A Bayesian network analysis on comparative efficacy of treatment strategies for dialysis patients with secondary hyperparathyroidism

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Abstract. For dialysis patients with end-stage kidney disease and secondary hyperparathyroidism (SHPT), there are three therapeutic treatment options: Cinacalcet, paricalcitol and cinacalcet plus low-dose vitamin D analogues. However, their comparative efficacy remains unclear at present. Thus, in the current study, a Bayesian network analysis was conducted to evaluate the relative efficacy and safety of these three therapeutic regimens. A comprehensive literature database query was performed. The primary outcome was the treatment effect on serum parathyroid hormone (PTH) levels. Secondary outcomes included the occurrence of nausea and hypocalcaemia. A total of 20 randomized clinical trials, including 5,390 dialysis patients, were entered into the analysis. Paricalcitol, cinacalcet plus vitamin D analogue and cinacalcet were significantly more efficacious in controlling PTH levels compared with conventional therapy (which comprises calcium-based phosphate binders, non-calcium-based phosphate binders and vitamin D analogues) [odds ratio (OR)=3.99, 2.91 and 2.47, respectively] and placebo (OR=20.32, 14.89 and 12.56, respectively). Paricalcitol was identified as the most efficacious of the three treatments. According to a ranking analysis, patients treated with cinacalcet had a higher possibility of frequently developing nausea and hypocalcaemia compared with patients treated with cinacalcet plus low-dose active vitamin D analogues. All three therapeutic treatment options were efficacious for the treatment of dialysis patients with SHPT in controlling PTH levels. Paricalcitol had the highest possibility of being the most optimal one. Thus, paricalcitol therapy may be the most optimal regimen in controlling PTH levels, but this should be confirmed by further study.

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Abbreviations: CKD, chronic kidney disease; SHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; RCT, randomized controlled trial

Key words: secondary hyperparathyroidism, cinacalcet, paricalcitol, vitamin D analogues, Bayesian network analysis

Introduction

Chronic kidney disease (CKD) has become a significant public health problem. In 2014, the United States National Center for Chronic Disease Prevention and Health Promotion reported an overall prevalence rate of CKD in adults of 10%, suggesting that >20 million Americans have CKD (1). In China, the prevalence was estimated to be 10.8% of the adult population in 2012, including ~119.5 million individuals with CKD (2). Secondary hyperparathyroidism (SHPT) is a common chronic complication of CKD, particularly in dialysis patients, with a prevalence rate of 28-54.5% (3,4). SHPT can result in fluctuating parathyroid hormone (PTH) levels that are refractory to treatment and in disordered mineral metabolism that increases the risk of cardiovascular disease, fractures and mortality (5,6).

An increasing number of options are currently available for the treatment of SHPT (7). Treatment with conventional medications, including calcium-based phosphate binders, non-calcium-based phosphate binders and vitamin D analogues, may cause hypercalcemia and hyperphosphatemia, potentially accelerating vascular calcification (3). Previously, two novel medications, cinacalcet and paricalcitol, have been increasingly prescribed for the treatment of SHPT. Cinacalcet was the first calcimimetic agent approved by the United States Food and Drug Administration for treating dialysis patients with SHPT and it has been demonstrated to reduce PTH levels and improve bone mineral metabolism without increasing all-cause mortality or adverse cardiovascular outcomes (8,9). Several randomized controlled trials (RCTs) have suggested that the use of cinacalcet plus vitamin D analogues can achieve a better treatment effect in patients with SHPT compared with conventional therapy, in terms of controlling PTH levels, serum calcium and phosphate levels (10,11). Paricalcitol is a third-generation selective vitamin D analogue, with a higher affinity for the parathyroid glands compared with the gastrointestinal tract and thus, it can effectively reduce PTH levels (12,13). However, it remains unclear as to which therapeutic regimen is most efficacious in controlling PTH levels with the most favorable side effect profile.

Bayesian network analyses are an extension of traditional meta-analysis that integrate direct and indirect evidence, and enable to concurrently compare and indirectly estimate the relative efficacy of several agents in the presence of inadequate data from direct head-to-head RCTs (14). A Bayesian network analysis was conducted to evaluate the relative efficacy and relatively common side effects of cinacalcet, paricalcitol and cinacalcet plus low-dose vitamin D analogues therapeutic regimens in dialysis patients with SHPT.

Materials and methods

Search strategy and selection criteria. A systematic review according to preferred reporting items for systematic reviews and meta-analyses guidelines (15) was performed in the present study. The search included PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), the Cochrane Library (https://www.cochranelibrary.com/), Embase (https://www.embase.com/), China Biology Medicine disc (http://sdd.sxsrsc.com/), Wanfang database (http://www.wanfangdata.com/) and the China National Knowledge Infrastructure (http://global.cnki.net/new/index.html) using the Population Intervention Comparison Outcome Study design (PICOS) strategy with advanced queries and with Medical Subject Headings (MeSH) search terms from inception to December 10th 2017 without language restrictions. Only patients with CKD on dialysis and SHPT that were treated with cinacalcet (Sensipar®), paricalcitol (Zemplar®) or cinacalcet plus vitamin D analogues, were included. Reference lists of review articles, meta-analyses and original studies were evaluated in order to determine further eligible trials.

PICOS criteria. Selection using PICOS was based on the following: Population, dialysis-dependent patients with CKD and SHPT; intervention, paricalcitol, cinacalcet or cinacalcet with a vitamin D analogues therapy regimens; comparator, placebo or conventional therapy; outcomes, abnormal PTH levels, hypocalcemia and/or nausea; and study design, RCTs.

MeSH search terms. Search terms included: Secondary hyperparathyroidism, dialysis, paricalcitol, cinacalcet and randomized controlled trials.

Study inclusion criteria. The following inclusion criteria were applied in the selection of eligible studies: i) RCTs; and ii) adult patients (≥18 years old) receiving dialysis for >3 months. Patients with parathyroidectomy or kidney transplantation were excluded.

Data extraction and quality assessment. Data were extracted from primary studies by two independent researchers, including article information (Jadad score, first author, publication year, geographic region) and participant characteristics (sample size, mean age, gender, duration of intervention). The five-point Jadad scale (16) was used to assess the methodological quality of studies, including randomization, blinding and withdrawals and dropouts. A score of ≤2 points was defined as low quality, while a score of ≥3 points was ranked as high quality.

Two reviewers (HY and PY) performed the title, abstract, content review and quality assessment of each trial and every comparison. Data extraction was performed by the same reviewers (HY and PY). Disagreements were resolved by discussion with a third researcher (YK) to reach consensus. All data were entered into Aggregate Data Drug Information System (ADDIS) 1.16.5 software (17) by one reviewer (ZZ) and was verified by a second reviewer (ZL).

Data analysis. Primary outcomes in this study included the rate of attaining normal PTH levels following treatment. Stata 14.0 (StataCorp LP, College Station, TX, USA) was used to assess consistency and inconsistency with the Bayesian method and to explore discrepancies among studies and differences among direct and indirect comparisons. Inconsistency was evaluated using the Higgins model. Basic network diagrams and comparison-adjusted funnel plots were also prepared with Stata 14.0 and 'network meta' orders.

Pair-wise meta-analysis of the same interventions was conducted using ADDIS with a random effects model. The GEADE approach was applied for rating the quality of evidence obtained for every comparison (18). Bayesian network analyses were performed using ADDIS with consistency and inconsistency models. For PTH analysis, 4 chains, including 20,000 burn-ins, 50,000 simulation iterations, 10,000 inference samples and a thinning interval of 10 for each chain were applied. To attain a good convergence property for symptoms of nausea and hypocalcaemia, 4 chains, including 20,000 burn-ins, 40,0000 simulation iterations and 160,000 inference samples with a thinning interval of 10 were used. A potential scale reduction factor parameter (PSRF) was assessed using the Brooks-Gelman-Rubin method to show convergence of the model. PSRF values <1.2 were acceptable and the closer to 1, the better the convergence effect. A sensitivity analysis was performed that included the trial with outcomes defined as ≥30% reduction in PTH using ADDIS software with the consistency random effects model.

The method named 'the effective sample size' was applied to calculate the effective sample size for indirect evidence in the present publication (19). It was used as an approach to measure the degree of power and precision from an indirect comparison to consider the collection of trials included in each comparison as one clinical trial.

Results

Literature selection and study characteristics. A total of 720 articles were identified in the initial literature query and 26 further articles were identified through screening references of various relevant systematic reviews. Following screening titles and abstracts, 40 articles eligible for PICOS analysis remained. Out of these, a total of 5,390 dialysis patients from 20 RCTs that met the inclusion criteria and were entered into the analysis (6,10,11,13,20-35) The selection procedure is summarized in Fig. 1. Eligible comparisons for the primary outcome are presented in Fig. 2 and a summary of the characteristics of included studies is presented in Tables I and II.

In the current study, the following treatment regimens were considered for analysis: i) Cinacalcet; ii) paricalcitol; iii) cinacalcet plus low-dose active vitamin D analogues; iv) conventional therapy, including phosphate binders and/or vitamin D analogues; and v) placebo.

Table I. Basic characteristics of included studies.

Author, year	Jadad score	Country (no. centers)	Age (years)		Gender (male/female)		Duration of dialysis (month)		Refs.
			T	C	T	C	T	C	
Moe *et al*, 2005	4	North America, Europe and Australia (182)	NS	NS	407/258	295/176	NS	NS	(8)
Fishbane *et al*, 2008	2	USA (42)	57.7±14.9[b]	59.0±12.4[b]	52/35	45/41	46.3±36.4[b]	46.8±44.1[b]	(10)
Urena-Torres *et al*, 2013	3	France	57.9±13.6[b]	57±14.6[b]	83/70	95/56	87.5±30.5[b]	84.2±33.4[b]	(11)
Martin *et al*, 1998	3	USA (multicenter)	54±14[b]	54±16[b]	21/19	19/19	NS	NS	(13)
Block *et al*, 2004	4	North America (63), Europe and Australia (62)	54±14[b]	55±15[b]	226/145	229/141	72±63[b]	72±68[b]	(20)
El-Shafey *et al*, 2011	2	Egypt (5)	51.5±12.7[b]	51.81±14.96[b]	27/28	14/13	48.1±25.1[b]	44.1±21.4[b]	(21)
Fukagawa *et al*, 2008	5	Japan (29)	54.7±11.0[b]	55.7±11.7[b]	40/32	37/34	170.4±93.7[b]	173.3±76[b]	(22)
Hansen *et al*, 2011	2	Denmark	63.5±15.3[b]	49.2±3.8[b]	28/17	27/14	38 (3-236)[a]	36 (3-262)[a]	(23)
Ketteler *et al*, 2012	3	12 countries worldwide (89)	NS	NS	87/81	47/53	NS	NS	(24)
Lindberg *et al*, 2003	4	USA (23), Canada (2)	52.7±16.4[b]	48.8±15.6[b]	24/15	22/17	60.3±58.3[b]	69.7±53.9[b]	(25)
Lindberg *et al*, 2005	4	USA, Canada, Australia	51.8±14[b]	53.5±13.9[b]	181/113	64/37	56.4±53.1[b]	63.6±65[b]	(26)
Martin *et al*, 2005	5	USA and Canada (65)	53±14[b]	54±15[b]	123/82	123/82	67±56[b]	62±55[b]	(27)
Messa *et al*, 2008	2	Europe (111)	58.5±14.5[b]	58.3±14.5[b]	224/144	117/67	64.1±72.1[b]	69.4±73.6[b]	(28)
Quarles *et al*, 2003	4	USA (17)	49.6±8.5[b]	47.9±14.2[b]	27/9	17/18	71.3±54.3[b]	71.1±66.2[b]	(29)
Ross *et al*, 2008	4	USA (multicenter)	57.0±1.62[b]	56.4±2.5[b]	37/24	22/5	NS	NS	(30)
Sprague *et al*, 2003	3	USA, Netherlands, Spain, Switzerland (27)	56.7±15.5[b]	56.6±14.3[b]	70/60	80/53	NS	NS	(31)
Sterrett *et al*, 2007	5	USA (47), Europe (10), Australia (5), Canada (4)	51.6±13.4[b]	52.9±15.2[b]	54/45	71/40	72±63[b]	66±67[b]	(32)
Wetmore *et al*, 2015	2	USA, Russia, Canada, Australia (58)	53 (21-81)[a]	55 (22-86)[a]	93/62	95/62	32.9[a] (4.3-216.7)	38.1 (4.5-308.2)[a]	(33)
Mei *et al*, 2016	3	China (12)	50.02±11.17[b]	50.12±11.34[b]	68/50	68/48	92.4±53.9[b]	89.7±55.1[b]	(34)
Han *et al*, 2015	2	China	58.9±19.8[b]	68.8±4.4[b]	28/22	29/21	51.3±17.9[b]	58.9±19.8[b]	(35)

Data are presented as [a]median (range), [b]mean ± standard deviation.

Table II. Treatment and outcome characteristics of included studies.

Author, year	Interventions		Dialysis modality (duration in weeks)	Target PTH level	At target		Nausea		Calcium abnormity		Refs.
	T	C			T (n)	C (n)	T (n)	C (n)	T (n)	C (n)	
Moe *et al*, 2005	30-180 mg/day cinacalcet	Placebo	HD and PD (26)	100-250 pg/ml	307	42	170	78	NS	NS	(8)
Fishbane *et al*, 2008	Cinacalcet with paricalcitol or doxercalciferol (2 μg or 1 μg, TIW)	2 μg paricalcitol, 1 μg doxercalciferol (TIW)	HD (33)	≥30% decrease	38	20	9	0	6	0	(10)
Urena-Torres *et al*, 2013	Cinacalcet plus calcitriol, 0.25 μg paricalcitol 1 μg or alfacalcidol 0.25 μg per day	Phosphate binders, vitamin D sterols	HD (52)	≥30% decrease	96	57	30	15	25	1	(11)
Martin *et al*, 1998	0.04 μg/kg TIW paricalcitol	Placebo	HD (12)	≥30% decrease	27	3	NS	NS	NS	NS	(13)
Block *et al*, 2004	30-180 mg/day cinacalcet	Placebo	HD (26)	≥30% decrease	239	42	119	70	19	3	(20)
El-Shafey *et al*, 2011	30-180 mg/day cinacalcet	Alfacalcidol TIW	HD (36)	150-300 pg/ml	30	5	7	1	6	0	(21)
Fukagawa *et al*, 2008	25-100 mg/day cinacalcet	Placebo	HD (14)	PTH ≤250 pg/ml	37	2	26	14	4	2	(22)
Hansen *et al*, 2011	18.1 μg/week paricalcitol	5.3 μg/week alfacalcidol	HD (16)	≥30% decrease	39	31	NS	NS	24	21	(23)
Ketteler *et al*, 2012	(Dose unavailable) Paricalcitol	Cinacalcet plus 1.0 μg doxercalciferol TIW or oral alfacalcidol 0.25 ug/day	HD (28)	150-300 pg/ml	62	39	NS	NS	6	52	(24)
Lindberg *et al*, 2003	20-50 mg/day cinacalcet	Placebo	HD (18)	≥30% decrease	14	3	8	12	3	0	(25)
Lindberg *et al*, 2005	30-180 mg/day cinacalcet	Placebo	HD\PD (26)	≥30% decrease	187	13	86	22	14	1	(26)
Martin *et al*, 2005	30-180 mg/day cinacalcet	Placebo	HD (26)	≥30% decrease	125	23	NS	NS	NS	NS	(27)
Messa *et al*, 2008	30-180 mg/day cinacalcet	Phosphate binders and vitamin D sterols	HD and PD (26)	PTH ≤300 pg/ml	261	40	32	3	NS	NS	(28)
Quarles *et al*, 2003	25-100 mg/day cinacalcet	Placebo	HD (18)	≥30% decrease	19	8	NS	NS	NS	NS	(29)
Ross *et al*, 2008	Paricalcitol	Placebo	HD, 62; PD, 26 (12)	≥30% decrease	53	3	NS	NS	1	0	(30)
Sprague *et al*, 2003	0.12 μg/kg paricalcitol	0.03 μg/kg paricalcitol	HD (32)	≥50% decrease	81	72	NS	NS	30	39	(31)
Sterrett *et al*, 2007	30-180 mg/day cinacalcet	Placebo	HD (52)	≥30% decrease	61	16	13	6	11	2	(32)
Wetmore *et al*, 2015	30-180 mg/day cinacalcet	0.5 mg calcitriol TIW	HD (40-52)	≥30% decrease	66	53	NS	NS	27	0	(33)
Mei *et al*, 2016	25-100 mg/day cinacalcet	Placebo	HD	PTH ≤250 pg/ml	30	4	34	3	9	2	(34)
Han *et al*, 2015	25-75 mg/day cinacalcet plus calcitriol 25 mg TIW	25-75 mg/day cinacalcet	HD (12)	25-75 pg/ml	47	41	NS	NS	NS	NS	(35)

HD, hemodialysis; PD, peritoneal dialysis; PTH, parathyroid hormone; T, treatment; C, control; NS, not stated; TIW, three times a week; KDOQI, Kidney Disease Outcomes Quality Initiative.

Table III. Parathyroid hormone response rates and efficacy from meta-analyses of direct comparisons between treatments.

Treatment group	Studies (n)	Patients (n)	Response rate		OR (95% CI)	I^2 (%)
			Treatment	Control		
Paricalcitol vs.						
Conventional therapy	2	343	120/172	103/171	1.51 (0.95-2.41)	0
Placebo	2	166	80/101	6/65	35.24 (13.7-93.11)	0.62
Cinacalcet vs.						
Conventional therapy	3	946	357/578	98/368	3.97 (1.07-14.70)	93.6
Placebo	9	3,765	1,265/2,115	185/1,650	11.48 (9.20-14.67)	12
Cinacalcet + vitamin D analogues vs.						
Conventional therapy	2	477	134/240	77/237	2.7 (1.85-3.95)	0

The response rate is defined as the number of responders/number of total randomized patients. OR, odds ratio; CI, confidence interval; I^2, heterogeneity.

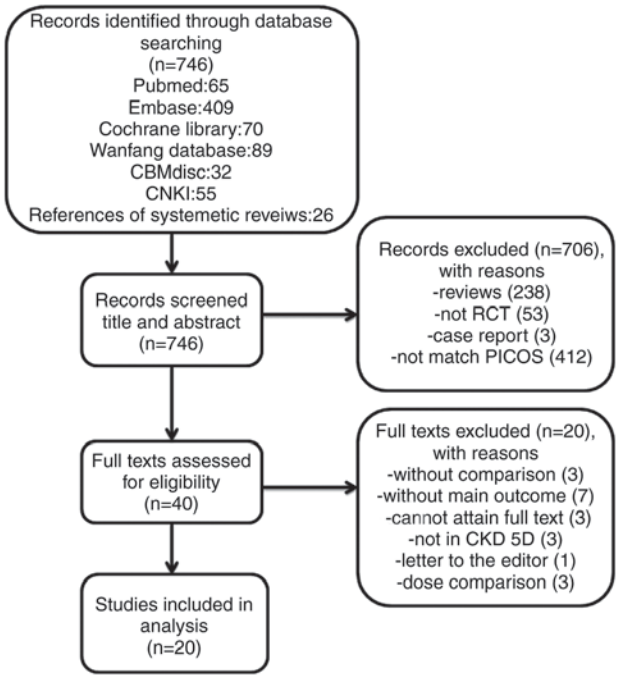

Figure 1. Flow diagram outlining the trial selection. RCT, randomized controlled trial; CBMdisc, China Biology Medicine disc; CNKI, China National Knowledge Infrastructure; PICOS, Population Intervention Comparison Outcome Study design; CKD, chronic kidney disease; CKD 5D, the fifth stage of chronic kidney disease with dialysis.

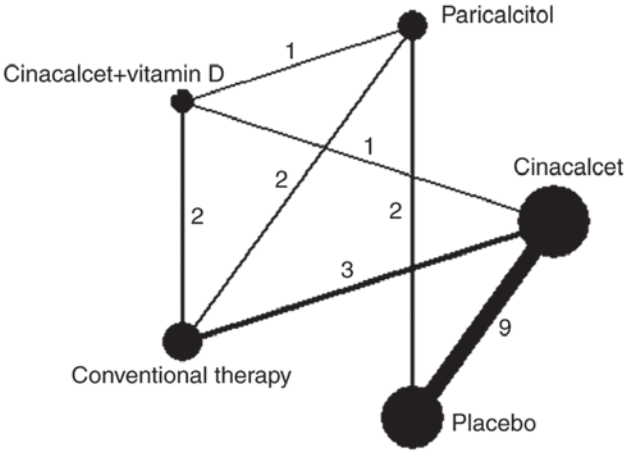

Figure 2. Network of interventional treatments. Numbers on connecting lines refer to head-to-head comparisons. Line thicknesses represented the number of studies performed using the two therapies. The sizes of the circle represented the number of the patients using this therapy.

In the present analysis, 3,552 patients were males (65.7%). Among the 20 trials, 14 (70.0%) (6,11,13,20,22,24-27,29-32,34) had detailed records on withdrawals and dropouts and 14 (70.0%) (6,11,13,20,22,24-27,29-32,34) had Jadad scores ≥3 points. A total of 17 (85.0%) (6,10,13,20-22,24-34) trials were reported as multicenter studies and 10 (50.0%) (6,20,24-28,31-33) were multinational.

Consistency and inconsistency of the network analysis. Consistency testing of the network analysis was performed using 'network meta' orders in Stata 14.0. The results suggested low heterogeneity among the data sets, with a standard deviation for estimating the heterogeneity between studies of 0.41 (P>0.05; data not shown). The method was further applied to test for inconsistency using the Higgins model, exhibiting no evidence for inconsistency, with P>0.05 (data not shown). As a consequence, the Bayesian network analysis was conducted with the consistency random effect models.

Meta-analysis results. Table III indicated that treatment strategies with cinacalcet and paricalcitol had significantly higher rates of controlling PTH levels compared with the placebo, with odds ratios (ORs) of 11.48 (95% confidence interval CI, 9.20-14.67) and 35.24 (95% CI, 13.7-93.11), respectively, and low heterogeneity was observed (I^2=12.0 and 0.62%). Cinacalcet plus low-dose active vitamin D analogues and paricalcitol had better effects in controlling PTH compared with conventional therapy with ORs of 1.51 (95% CI, 0.95-2.41) and 2.7 (95% CI, 1.85-3.95), respectively, with little heterogeneity (I^2=0.0% for both). In addition, cinacalcet had significantly higher rates of controlling PTH levels compared with conventional therapy,

Table IV. Estimated effects and quality ratings based on parathyroid hormone levels for treatment comparisons.

	Direct evidence		Indirect evidence		Network meta-analysis	
Treatment group	OR (95% CI)	Quality	OR (95% CI)	Quality	OR (95% CI)	Quality
Cinacalcet vs.						
Cinacalcet + vitamin D analogues	1.32 (-0.57, 3.38)	Low	-0.20 (-1.33, 0.96)	Low	0.17 (-0.80, 1.22)	Low
Conventional therapy	-1.37 (-2.15, -0.62)	Low	0.44 (-0.85, 1.82)	Low	-0.90 (-1.63, -0.12)	Low
Placebo	-2.44 (-2.95, -1.92)	Moderate	-3.81 (-5.66, -1.95)	Moderate	-2.54 (-3.05, -2.01)	Moderate
Paricalcitol vs.						
Cinacalcet + vitamin D analogues	0.77 (-0.76, 2.31)	Moderate	-0.06 (-1.33, 1.28)	Moderate	0.31 (-0.70, 1.30)	Moderate
Conventional therapy	-0.56 (-1.65, 0.45)	Moderate	-2.23 (-3.36, -1.17)	Moderate	-1.37 (-2.27, -0.53)	Moderate
Placebo	-3.72 (-5.15, -2.45)	High	-2.40 (-3.69, -1.12)	High	-3.00 (-4.05, -2.09)	High
Cinacalcet + vitamin D analogues vs.						
Conventional therapy	-0.98 (-2.11, 0.11)	Low	-1.23 (-2.83, 0.17)	Low	-1.07 (-1.96, -0.23)	Low

OR, odds ratio; CI, confidence interval.

with OR 3.97 (95% CI, 1.07-14.70), but high heterogeneity was observed (I^2=93.6%).

In addition, a novel GRADE approach was applied for rating the quality of evidence obtained for every comparison (18). The comparison of paricalcitol vs. placebo exhibited a high quality of evidence. Three other pairs exhibited moderate qualities (cinacalcet vs. placebo, cinacalcet + vitamin D analogues vs. paricalcitol and paricalcitol vs. conventional therapy; Table IV).

Bayesian network analysis results. All 20 included trials reported the number of patients reaching normal PTH levels following treatment (6,10,11,13,20-35). As presented in Table V, treatment with paricalcitol, cinacalcet and cinacalcet plus vitamin D analogues improved clinical outcomes for normalized serum PTH compared with conventional therapy or the placebo with regards to consistency and inconsistency models.

Furthermore, based on the Bayesian probability framework, the primary outcome was ranked as paricalcitol > cinacalcet plus low-dose active vitamin D analogues > cinacalcet > conventional treatment > placebo. As presented in Table VI, paricalcitol had the highest probability of being the most effective therapy (68%), followed by cinacalcet plus low-dose active vitamin D (45% probability for rank 2) and cinacalcet (59% probability for rank 3).

Regarding the occurrence of nausea, a frequent side effect of cinacalcet, 11 studies were included (6,10,11,20-22,25, 26,28,32). The ranks of the incidence of nausea were cinacalcet (74%) > placebo (44%) > cinacalcet plus low-dose active vitamin D analogues (52%) > conventional treatment (96%; data not shown).

Hypocalcaemia was reported in 10 studies (10-11,20-22, 25,26,32-34). The ranks of incidence of hypocalcaemia were cinacalcet (100%) > cinacalcet plus low-dose active vitamin D analogues (99%) > placebo (99%) > conventional treatment (100%; data not shown).

Sensitivity analysis. As trial outcomes differed, with ≥30% reduction in PTH in certain cases (10,11,13,20,23,25-27, 29,30,32,33) and numerical or guideline-based targets (6,21,22,24,28,31,34,35) in others, a sensitivity analysis was performed that solely included trials with the outcome defined as ≥30% reduction in PTH. The result suggested that paricalcitol had the highest probability of being the most effective therapy (85%). However, cinacalcet (54%) obtained second place while cinacalcet plus low-dose active vitamin D analogues (52%) ranked third (data not shown).

Publication bias. A funnel plot analysis was performed to assess publication bias. The results presented in Fig. 3 exhibited little publication bias.

Sample size. A method called effective sample size was applied to calculate the effective sample size for indirect evidence in the present publication (19). The results suggested this number was 112 in the comparison of conventional treatment and placebo and 312 in the comparison of paricalcitol and conventional treatment (data not shown). These values were below the

Table V. Bayesian network analysis of parathyroid hormone levels.

A. Consistency model

Treatment group	Cinacalcet	Cinacalcet + vitamin D analogues	Paricalcitol	Placebo	Conventional therapy
Cinacalcet	-	1.19 (0.47-3.31)	1.62 (0.65-4.39)	0.08 (0.05-0.13)	0.41 (0.20-0.88)
Cinacalcet + vitamin D analogues	0.84 (0.30-2.15)	-	1.37 (0.51-3.65)	0.07 (0.02-0.18)	0.34 (0.14-0.78)
Paricalcitol	0.62 (0.23-1.54)	0.73 (0.27-1.97)	-	0.05 (0.02-0.12)	0.25 (0.10-0.57)
Placebo	12.56 (7.44-21.10)	14.89 (5.48-43.53)	20.32 (8.18-56.63)	-	5.09 (2.25-12.12)
Conventional therapy	2.47 (1.14-5.04)	2.91 (1.28-6.95)	3.99 (1.76-9.93)	0.20 (0.08-0.44)	-

B. Inconsistency model

Treatment group	Cinacalcet	Cinacalcet + vitamin D analogues	Paricalcitol	Placebo	Conventional therapy
Cinacalcet	-	2.02 (0.53-11.03)	2.94 (0.66-20.96)	0.09 (0.05-0.14)	0.29 (0.14-0.64)
Cinacalcet + vitamin D analogues	0.50 (0.09-1.89)	-	1.50 (0.49-4.58)	0.04 (0.01-0.19)	0.38 (0.16-0.89)
Paricalcitol	0.34 (0.05-1.52)	0.67 (0.22-2.02)	-	0.03 (0.01-0.09)	0.43 (0.15-1.16)
Placebo	11.67 (7.31-18.54)	23.60 (5.23-115.12)	35.54 (11.23-126.85)	-	14.95 (3.35-80.01)
Conventional therapy	3.44 (1.57-7.03)	2.64 (1.13-6.18)	2.34 (0.86-6.79)	0.07 (0.01-0.30)	-

Data are presented as odds ratio (95% confidence interval).

Table VI. Ranking of treatment based on parathyroid hormone levels.

	Rank				
Treatment	1	2	3	4	5
Cinacalcet	0.1	0.31	0.59	0.01	0
Cinacalcet + vitamin D analogues	0.22	0.45	0.32	0.01	0
Paricalcitol	0.68	0.24	0.08	0	0
Placebo	0	0	0	0	1
Conventional therapy	0	0	0.02	0.98	0

Data are presented as the probability.

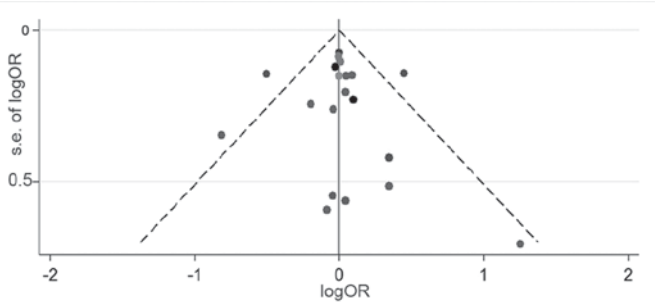

Figure 3. Publication bias based on parathyroid hormone levels. Substantial publication bias is not suggested by the funnel plot. OR, odds ratio; s.e., standard error.

number of patients included in the analysis performed in the present study.

Discussion

Previous meta-analysis suggested that all treatment strategies of cinacalcet, paricalcitol and cinacalcet plus vitamin D analogues were effective at controlling PTH levels among dialysis-dependent patients with CKD (9,36). However, due to inadequate data from direct head-to-head RCTs, the best strategy cannot be identified. Thus, a Bayesian network analysis was performed in the present study to take advantage of direct evidence to indirectly estimate the relative efficacy. The analysis revealed that among the treatment strategies, paricalcitol was the best therapeutic approach for patients with CKD and SHPT in the dialysis stage, followed by cinacalcet plus low-dose active vitamin D, cinacalcet, conventional therapy and placebo. It was further revealed that treatment with cinacalcet plus low-dose active vitamin D analogues may reduce the incidence of nausea and hypocalcaemia compared with cinacalcet alone.

The results demonstrated that both cinacelcet and paricalcitol are more efficient at controling iPTH than conventional therapy, which is consistent with findings from previous meta-analyses (9,36,37). As a calcimimetic agent, cinacalcet acts on vitamin D and Ca^{2+}-sensing receptors of the parathyroid glands to suppress PTH secretion and to reduce PTH serum levels (22,38,39). Treatment with cinacalcet produces a greater proportion of patients, who achieved the Kidney Disease Outcomes Quality Initiative (KDOQI) target (target, a PTH of 150-300 pg/ml; OR=10.75; 95% CI, 6.65-17.37) when compared with conventional therapy (9). Rat models of SHPT demonstrated that cinacalcet attenuates the progression of parathyroid hyperplasia by reducing the number of parathyroid cells and decreasing the weight of the parathyroid (40). Yamada *et al* (41) reported that cinacalcet therapy combined with vitamin D analogues significantly decreased the volume of the parathyroid gland and PTH serum levels in hemodialysis patients with SHPT. These findings support the application of combination therapy to enable patients to achieve KDOQI targets (OR=3.51; 95% CI, 2.38-5.17) (37). Paricalcitol was further reported to be superior to conventional therapy in terms of decreasing serum PTH levels (36). Paricalcitol is a tissue-selective vitamin D sterol with an increased affinity for the parathyroid glands compared with the intestine (42). Thus, it can differentially regulate PTH secretion from parathyroid glands and absorption of calcium and phosphate by the gastrointestinal tract.

The present analysis suggested that treatment strategies with cinacalcet, cinacalcet plus low-dose active vitamin D analogues and paricalcitol were superior to conventional therapy in dialysis patients with SHPT. In addition, consistent with previous observations (25,43), it was revealed that paricalcitol may be the most effective drug for controlling PTH and serum calcium. Previously, a retrospective cohort study suggested that patients receiving paricalcitol had a 74% lower parathyroidectomy incidence rates compared with patients receiving cinacalcet (43). Even with adjustment for comorbidities, gender, therapy time and other risk factors, the risk of parathyroidectomy was increased in the cinacalcet group compared with the paricalcitol group (43). Collectively, the data from the current study and the literature suggested that paricalcitol may provide marked benefits for treating SHPT in dialysis patients with advanced CKD.

Based on the results of the Bayesian network analysis, insufficient data was obtained to suggest that cinacalcet plus low-dose vitamin D analogues provided increased control of PTH levels compared with cinacalcet alone. However, with lower a probability for developing nausea or hypocalcaemia, cinacalcet plus vitamin D analogues may be a more suitable treatment, improving hypocalcaemia and/or hyperphosphatemia side effects caused by cinacalcet (40,44). The combination of cinacalcet plus low-dose vitamin D therapy

further allows reducing the dosage of cinacalcet, resulting in decreased occurrence of nausea (9).

There are several limitations to the present network analysis. Due to the absence of head-to-head RCTs on paricalcitol and cinacalcet plus vitamin D analogues in dialysis patients with SHPT, future studies are required for further elucidation. Only two trials included peritoneal dialysis patients and therefore the determined outcomes may be more relevant for hemodialysis patients. Calcium and phosphate burden, and vascular calcification effects of the treatments in patients with SHPT were not sufficiently considered. Finally, included studies applied varying treatment dosages, which may affect the drawn conclusions.

In conclusion, all three therapeutic treatment options were efficacious in the treatment of dialysis patients with advanced CKD and SHPT. To maintain stable control of serum PTH levels with potentially fewer side effects, including nausea and hypocalcaemia, cinacalcet with low-dose vitamin D analogues was determined to be a safe and efficacious option. Among the therapeutic regimens studied, paricalcitol may offer the best profile for efficacy with the lowest rates of side effects.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

HY and PY conceived and designed the study. HY, PY and YK collected and abstracted the data. HY, ZZ, AH and ZL undertook the statistical analysis. HY, AH, ZL and ZZ drafted the manuscript. All authors had access to the data and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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