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Network meta-analysis of efficacy and safety of chlorthalidone and hydrochlorothiazide in hypertensive patients

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Hypertension is a chronic condition leading to increased stress on the heart and blood vessels, a critical risk factor for clinically significant events such as myocardial infarction heart failure, stroke and death. Chlorthalidone and hydrochlorothiazide are first-line antihypertensive agents for most patients with hypertension. The aim of our meta-analysis was to compare the efficacy and safety of both therapies in patients with hypertension. Searches of electronic databases PubMed, MEDLINE, Scopus, PsycInfo and eLIBRARY.ru, were performed. We used network meta-analysis to combine direct and indirect evidence. Forest plots and closed loops depict estimated results from studies included in our meta-analysis. Of 1289 identified sources, only 37 were included in our meta-analysis. Our analysis has demonstrated a slight superiority for chlorthalidone regarding SBP and not statistically significant differences regarding DBP. Simultaneously, hydrochlorothiazide seems to be a safer choice of therapy, as evidenced by the levels of serum potassium. The two diuretics can be used interchangeably. *Blood Press Monit* 26: 160–168 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

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Keywords: blood pressure, chlorthalidone, clinical trial, controlled, diuretics, double blind, hydrochlorothiazide, hypertension, hypokalemia, hyponatremia, potassium, randomi*, sodium

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Introduction

Blood pressure (BP) is the force that circulating blood places against the walls of blood vessels [1]. Hypertension is defined as SBP (normal values <130 mmHg) above 140 mmHg and DBP (normal values <85 mmHg) above 90 mmHg [1,2]. Hypertension is a condition that increases stress on the heart and blood vessels and predisposes for clinically significant events including myocardial infarction, heart failure, stroke, ischemic heart disease mortality and death [3–5].

The first-line antihypertensive agents for most patients with hypertension are thiazide diuretics for more than 4 decades. Chlorthalidone, considered a thiazide-like and hydrochlorothiazide considered a thiazide-type are two such agents [6]. Both hydrochlorothiazide and chlorthalidone were approved by the US Food and Drug Administration more than 50 years ago. Comparable efficacy of both preparations was documented soon after approval but at much higher doses than are currently used [7]. Several years later, the study advisory board for the landmark multicenter Multiple Risk Factor Intervention Trial, recommended that all patients be given chlorthalidone exclusively because of the unfavorable trend in mortality in hydrochlorothiazide-treated patients [8,9].

Many of the differences in effectiveness and safety of hydrochlorothiazide and chlorthalidone are thought to be due to their different pharmacodynamic and pharmacokinetic effects. The common sulfonamide group in the structure of both drugs inhibits carbonic anhydrase activity, which may be associated with lower vascular contractility. Both drugs are concentrated in the kidney and secreted into the tubular lumen [10]. Therefore, their therapeutic diuretic effects are often achieved with relatively low plasma concentrations, also leading to modest natriuresis and diuresis, because of inhibition of the sodium-chloride cotransporter in the luminal membrane of the distal convoluted tubule of the ascending loop of Henle [11,12].

These two drugs have a different pharmacokinetic property in regard to their duration of action. Hydrochlorothiazide reaches its peak of action after 4–6 h and despite its short duration of action – up to 12 h – its pharmacodynamics response can be much longer, which allows once-daily dosing [10]. Chlorthalidone has a very high volume of distribution because it is taken up into red blood cells and is bound to carbonic anhydrase which may explain a longer duration of action [13]. This may result in a 'drug reservoir' that keeps drug levels higher for a longer time [14,15]. Chlorthalidone could lead to

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lower intracellular pH, and cell volume due to the ability to inhibit carbonic anhydrase more than hydrochlorothiazide [11,15].

The primary point of this network meta-analysis (NMA) is to compare the efficacy of chlorthalidone and hydrochlorothiazide in the population with hypertension. A secondary point of our analysis was to decipher the changes in serum potassium levels caused by chlorthalidone and hydrochlorothiazide. Both drugs increase potassium and hydrogen ions and promote increased reabsorption of calcium through increased expression of a sodium-calcium exchange channel [10].

Methods

The objective of this analysis was to compare the efficacy of chlorthalidone and hydrochlorothiazide on adult hypertensive patients and to assess their safety profiles.

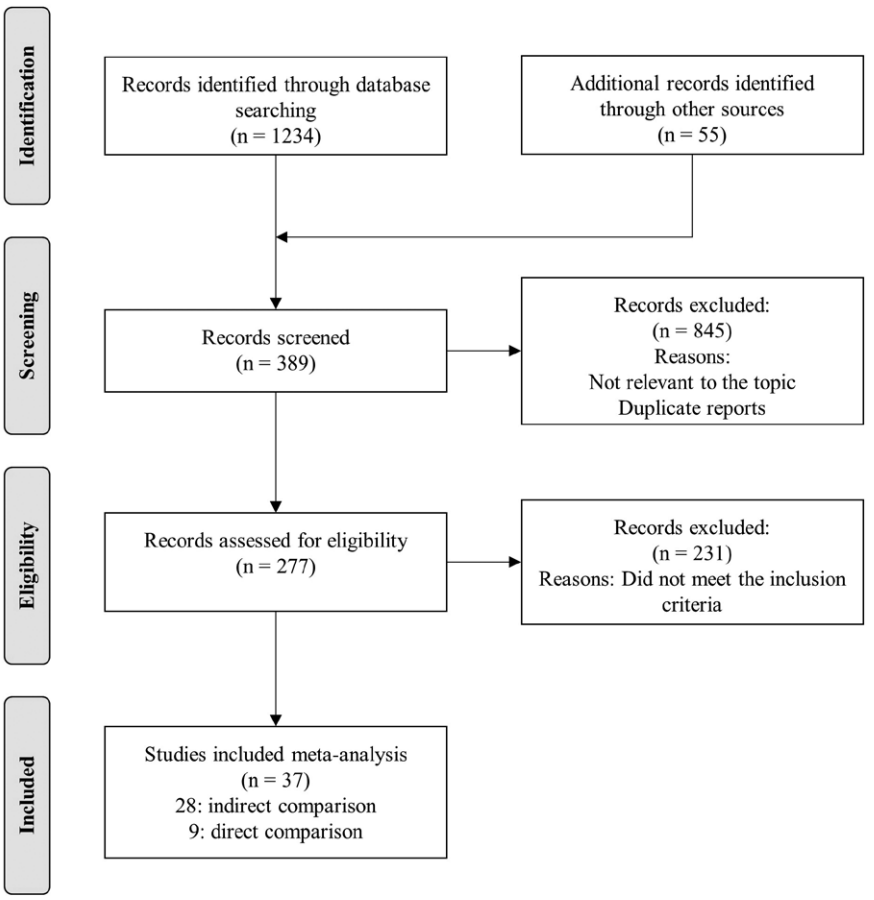
Data sources and search strategy

In our meta-analysis, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. We searched for evidence in PubMed, Medline, Scopus, PsycInfo and eLIBRARY.ru, as well as registries for data of clinical trials (*http://www.clinicaltrialsregister.eu* and *http://ClinicalTrials.gov*) (1975–2018/Sept) using the following keywords: hydrochlorothiazide, chlortalidone, diuretics, hypertension, blood pressure, hypokalemia, hyponatremia, potassium, sodium, clinical trial, controlled, randomi*, double blind. The following search strategy was applied: diuretics AND hydrochlorothiazide OR chlorthalidone AND hyponatremia OR sodium AND blood pressure OR hypertension AND hypokalemia OR potassium AND clinical trial AND controlled AND randomized OR double-blind OR observational. We search for full-text articles and abstracts published in Latin (English) and Cyrillic. Results in Cyrillic were not found. Searched studies were carefully reviewed, sorted and assessed. Figure 1 represents a PRISMA flow-diagram which describes the process of screening of identified studies.

Inclusion criteria

To be included in the NMA, studies were demanded to meet the following criteria: (1) randomized controlled studies and observational studies investigating different

Fig. 1



Flowchart of the study selection process.

doses of chlorthalidone and hydrochlorothiazide; (2) studies comparing the efficacy of hydrochlorothiazide and chlorthalidone indirectly, through placebo and such directly comparing both products; (3) chlorthalidone and hydrochlorothiazide alone or in combination with other antihypertensive regimen; (4) determination of changes in SBP and DBP and changes in SBP or DBP; (5) determination of changes in the serum potassium and sodium levels and (6) type of participants: patients with mild to moderate essential hypertension.

Data extraction, quality assessment and statistical analysis

Data about SBP, DBP and changes in serum potassium levels were presented as a weighted mean difference with a 95% confidence interval (CI). The changes of BP and serum potassium and sodium levels were computed as the difference in the BP values at the final follow-up (or specific time-point if multiple time-points were provided) compared to the baseline measurement. All data extracted were recorded in Microsoft Excel and the calculations and graphics are made by module MetaXL (add-ins on Microsoft Excel). In the present meta-analysis, both fixed- and random-effect models were applied. The random-effects model was used to take into account the possible methodological variation between studies. If the difference between random effects variance and inconsistency variance was large ($P<0.05$), then significant heterogeneity was present. The results of our meta-analyses are presented visually by forest plots.

Score developed from the criteria of Jadad was utilized to assess study quality which had a possible range from zero to five, including double-blinding, randomization and drop-outs. It was defined as high quality if a study scored range from three points to five points. Only the studies which are not blind and randomized were deemed to be of weak quality due to their minimum scores regarding questions of randomization and blinding.

Parallel to the traditional statistical analysis, we have performed an NMA. This type of analysis allows us to investigate the combination of direct and indirect comparisons of different drugs. Mixed treatment comparison is combining results of direct and indirect estimates providing a more refined and precise estimate of the interventions. All graphics of the NMA, summarize the number of studies comparing different treatments and number of patients who have been involved in each treatment (see Tables 1 and 2). The sizes of the nodes and the thicknesses of the edges represent the amounts of respective evidence for specific nodes and comparisons.

Results

The complete study selection process is shown in Fig. 1. We screened a total of 1289 articles, abstracts and meta-analysis. We excluded 1012 which were duplicated or unrelated to the topic, 277 proved relevant to the topic. Only 37 complied with our inclusion criteria and were included in our meta-analysis. Twenty-eight (2–29) from these 37 were dealing with indirect comparison between hydrochlorothiazide and chlorthalidone through placebo and 9 [8,44–51] with direct comparison between both preparations. Summarized extracted data about the year of publication, duration of treatment, number of patients and baseline SBP/DBP levels, levels of serum sodium, levels of serum potassium is presented in Tables 1 and 2. These studies were published between 1975 and 2018. The duration of trials covering indirect comparing was between 4 and 52 weeks and for direct comparison duration of trials was between 6 and 346 weeks. Even though the duration for the indirect comparisons is 4–52 weeks – only one of the studies is beyond the 12-week mark and for the direct comparison where studies were between 6 and 346 weeks only two of the studies were beyond the 18-week mark. In total, 6045 patients participated in the trials representing indirect comparison; and 51 789 patients participated in the trials related to direct comparisons. Patients with mild to moderate essential hypertension of both sexes were included. Four trials were observational and 33 were randomized controlled. Due to a great variety of doses, we chose to analyze the data for most commonly used 12.5–25 mg for both preparations. There are only two studies where 15 mg chlorthalidone dose was used [24,39]. All of the included studies were published in English.

Indirect treatment comparison

Figure 2a presents the results from indirect comparison of chlorthalidone and hydrochlorothiazide. The analysis made shows that chlorthalidone reduced the SBP on average between 4 and 5 mmHg more compared with hydrochlorothiazide. We calculated weighed mean difference (WMD) (95% CI) equal to –4.74 mmHg (–7.20, –2.28). Based on this analysis, we can claim that in these doses chlorthalidone is more effective than hydrochlorothiazide and the difference is considered to be statistically significant. There are more studies comparing hydrochlorothiazide with placebo, while the number of publications with chlorthalidone compared with placebo is relatively small.

Figure 2b presents the results from indirect comparison of chlorthalidone and hydrochlorothiazide through comparator placebo. Our analysis shows that chlorthalidone reduced the DBP by less than 1 mmHg on average compared to hydrochlorothiazide. Calculated WMD (95% CI) is –0.59 mmHg (–2.02, 0.84) which means that the difference between the two treatments is considered to be statistically not significant. There are more studies comparing hydrochlorothiazide with placebo, while the number of publications with chlorthalidone compared with placebo is relatively small.

Mixed treatment comparison

Figure 3a presents the results from direct comparison (chlorthalidone vs hydrochlorothiazide) and indirect comparisons

Table 1 Characteristics of articles included in this meta-analysis – indirect comparison

Study: first author (year)	Study design	Sample size[a]	Mean baseline blood pressure (mmHg)		Mean baseline potassium (K+) (mEq/L)	Mean baseline sodium (Na+) (mEq/L)	Dose (daily)		Follow-up or treatment duration (weeks)
			Systolic	Diastolic			Hydrochlorothiazide	Chlorthalidone	
Benz *et al.* (1998) [16]	Randomised, double-blind, multiple dose, placebo-controlled, multifactorial, parallel trial	194	153.2	101.0	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8
Canter *et al.* (1994) [17]	Randomised to an 8 week, multicentre, double-blind trial	460	Not reported/not applicable	100–115	Not reported/not applicable	Not reported/not applicable	25 mg	Not reported/not applicable	8
Chrysant (1994) [18]	Multicenter, double-blind, placebo-controlled outpatient study	252	155.3	103.3	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	12
Chrysant *et al.* (1996) [19]	Randomized, double-blind, parallel study	85	150?	95–114	Not reported/not applicable	Not reported/not applicable	25 mg	Not reported/not applicable	6
Chrysant *et al.* (2004) [20]	Randomized, double-blind, factorial design study	130	153.8	103.6	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8
Edes *et al.* (2009) [21]	Multinational study consisted of a 4 week	556	153.3	97.8	Not reported/not applicable	Not reported/not applicable	25 mg	Not reported/not applicable	8
Frishman *et al.* (1994) [22]	Single-blind run-in phase on placebo treatment,	91	151	101	Not reported/not applicable	Not reported/not applicable	25 mg	Not reported/not applicable	12
Goldberg *et al.* (1989) [23]	Followed by an 8-week randomized, double-blind	98	151	99.9	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicableA	8
Grimm *et al.* (2002) [24]	Phase with four parallel treatment arms	102	148.6	81.3	4.45	Not reported/not applicable	15 mg	Not reported/not applicable	12
Horie *et al.* (2007) [25]	Randomized, double-blind, placebo-controlled, 3 × 4 factorial trial	146	140–200	95–114	Not reported/not applicable	Not reported/not applicable	12.5 mg	NR/NA	8
Hulley *et al.* (1985) [26]	Randomized, double-blind, 4 × 3 factorial, modified fixed-dose multicenter trial	551	172.4	75.4	4.4	Not reported/not applicable	Not reported/not applicable	25 mg	52
Jounela *et al.* (1994) [27]	Randomized, multicenter, double-blind, parallel-group study	67	152	99.8	4.1	141.6	12.5 mg/25 mg	Not reported/not applicable	6
Kochar *et al.* (1999) [28]	Randomised, double-blind, placebo-controlled, 3 × 3 factorial trial	167	151	100	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8
Lacourciere and Arnott (1994) [29]	Randomized, blinded trial	60	158	101	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	12
Materson *et al.* (1978) [30]	Double-blind, parallel group trial	60	145.7	96.5	Not reported/not applicable	Not reported/not applicable	Not reported/not applicable	12.5 mg/ 25 mg	12
McGill and Reilly (2001) [31]	Randomized, double-blind, placebo-controlled study	195	153.5	100.6	Not reported/not applicable	Not reported/not applicable	12.5 mg/ 25 mg	Not reported/not applicable	8
Morledge *et al.* (1986) [32]	Parallel 3 × 4 factorial design study	129	176	84	>3.5	Not reported/not applicable	Not reported/not applicable	12.5 mg/ 25 mg	12
Papademetriou *et al.* (2000) [33]	Multicenter, double-blind, placebo-controlled study	138	152	100	Not reported/not applicable	Not reported/not applicable	12.5 mg	Not reported/not applicable	8
Papademetriou *et al.* (2006) (ATTACH) [34]	Multicenter, randomized, double-blind, placebo-controlled, parallelgroup study	305	151	100	>3.5	Not reported/not applicableA	12.5 mg/25 mg	Not reported/not applicable	8
Pool *et al.* (1997) [35]	Randomized, placebo-controlled study	64	149.5	100.1	Not reported/not applicable	Not reported/not applicable	12.5 mg	Not reported/not applicable	8
Pool *et al.* (2007) [36]	Not reported/not applicable	505	150.5	99.2	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8
Pordy (1994) [37]	Multicenter, randomized, double-blind, placebo-controlled parallel group, unbalanced factorial study	295	Not reported/not applicable	95–116	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicableA	4
Scholze *et al.* (1993) [38]	Factorial, randomized, double-blind, parallel group trial	135	Not reported/not applicable	100–115	>3.5	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	6
Vardan *et al.* (1987) [39]	Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial	136	144	97	4.3	Not reported/not applicable	Not reported/not applicable	15 mg/ 25 mg	12
Villamil *et al.* (2007) [40]	Multicenter, placebo-controlled, double-blind, 4 × 3 factorial design study	832	153.8	99.2	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8
Weir *et al.* (1992) [41]	Double-blind, parallel-group phase: 4 × 3 factorial	151	Not reported/not applicable	95–111	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	12
Zachariah *et al.* (1993) [42]	Double-blind placebo-controlled trial	Not reported/not applicable	Not reported/not applicable	95–115	Not reported/not applicable	Not reported/not applicable	25 mg	Not reported/not applicable	6
Yodfat and Zimilchman(1994) [43]	Double-blind, placebo-controlled trial	141	Not reported/not applicable	>100	Not reported/not applicable	Not reported/not applicable	12.5 mg/25 mg	Not reported/not applicable	8

[a]The sample size includes only patients participating in the comparative analysis.

Table 2 Characteristics of articles included in this meta-analysis – mixed treatment comparison

Study: first author (year)	Study design	Sample size[a]	Mean baseline blood pressure (mmHg)		Mean baseline potassium (K+) (mEq/L)	Mean baseline sodium (Na+) (mEq/L)	Dose (daily)		Follow-up or treatment duration (weeks)
			Systolic	Diastolic			Hydrochlorothiazide	Chlorthalidone	
Bakris *et al.* (2012) [44]	Randomized, double-blind, double-dummy, study	609	164.6	95.4	Not reported/not applicable	Not reported/not applicable	12.5 mg + azilsartan medoxomil 40 mg)	12.5 mg (+ azilsartan medoxomil 40 mg)	6
Dhalla *et al.* (2013) [45]	Propensity score-matched observational study	29873	Not reported/not applicable	Not reported/not applicable	>3.5	>130	12.5 mg/25 mg	12.5 mg/25 mg	260
Dorsch *et al.* (2011) [46]	Retrospective observational cohort analysis comparing study	6441	142.3	Not reported/not applicable	4.4	Not reported/not applicable	Individual	Individual	364
Ernst *et al.* (2006) [47]	Randomized, single-blinded, 8-week active treatment study	30	142.0	93.2	4.20	Not reported/not applicable	50 mg	25 mg	8
Kwon *et al.* (2013) [48]	Open-label, randomized, prospective cross-over study	28	152.0	94.0	4.10	143	12.5 mg (+ candesartan 8 mg)	6.25 mg (+candesartan 8 mg)	4
Pareek *et al.* (2009) [49]	Randomized, comparative, multicenter parallel group, open-lebel study	131	152.0	95.0	4.15	139	12.5 mg (+lasartan 25 mg)	6.25 mg (+lasartan 25 mg)	8
Pareek *et al.* (2016) [50]	Double-blind, double-dummy, randomized, parallel group, comparative, multicentric study	34	148.7	93.7	Not reported/not applicable	Not reported/not applicable	12.5 mg	6.25 mg	12
Saseen *et al.* (2015) [8]	Retrospective analysis of patients diagnosed with hypertension	856	136.2	76.9	4.04	Not reported/not applicable	25 mg	25 mg	18
van Blijderveen *et al.* (2014) [51]	Population-based observational case-control study	13787	Not reported/not applicable	Not reported/not applicable	Not reported/not applicable	>130	12.5 mg/25 mg	12.5 mg/25 mg	Not reported/not applicable

[a]The sample size includes only patients participating in the comparative analysis.

through placebo. The analysis performed showed that chlorthalidone reduced the SBP on average between 2 and 3 mmHg, compared to hydrochlorothiazide. Calculated WMD (95% CI) is –2.35 mmHg (–5.52, 0.83), indicating a statistically nonsignificant difference. There are more studies comparing hydrochlorothiazide with placebo, while the number of publications with chlorthalidone compared with placebo or hydrochlorothiazide is relatively small.

Figure 3b presents the results from direct comparison between chlorthalidone and hydrochlorothiazide and indirect through placebo. The analysis shows that chlorthalidone reduced the DBP on average by less than 1 mmHg compared with hydrochlorothiazide. Calculated WMD is equal to –0.67 mmHg (–1.92, 0.57), which means that the difference is considered to be statistically not significant and we could not conclude which preparation is more effective for reduction of DBP. There are more studies comparing hydrochlorothiazide with placebo, while the number of publications with chlorthalidone compared with placebo is relatively small.

Figure 2c presents the results from indirect comparison of chlorthalidone and hydrochlorothiazide by placebo regardless of the dose. The analysis shows that chlorthalidone reduced the serum potassium levels with WMD (95% CI) equal to –0.28 mEq/L (–0.41, –0.15) compared with hydrochlorothiazide, which means that the difference between the two treatments is statistically significant and we could claim that hydrochlorothiazide has relatively safer profile in terms of serum potassium levels. There are more studies comparing hydrochlorothiazide with placebo, while the number of publications with chlorthalidone compared with placebo is relatively small.

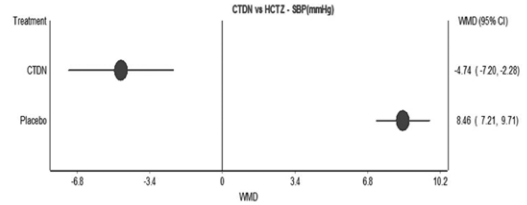
Figure 3c presents the results from direct comparison (chlorthalidone vs. hydrochlorothiazide) and indirect through placebo regardless of the dose. Our analysis shows that chlorthalidone reduced the serum potassium levels with WMD (95% CI) equal to –0.23 mEq/L (–0.27, –0.19) compared with hydrochlorothiazide, which means that the difference between the two treatments is statistically significant. Thus, hydrochlorothiazide appears to be safer in regards to serum potassium levels. The number of studies comparing hydrochlorothiazide with placebo predominated, while the number of publications with chlorthalidone compared with placebo is relatively small.

Only one study [49] directly compared the two preparations in regard to their effects on serum sodium levels. Pareek *et al.* conclude that there are no significant changes in serum electrolytes, blood sugar and other laboratory parameters in patients treated with chlorthalidone and hydrochlorothiazide.

Discussion

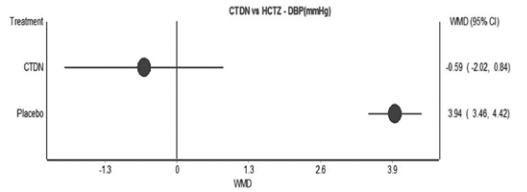
Worldwide, hydrochlorothiazide is used more often than chlorthalidone [15,52–54], but in recent years, it has been actively debated whether hydrochlorothiazide and

Fig. 2



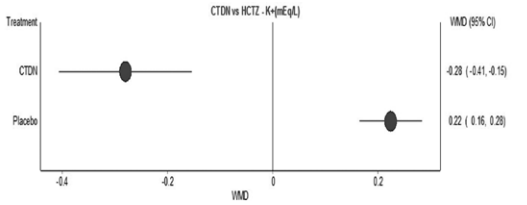
ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo (Pooled)	HCTZ	Placebo	-8.46	-9.71	-7.21
2	CTDN - Placebo (Pooled)	CTDN	Placebo	-13.21	-15.32	-11.09
	Indirect estimates (source IDs)					
3	**Indirect CTDN vs HCTZ (2, 1)**	**CTDN**	**HCTZ**	**-4.74**	**-7.20**	**-2.28**
	Result estimates (source IDs)					
	Placebo (1)	Placebo	HCTZ	8.46	7.21	9.71
	CTDN (3)	CTDN	HCTZ	-4.74	-7.20	-2.28

Figure 2A SBP



ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo (Pooled)	HCTZ	Placebo	-8.46	-9.71	-7.21
2	CTDN - Placebo (Pooled)	CTDN	Placebo	-13.21	-15.32	-11.09
	Indirect estimates (source IDs)					
3	**Indirect CTDN vs HCTZ (2, 1)**	**CTDN**	**HCTZ**	**-4.74**	**-7.20**	**-2.28**
	Result estimates (source IDs)					
	Placebo (1)	Placebo	HCTZ	8.46	7.21	9.71
	CTDN (3)	CTDN	HCTZ	-4.74	-7.20	-2.28

Figure 2B DBP

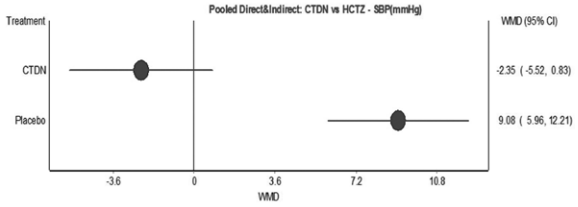


ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo	HCTZ	Placebo	-0.22	-0.28	-0.16
2	CTDN - Placebo	CTDN	Placebo	-0.50	-0.62	-0.39
	Indirect estimates (source IDs)					
3	Indirect CTDN vs HCTZ (2, 1)	CTDN	HCTZ	-0.28	-0.41	-0.15
	Result estimates (source IDs)					
	Placebo (1)	Placebo	HCTZ	0.22	0.16	0.28
	CTDN (3)	**CTDN**	**HCTZ**	**-0.28**	**-0.41**	**-0.15**

Figure 2C K+ (mEq/L)

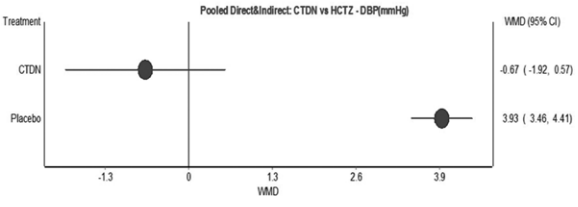
Forest plots indirect comparisons: (a) SBP; (b) DBP; (c) serum potassium.

Fig. 3



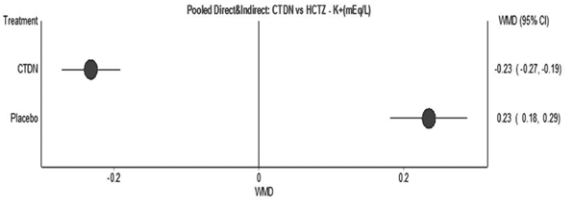
ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo	HCTZ	Placebo	-8.46	-9.71	-7.21
2	CTDN - Placebo	CTDN	Placebo	-13.21	-15.32	-11.09
3	CTDN - HCTZ	CTDN	HCTZ	-1.81	-2.97	-0.65
	Indirect estimates (source IDs)					
4	Indirect Placebo vs HCTZ (2, 3)	Placebo	HCTZ	11.39	8.98	13.81
5	Indirect CTDN vs HCTZ (2, 1)	CTDN	HCTZ	-4.74	-7.20	-2.28
	Result estimates (source IDs)					
	Placebo (1, 4)	Placebo	HCTZ	9.08	5.96	12.21
	CTDN (3, 5)	**CTDN**	**HCTZ**	**-2.35**	**-5.52**	**0.83**

Figure 4A SBP



ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo DPB	HCTZ	Placebo	-3.94	-4.42	-3.46
2	CTDN - Placebo DPB	CTDN	Placebo	-4.53	-5.88	-3.19
3	CTDN - HCTZ (DPB)	CTDN	HCTZ	-0.94	-3.45	1.58
	Indirect estimates (source IDs)					
4	Indirect Placebo vs HCTZ (2, 3)	Placebo	HCTZ	3.60	0.74	6.45
5	Indirect CTDN vs HCTZ (2, 1)	CTDN	HCTZ	-0.59	-2.02	0.84
	Result estimates (source IDs)					
	Placebo (1, 4)	Placebo	HCTZ	3.93	3.46	4.41
	CTDN (3, 5)	**CTDN**	**HCTZ**	**-0.67**	**-1.92**	**0.57**

Figure 4B: DBP



ID	Comparison	Active	Control	WMD	LCI 95%	HCI 95%
	Direct estimates					
1	HCTZ - Placebo: K+	HCTZ	Placebo	-0.22	-0.28	-0.16
2	CTDN - Placebo: K+	CTDN	Placebo	-0.50	-0.62	-0.39
3	CTDN - HCTZ	CTDN	HCTZ	-0.23	-0.27	-0.18
	Indirect estimates (source IDs)					
4	Indirect Placebo vs HCTZ (2, 3)	Placebo	HCTZ	0.28	0.16	0.40
5	Indirect CTDN vs HCTZ (2, 1)	CTDN	HCTZ	-0.28	-0.41	-0.15
	Result estimates (source IDs)					
	Placebo (1, 4)	Placebo	HCTZ	0.23	0.18	0.29
	CTDN (3, 5)	**CTDN**	**HCTZ**	**-0.23**	**-0.27**	**-0.19**

Figure 4C: K+

Forest plots mixed treatment comparisons: (a) SBP; (b) DBP; (c) serum potassium.

chlorthalidone should be considered interchangeable agents. Accumulating data suggests that chlorthalidone might have to be preferred over hydrochlorothiazide [46,55]. Numerous authors attempt to compare their efficacy in the management of hypertension. Cooney *et al.* conducted a review summarizing the data comparing the two drugs' pharmacology, antihypertensive effect and impact on clinical outcomes and came to the conclusion that it is unclear if there is prevalence in preventing cardiovascular events for either drug [15]. Dorsch *et al.*, in their retrospective cohort study, attempted to define the effects of chlorthalidone compared with hydrochlorothiazide on cardiovascular event (CVE) rates. They estimated that chlorthalidone reduces CVEs more than hydrochlorothiazide, suggesting that chlorthalidone may be the preferred thiazide-type diuretic for hypertension in patients at high risk of CVEs [46]. Roush *et al.* conducted a systematic review and concluded that although hydrochlorothiazide is the most commonly used, there are far better alternatives for the treatment of left ventricular hypertrophy having chlorthalidone, indapamide and potassium-sparing diuretics in mind [56]. Other authors also summarized the existing evidence regarding the differences between the efficacy of chlorthalidone and hydrochlorothiazide, including numerous and various studies [57–61].

Most of these comparisons are based primarily on indirect estimations or attempts for direct comparisons. This is the main reason why we decided to use NMA and combine different types of evidence in order to get a more definite estimation of the superiority of chlorthalidone or hydrochlorothiazide in a hypertensive population. We have already discussed direct comparisons of the efficacy of chlorthalidone and hydrochlorothiazide alone or in combination with an article submitted for publication. Based on the results obtained, we can assume that chlorthalidone has more potency to decrease SBP than hydrochlorothiazide. It should be noted; however, that indirect comparisons produce a statistically significant result while a mixed treatment comparison result lacks statistical significance. Two observational studies providing a direct comparison of hydrochlorothiazide and chlorthalidone stand out for their larger sample size and longer duration of follow-up [45,46], giving the expectation of a more prominent and sustained effect. However, the number of limitations intrinsic to these studies like unmeasured confounding, selection bias, information bias, unmeasured differences in baseline characteristics or physician treatment approaches is an indication that conclusions based only on longer follow-up can be confounding. The result regarding safety monitoring of serum potassium levels is in favor of hydrochlorothiazide the difference is considered to be statistically significant for the two comparison methods.

Our analysis once again underlines the slight prevalence in the efficacy of chlorthalidone pointed out by other authors. Although our attempt to broaden the analysis by combining types of evidence included, we could not reach statistical significance in favor of chlorthalidone in the mixed treatment comparison. This may be due to a number of limitations intrinsic to the analysis. First of all, high quality trials investigating the efficacy of CTLD are scarce as are trials investigating changes of serum potassium and sodium levels during treatment with HCTZ and CTLD. Second, we have evaluated the effects of hydrochlorothiazide and chlorthalidone using data for combined doses. All studies included in our statistical analysis were conducted relatively recently. Some differences in the inclusion and exclusion criteria, the way of measuring BP that could contribute to a different rate of heterogeneity in the studies were avoided by sensitivity analysis.

Conclusion

Although hydrochlorothiazide and chlorthalidone are designated as alternatives by guidelines discussing treatment of hypertension, hydrochlorothiazide seems to be the most commonly used diuretic. Our analysis; however, demonstrates superiority of chlorthalidone with regards to control of SBP and DBP. What is more, there are no significant differences between the safety profiles of the two medications. Our conclusion is that chlorthalidone and hydrochlorothiazide should be considered interchangeable and chlorthalidone should be more widely applied in clinical practice.

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Conflicts of interest

S.D., V.P., K.U., and E.F. are employees of Tchaikapharma High Quality Medicines Inc. For the remaining authors, there are no conflicts of interest.

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