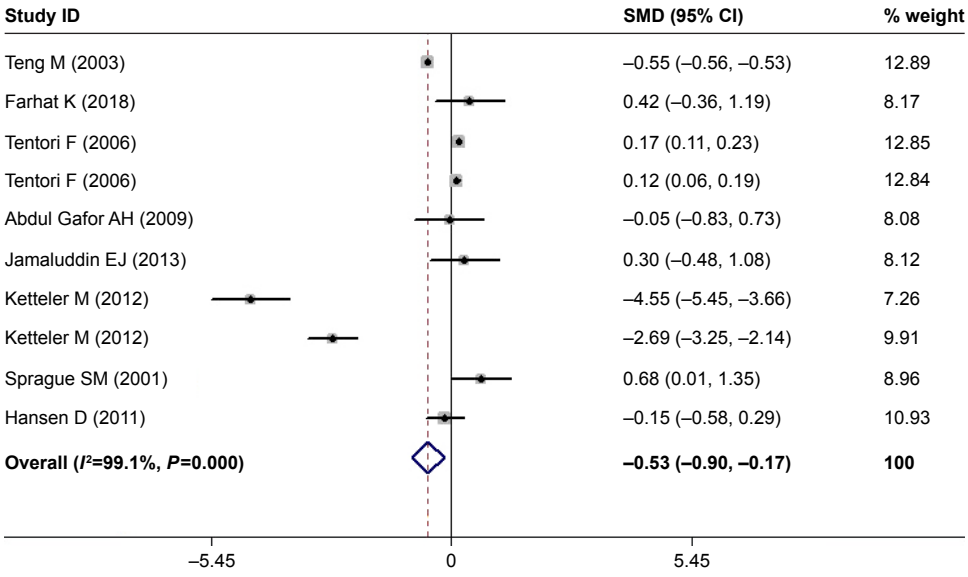

Figure 3 Forest plot showing the effect of paricalcitol on the intact parathyroid hormone.
Note: Weights are from random effects analysis.
Abbreviation: SMD, standard mean difference.

Mean serum phosphorus level change from baseline

Eight studies reported the data of serum phosphorus.[18,19,36,37,39,41,42,44] In both the paricalcitol and other VDRA groups, the serum phosphorus decreased in three studies[39,41,42] and increased in four studies.[18,19,36,37,44] The aggregated result showed that patients who received paricalcitol had a similar change in serum phosphorus level with those treated with other VDRAs (SMD =0.06, 95% CI: –0.26, 0.37; P=0.727) (Figure 5). There was significant heterogeneity among the included studies (I^2=98.7%, P<0.001).

Sensitivity analysis was conducted. When we excluded the trial with outlier,[44] the pooled result changed substantially, in which paricalcitol was associated with a greater

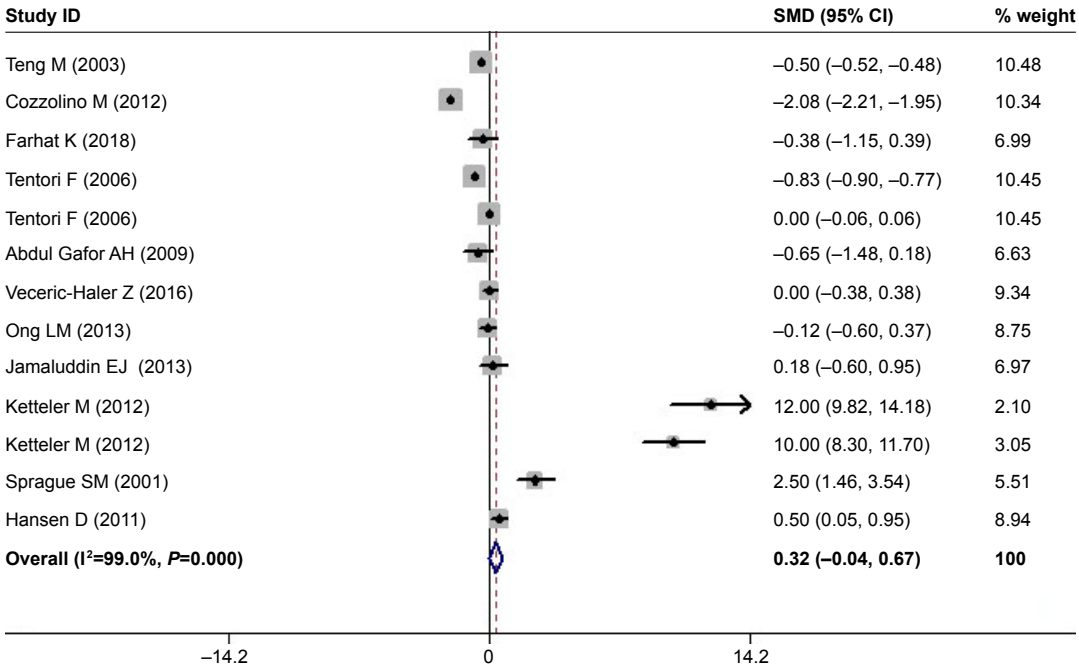

Figure 4 Forest plot showing the effect of paricalcitol on the serum calcium level.
Note: Weights are from random effects analysis.
Abbreviation: SMD, standard mean difference.

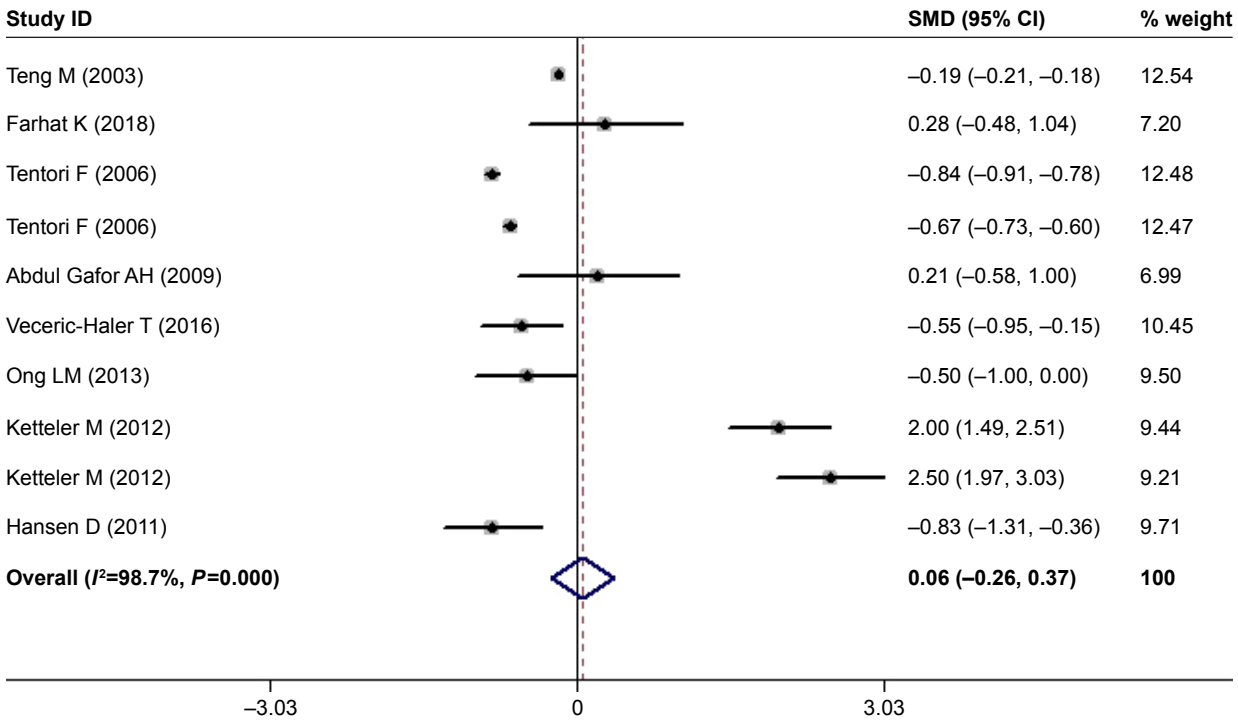

Figure 5 Forest plot showing the effect of paricalcitol on the serum phosphorus level.
Note: Weights are from random effects analysis.
Abbreviation: SMD, standard mean difference.

serum phosphorus change than other VDRAs (SMD =–0.41, 95% CI: –0.74, –0.08; P=0.016); however, there was still substantial heterogeneity among the remaining studies (I^2=98.9%, P<0.001). When we removed studies with small sample size,[36,39] the overall estimate change slightly (SMD =0.13, 95% CI: –0.23, 0.50; P=0.464), but the heterogeneity was still present (I^2=99.1%, P<0.001).

Mean serum change in calcium phosphate product

Five studies reported the data of serum change in calcium phosphate product.[19,41–44] Pooled estimate suggested that paricalcitol was associated with a greater change in calcium phosphate product (SMD =2.13, 95% CI: 0.19, 4.07; P=0.031). There was significant heterogeneity among the included studies (I^2=98.1%, P<0.001).

Proportion of subjects with a ≥50% reduction in iPTH

Three studies reported the data of patients with a ≥50% reduction in iPTH.[19,40,43] There was no significant difference in the proportion of subjects with a ≥50% reduction in iPTH between the paricalcitol and other VDRA groups (RR =0.99, 95% CI: 0.76, 1.31; P=0.967). The test for heterogeneity was not significant (I^2=0.0%, P=0.735).

Adverse events

The data of adverse events were reported in three studies.[40,42,44] The incidence of adverse events in paricalcitol and other VDRA groups was 88.89 and 88.01%, respectively. Pooled estimate showed that there was no significant difference in the incidence of adverse events between the two groups (RR =1.02, 95% CI: 0.93, 1.12; P=0.674). There was a moderate heterogeneity among the included studies (I^2=56.0%, P=0.103).

Publication bias

We used the Egger's and Begg's tests to assess the publication bias, and the results showed that no publication bias existed among the included studies (Egger's test: t=–0.34, P=0.679; Begg's test: Z=0.28, P=0.735).

Discussion

The aim of this study was to compare the efficacy and safety of paricalcitol with other VDRAs in dialysis patients. Our results suggested that patients treated with paricalcitol had a significantly prolonged OS and greatly reduced iPTH level as compared with those with other VDRAs. Moreover, the serum changes in calcium, phosphate, and calcium phosphate product were comparable between the paricalcitol and other VDRAs. Patients in these two groups had a similar incidence of adverse events.

To the best of our knowledge, this is the first comprehensive meta-analysis to assess the efficacy and safety of paricalcitol with other VDRAs in patients undergoing hemodialysis. In the present study, we found that patients treated with paricalcitol had a significant survival advantage than those treated with other VDRAs. Our result was consistent with the previous published studies. Teng et al[18] conducted a historical cohort study to compare the survival rate among patients who received paricalcitol (n=29,021) or calcitriol (n=38,783).[18] At the end of 36-month follow-up, the mortality rates in these two groups were 3,417 deaths during a total of 19,031 person-years of observation (0.18 per person-year) and 6,805 deaths during 30,471 person-years (0.223 per person-year).[18] The mortality rates between them was significantly different (rate ratio =0.80, 95% CI: 0.77, 0.84; $P<0.001$).[18] Moreover, patients who switched from calcitriol to paricalcitol achieved a survival benefit than those who switched from paricalcitol to calcitriol.[18] However, in another clinical trial,[37] they reported a different result, in which paricalcitol had a comparable mortality rate with doxercalciferol. In that study, hemodialysis patients received paricalcitol (n=2,087), doxercalciferol (n=2,432), or calcitriol (n=3,212).[37] At the end of 37-week follow-up, the mortality rates (deaths/100 patient-years) in these patients were 15.3 (95% CI: 13.6, 16.9), 15.4 (95% CI: 13.6, 17.1), and 19.6 (95% CI: 18.2, 21.1).[37] Patients treated with paricalcitol achieved a similar mortality rate than those with doxercalciferol but a significantly lower mortality rate than those with calcitriol.[37] The estimates of the HRs for paricalcitol vs doxercalciferol were 0.99 (95% CI: 0.84, 1.15) and were not significantly different.[37]

In terms of the iPTH level, we found that both paricalcitol and other VDRAs were associated with a reduction in serum iPTH level; however, the mean change in paricalcitol group was greater than that in other VDRA group. Our results were supported by most of the included studies.[18,19,39,44] Ketteler et al[44] performed an international, multicenter RCT, in which patients were randomly assigned to receive paricalcitol or cinacalcet plus low-dose vitamin D. At the end of 28-week follow-up, the mean iPTH reduction was −244.2 pg/mL in the IV paricalcitol group as compared with −78.4 pg/mL in the cinacalcet group.[44] Also, in the oral stratum, the mean iPTH reduction in the oral paricalcitol group was −216.3 pg/mL compared with −150.3 pg/mL in the cinacalcet group.[44] This indicated that paricalcitol would result in a greater reduction in iPTH level than cinacalcet no matter what the model of its administration was.[44]

Regarding the serum calcium and phosphorus levels, several studies demonstrated that paricalcitol had similar serum changes in calcium and phosphorus than in other VDRAs.[39,41–43] In a RCT that compared the efficacy and safety of oral paricalcitol with oral calcitriol,[42] the serum calcium and phosphorus changes did not differ between the two groups.[42] At the 24 weeks, the serum calcium increased by 0.20 mmol/L in the oral paricalcitol group, compared with 0.19 mmol/L in the oral calcitriol group.[42] The changes between them were not significant ($P>0.05$). In addition, the serum phosphate change was not significant between them, with a 0.01 mmol/L decrease in the oral paricalcitol group and 0.27 mmol/L increase in the oral calcitriol group.[42] Contrast to their results, Ketteler et al[44] found significant differences in serum calcium and phosphorus levels between paricalcitol and cinacalcet groups. In that study, oral paricalcitol increased the calcium level by 0.3 mg/dL, whereas cinacalcet reduced it by 0.7 mg/dL ($P<0.05$).[44] As for the serum phosphorus level, oral paricalcitol increased it by 0.7 mg/dL, whereas cinacalcet increased it by 0.2 mg/dL ($P<0.05$).[44] The authors concluded that paricalcitol was more effective than cinacalcet in achieving the optimal control of calcium and phosphorus.[44]

According to this study, we found that the incidence of adverse events between paricalcitol and other VDRA groups was not significantly different. The most common adverse events related to paricalcitol included hypercalcemia, hyperphosphatemia, and cardiovascular disorders. Akizawa et al[40] reported that 47 (37.0%) and 17 (13.4%) patients in the paricalcitol group developed hypercalcemia and hyperphosphatemia, compared with 51 (39.8%) and 14 (10.9%) patients in the maxacalcitol group, respectively. And the differences between the two groups were not significant.

The present has several potential limitations that should be considered when interpreting our results. First, our meta-analysis was performed based on 13 studies and some of them had a relatively small sample size (n<50). Compared with large-scale trials, studies with small sample size would result in an overestimation of treatment effect. Second, substantial heterogeneity was observed among the included studies. However, one should not be surprising given the differences in patient characteristics (gender, race, age, and comorbidities), treatment regimen (mode of paricalcitol administration, dosage of paricalcitol, and comparators), and study design (RCT or non-RCT, multicenter trial, and sample size). These factors might explain the resources of the heterogeneity. Third, there was variability among the included studies in the length of follow-up and this was particularly important for evaluating the serum changes in iPTH, calcium, and phosphate. Fourth, although not all of the included studies were RCTs, it did not impact the credibility

of our results, since the baseline characteristics in each study were well matched for each group, and there was no significant difference between the two groups.

Conclusion

This study indicated that paricalcitol was crucial in reducing the mortality and iPTH level in patients undergoing hemodialysis. Moreover, both paricalcitol and other VDRAs were effective in the control of the serum calcium and phosphorus levels. Given the potential limitations in this study, more prospective large-scale, well-conducted RCTs are needed to confirm these findings.

Author contributions

YL and L-YL are co-first authors. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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