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Full Length Research Paper

A meta-analysis of the efficacy and safety of arotinolol in the treatment of Chinese patients with essential hypertension

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Arotinolol had been used for treatment of essential hypertension. We conducted a meta-analysis to compare the efficacy and safety of arotinolol with other antihypertensive drugs in treating essential hypertension. Medical databases and review articles were screened with prespecified criteria for randomized controlled trials that reported the effects of and adverse reactions to arotinolol and other antihypertensive drugs in treating essential hypertension. Literature identified meta-analysed using RevMan4.2. Methodology quality of the selected studies was conducted using a Jadad scale. The results were that a total of 176 articles had been found of which 6 were finally included for meta-analysis. The meta-analysis compared the efficacy and safety of arotinolol with other common antihypertensive drugs, including enalapril, felodipine, imidapril, cilinidipine, metroprolol and atenolol. Results indicated that there were no evidence for differences in safety and efficacy. Homogeneity test, $\chi^2 = 4.41$, df = 7, P = 0.73 (efficacy); $\chi^2 = 2.96$, df = 4, P = 0.56 (safety); combined test, Z = 0.64 (P = 0.52), OR = 1.17, 95% confidence interval (CI) (0.72, 1.85) (efficacy); Z = 1.75 (P = 0.08), OR = 0.60, 95% CI (0.34, 1.06) (safety). There was no significant difference in efficacy and safety between arotinolol and other common antihypertensive drugs used for treating essential hypertension.

Key words: Meta-analysis, arotinolol, essential hypertension, efficacy, safety.

INTRODUCTION

Hypertension is a common clinical problem internationally. It is a significant risk factor for cardiovascular disease and one of the leading attributable risk factors for premature death (Novo et al., 2009). World Health Organization (WHO) research and Chinese health and nutrition studies suggest that only 30% of hypertension patients achieve blood pressure control within the safe limits (Papadopoulos and Papademetriou, 2008).

Hypertension has two primary variants: night-time dipping and non-dipping. It is more difficult to control patients with non-dipping hypertension and they are more prone to target organ damage, including brain, eyes, heart, arteries and kidneys (Kanbay et al., 2008; Neutel et al., 1993; Pickering and James, 1994; White, 2000). Arotinolol (Almarl^{TM}) has been reported to be effective for mild or moderate essential hypertension, since it is a combined β and α receptor blocker (Cai et al., 1998; Chen et al., 2005; Liu, 2001; Sun et al., 1996; Wang et al., 2002; Zhang et al., 2003). Arotinolol can reduce non-dipper hypertension patients' high blood pressure at night and may therefore reduce the incidence of cardiovascular diseases (Huang et al., 2004; Wu et al., 2001).

Arotinolol has also been reported to reduce hypertension in the elderly without renal damage (Miyauchi et al., 1999).

We report a meta-analysis of the published randomized controlled trials of arotinolol for treating essential hypertension in the elderly. Analysis was focused on clinical effect and safety.

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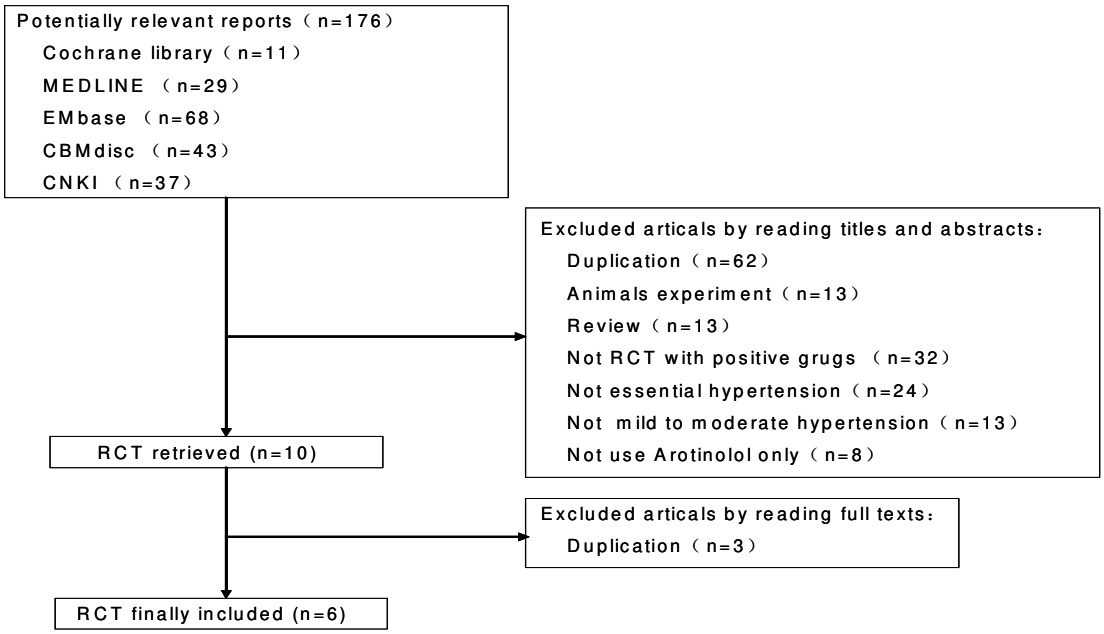

Figure 1. Flow chart outlining the literature search

METHODOLOGY

Protocol and inclusion criteria were identical to those of a previous meta-analysis (Sackett et al., 2002). Inclusion criteria were:

1. Randomized clinical trials of arotinolol for primary hypertension, including trials with double-blind and single-blind allocation.
2. Patients with mild or moderate hypertension according to the Prevention and Cure Guidelines For Hypertension in China, 1999 (China. DCopacgi, 2000) or World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension (1999)
3. Studies comparing patients given arotinolol with another single anti-hypertensive agent
4. Publication in English or Chinese.

Exclusion criteria were:

1. Studies of patients with severe cardiovascular or cerebrovascular disease, severe respiratory disease, renal or hepatic dysfunction, or, diabetes.
2. Studies comparing arotinolol with combination anti-hypertensive therapy.

Outcome measures were:

1. Response rate
2. Adverse reaction incidence rate.

Effectiveness criteria were based on the effectiveness criteria for hypertension specified in 'Guidelines for New Drug Clinical Research (Chinese Ministry of Health, 1993).

Adverse reactions were assessed according to symptoms, physical signs and laboratory results. Literature searches were performed using the Cochrane controlled trial register (CCTR) (2008/3), MEDLINE (1991 to 2009/3), EMbase (1991 to 2009/3), CBMdisc (1991 to 2009/3), China National Knowledge Infrastructure (CNKI, 1994 to 2009/3) and other relevant databases, as specified in the Cochrane collaboration handbook 4.2.7 (Sackett et al., 2002). Key words used were "Arotinolol", "Almarl" or "hypertension". Relevant literature already known to the researchers was also included. Literature screening was performed by two independent investigators. All references were carefully evaluated according to the inclusion/exclusion criteria and if both, a third independent investigator was screened the literature and the majority decision was accepted.

Methodology quality of the enrolled studies was evaluated using a Jadad scale (Jadad et al., 1996). Scores were 1 to 5, where 1 to 2 was considered low quality and 3 to 5 was considered high quality.

Data were analyzed by two independent evaluators. Meta-analysis was performed with RevMan4.2 provided by the Cochrane Collaboration. Differences between the research reports were evaluated using chi-square test with $\alpha = 0.1$. Extent of difference was assessed using the I^2 index: $I^2 < 25\%$, indicated a small difference; $I^2 = 25$ to 50% indicated a moderate difference and $I^2 > 50\%$, indicated a large difference. If there were no significant differences between results, a fixed-effect model was used to perform combination analysis. Otherwise, a random effects model was used for analysis and subgroup analysis was conducted to investigate the causes of the difference. Potential causes of differences include methodology quality, duration of treatment, drug dose, etc.

RESULTS

Figure 1 illustrates the literature screening process. The preliminary scan identified 176 references. After careful screening including assessment of the full text of reports, six studies completely fulfilled the inclusion criteria (Cai et al., 1998; Chen et al., 2005; Liu and Yuan, 2001; Sun et al., 1996; Wang et al., 2002; Zhang et al., 2003). All six studies were randomized controlled trials which reported

Table 1. General characteristics of all studies.

S/N	Research (PI/year)	Experimental design	Group	Dose	Periods of treatment (weeks)	Effective rate (%)	Incidence of adverse reactions (%)
1	Liu (2001)	Randomized controlled	Arotinolol	10 mg, bid	6	86.7	-
			Imidapril	5 mg, qd	6	90	-
			Enalapril	5 mg, qd	6	83.3	-
2	Wang et al., (2002)	Randomized controlled	Arotinolol	5 mg, qd	8	87.1	6.5
			Felodipine	5 mg, qd	8	71.8	25
3	Zhang et al., (2003)	Randomized controlled	Arotinolol	10 mg, bid	6	85	15
			Cilnidipine	5 mg, qd	6	86.4	22.7
			Imidapril	5 mg, qd	6	90	15
4	Chen et al., (2005)	Randomized controlled	Arotinolol	5 mg, bid	4	90.0	-
			Metoprolol	25 mg, bid	4	89.4	-
5	Cai (1998)	Randomized controlled	Arotinolol	10 mg, bid	4	91.2	3.0
			Metroprolol	25 mg, bid	4	79.3	10.3
6	Sun et al., (1996)	Randomized controlled double-blind	Arotinolol	10 mg, bid	4	75.8	25.8
			Atenolol	12.5 mg, bid	4	80.0	30.0

effectiveness data in both test and control groups, and all reported patient disposition, including withdrawals and patients lost to follow up. Adverse reactions were reported in four studies. Tables 1 and 2 list the general characteristics and baseline information of the included studies, respectively. Three studies reported detailed randomization protocols and one reported that it was a 'blind' trial. Based on the Jadad scale criteria, 4 studies were considered to be carried out with high quality methodology (3 points), 2 studies were considered to be of low methodological quality (2 points) (Table 3).

Comparison of included studies

The effectiveness rates and the safety data for arotinolol in the six studies were not significantly different. Effectiveness rates differences: $\chi^2 = 4.41$, df = 7, P = 0.73; adverse reaction rates: $\chi^2 = 2.96$, df = 4, P = 0.56.
Since there were no significant heterogeneities between studies in efficacy analysis and safety analysis, a fixed-model was used for meta-analysis.

Meta-analysis of the effect of arotinolol in treatment of essential hypertension

In the included studies, several drugs had been used as comparators, including: enalapril, felodipine, Imidapril, cilinidipine, metroprolol, and atenolol. Treatment durations ranged between 4 to 8 weeks. Since there were no significant differences between the effectiveness rates of the studies, a fixed-effect model was used to conduct meta-analysis. Figure 2 shows there was no statistical difference in effectiveness rates for treatment of hypertension between the control drugs and arotinolol: Z = 0.64 (P = 0.52), OR = 1.17, 95% CI (0.72, 1.85). Subgroup analysis (according to different anti-hypertension drug in control groups) suggested that there was still no significant difference in effectiveness rates of hypertension treatment between arotinolol and the control drugs [beta receptor blocker: Z = 0.28 (P = 0.78), OR = 1.10, 95% CI (0.58, 2.09); calcium channel blocker: Z = 1.13 (P = 0.26), OR = 1.80, 95% CI (0.65, 4.99); angiotensin-converting enzyme inhibitors: Z = 0.26 (P = 0.79), OR = 0.87, 95% CI (0.31, 2.24)].

Meta-analysis of the safety of arotinolol

Table 4 lists adverse reactions reported in the four included studies. Since there were no significant differences between the safety data of these studies, a fixed-effect model was used for meta-analysis. Figure 3 shows there was no statistical difference in adverse reaction incidences of hypertension treatment between

Table 2. Baseline information of all studies.

Research (PI/year)	Group	Cases	Withdraw cases	Age (y)	Diastolic pressure (mmHg)	Systolic pressure (mmHg)
Liu and Yuan (2001)	Arotinolol	20	0	-	102.4 ± 4.8	134.7 ± 10.7
	Imidapril	20	0	-	102.5 ± 3.4	135.6 ± 14.8
	Enalapril	20	0	-	102.2 ± 3.8	134.8 ± 12.6
Wang et al., (2002)	Arotinolol	31	0	59.9 ± 5.14	100 ± 3	157 ± 6
	Felodipine	32	0	60.1 ± 6.04	101 ± 3	155 ± 6
Zhang et al., (2003)	Arotinolol	20	0	52 ± 12	102 ± 5	152 ± 19
	Cilnidipine	22	0	55 ± 8	101 ± 3	148 ± 11
	Imidapril	20	0	51 ± 11	103 ± 3	153 ± 16
Chen et al., (2005)	Arotinolol	44	0	48.7 ± 9.4	103.9 ± 5.9	162.6 ± 12.1
	Metoprolol	47	0	49.7 ± 8.1	103.4 ± 4.4	160.1 ± 10.6
Cai (1998)	Arotinolol	33	0	47.5 ± 9.1	102.6 ± 6.1	155.1 ± 11.1
	Metoprolol	29	0	52.1 ± 8.2	102.8 ± 7.0	152.9 ± 13.1
Sun et al., (1996)	Arotinolol	62	0	-	100.7 ± 5.0	163.7 ± 15.0
	Atenolol	60	0	-	100.4 ± 5.4	163.5 ± 16.0

Table 3. Jadad scale.

Research (PI/year)	Random method	Withdraw and lost to follow-up	Blinding	Jadad score
Liu and Yuan (2001)	2	1	0	3
Wang et al., (2002)	1	1	0	2
Zhang et al., (2003)	2	1	0	3
Chen et al., (2005)	2	1	0	3
Cai (1998)	1	1	0	2
Sun et al., (1996)	1	1	1	3

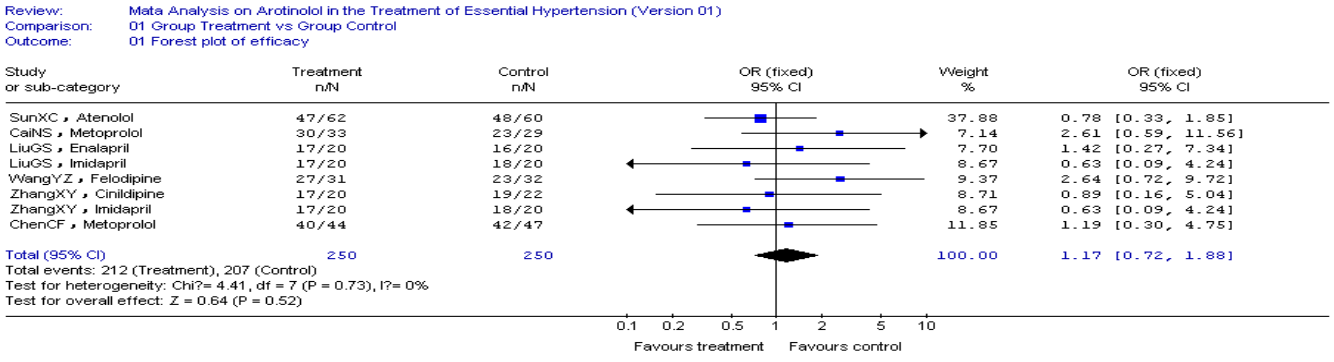

Figure 2. Forest plot of efficacy.

Table 4. Adverse reactions in the studies.

Research (PI/year)	Groups	Studied cases	Bradycardia	Palpitation	Flush	Edema of lower extremity	Dry Cough	Headache	Hypodynamia	Diarrhoea	Others	Totoal incidence (%)
Wang et al., (2002)	Arotinolol	31	2	-	-	-	-	-	-	-	-	6.5
	Felodipine	32	-	3	2	1	-	-	-	-	2	25
Zhang et al., (2003)	Arotinolol	20	-	-	-	-	-	-	2	1	-	15
	Cilnidipine	22	-	1	1	-	-	3	-	-	-	22.7
	Imidapril	20	-	-	1	-	2	-	-	-	-	15
Cai (1998)	Arotinolol	33	1	-	-	-	-	-	-	-	-	3.0
	Metoprolol	29	2	-	-	-	-	-	-	-	1	10.3
Sun et al., (1996)	Arotinolol	62	-	2	-	-	-	-	2	-	12	25.8
	Atenolol	60	-	2	-	-	-	-	2	3	11	30

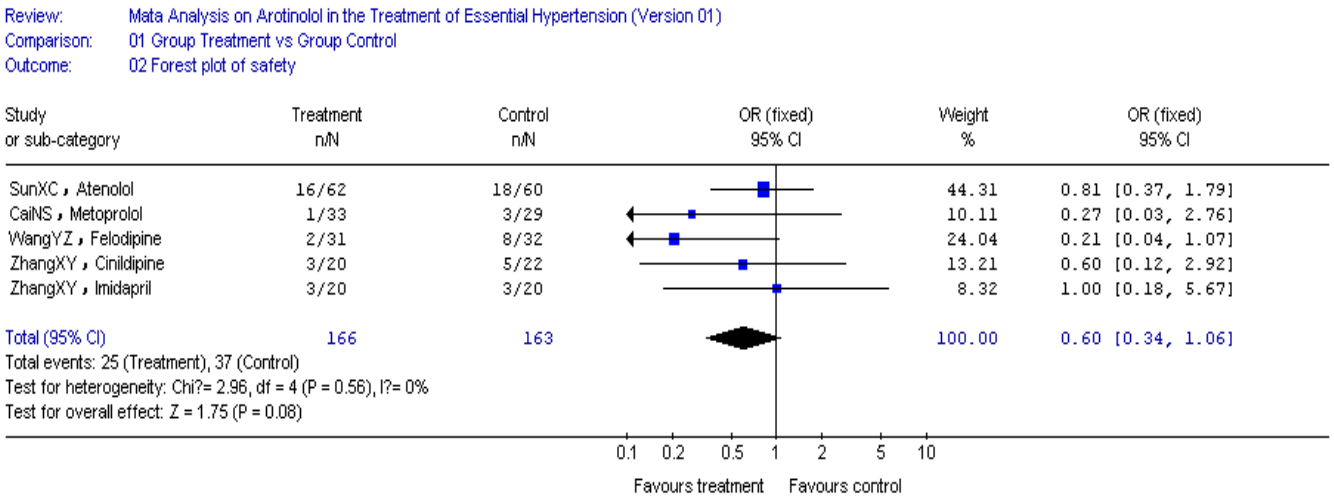

Figure 3. Forest plot of safety.

the control drugs and arotinolol: Z = 1.75(P = 0.08), OR = 0.6, 95% CI (0.34, 1.06). Subgroup analysis (according to different anti-hypertension drug in control groups) suggested that there was still no significant difference in adverse reaction incidences of hypertension treatment between arotinolol and the control drugs [beta receptor blocker: Z = 0.90 (P = 0.37), OR = 0.71, 95% CI (0.34, 1.49); calcium channel blocker: Z = 1.87 (P = 0.06), OR = 0.35, 95% CI (0.11, 1.05); angiotensin-converting enzyme inhibitors: only one trial].

DISCUSSION

The meta-analysis results showed that arotinolol is effective for treatment of mild or moderate essential hypertension, and like candesartan (Cui et al., 2011), it is similarly as effective as other common anti-hypertensive drugs. Arotinolol is a combined α and β adrenoceptor blocker: α receptor, blockade dilates arterioles and veins reducing cardiac preload and after-load, thus lowering blood pressure; β receptor blockade causes reduced heart rate, inhibits myocardial contraction and decreases cardiac output, thus lowering blood pressure. It has been reported that arotinolol treatment can convert non-dipping hypertension to dipping hypertension with consequent nocturnal blood pressure reduction in non-dipper patients (Huang et al., 2004; Wu et al., 2001). Arotinolol is predominantly metabolized by liver and has no obvious influence on kidney function (Gan et al., 2005). Theoretically, arotinolol could block renal α and β receptors, reducing renin-angiotensin system activity and improving glomerular filtration rate (GFR). Therefore, arotinolol may be a good choice for hypertension patients with renal dysfunction. Furthermore, arotinolol has been reported to be effective in treatment of obstinate hypertension (Yu and Luo, 2004).

In this meta-analysis, the safety of arotinolol was not significantly different from the safety of other antihypertensive agents. Adverse reactions of arotinolol included bradycardia (2), generalized weakness (2) and diarrhea (1). Other adverse reactions, such as flush, dry cough, headache, palpitation and dizziness were not observed. Arotinolol adverse reactions may be due to dual α and β receptor blockade. By blocking both receptors simultaneously, α receptor blockade-mediated reflex sympathetic excitation may be reduced by β receptor blockade. However, β receptor blockade may cause heart rate reduction, meaning that arotinolol should be used with caution in patients with bradycardia or heart block.

Adverse changes in carbohydrate/lipid metabolism were not observed in the selected studies: this has been reported for arotinolol (Guo, 2008), and is because whilst β receptor blockade may affect carbohydrate/lipid metabolism this effect may be alleviated by α receptor blockade.

This meta-analysis reviews the effectiveness and safety of arotinolol for treatment of hypertension. However, the analysis sample was small and the six selected studies were all not of high quality, Only 3 studies reported the specific randomization grouping method. Only 1 study reported the blinding method adopted. Although, baseline data was reported for all studies, between-group differences were statistically significant, possibly due to selection bias.

Therefore, the meta-analysis is of limited power. Selectivity bias, implementation bias and measurement bias may exist because blinding methods were not described for all studies. Further studies with randomized controlled blinded methodologies and long term follow-up are needed to further prove the validity of treatment with arotinolol. When more data is available, a further meta-analysis will be appropriate.

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