

Original Article

The efficacy and safety of lithium carbonate in combination with radioactive iodine therapy of hyperthyroidism: a meta-analysis and systematic review

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Abstract: Background: Several treatment options are available for patients with hyperthyroidism, such as antithyroid drugs and radioactive iodine. Recently, increasing number of patients with hyperthyroidism take lithium carbonate in combination with radioactive iodine. Numerous clinical studies have been done to evaluate the efficacy and safety of lithium carbonate in combination with radioactive iodine therapy of hyperthyroidism. However, the results are conflicting. The aim of the present study was to evaluate the efficacy and safety of lithium carbonate in combination with radioactive iodine therapy in patients with hyperthyroidism. Methods: Trials were retrieved through Pubmed, Sinomed and China National Knowledge Infrastructure (CNKI). Meta-analysis was used following a random effects model to analysis the data if there was no significant difference in homogeneity among trials. The pooled relative risk (RR) and 95% confidence interval (CI) were used to describe the outcome indicator. Results: Twelve randomized controlled trials were enrolled in the meta-analysis, the twelve clinical trials randomized a total of 1754 patients. The number of people being cured in the test group is 673, the cure rate is 75.53%; while the control group is 552, the cure rate is 63.96% (RR 1.17; 95% CI, 1.11-1.24; P<0.00001). In addition, no severe side effects were observed in the test group. Conclusion: Lithium carbonate in combination with radioactive iodine therapy significantly elevates the cure rate without severe side effects in patients with hyperthyroidism.

Keywords: Lithium carbonate, hyperthyroidism, randomized controlled trials, ¹³¹-iodine

Introduction

Radio iodine therapy is an effective treatment for hyperthyroidism. The treatment of hyperthyroidism by means of radioactive iodine is a commonly recognized and widely used therapeutic procedure in patients with preserved iodine uptake capacity of the thyroid gland [1]. The efficacy of radioisotopes was affected by some elements, including previous treatment with antithyroid drugs, 24-h thyroidal radioactive iodine uptake and so forth. Radioactive iodine is the first choice in some countries. Nevertheless, hypothyroidism and the recurrence of hyperthyroidism are the two common complications after ¹³¹-iodine treatment, in order to reduce the complications, Several adjuncts have been used with radioiodine to increase its effectiveness. Lithium carbonate is one of them.

Lithium carbonate is a medication diffusely used to treat bipolar affective disorders and acute manic depressive disorders. It has also been shown that lithium carbonate has antithyroid actions similar to those of inorganic iodide and has proven effective. Accordingly, its use as an adjunct to radioiodine in the therapy of hyperthyroidism was controversial, but information is confined [2, 3]. To resolve this question, we conducted a literature search to assess the efficacy of radio iodine combined with lithium in patients with hyperthyroidism.

Methods and materials

Search strategy

We conducted a search of the following databases from 1976 to 2014: Pubmed, Sinomed and China National Knowledge Infrastructure (CNKI) for (lithium carbonate or comicality or lip-

Endocrinology and metabolism

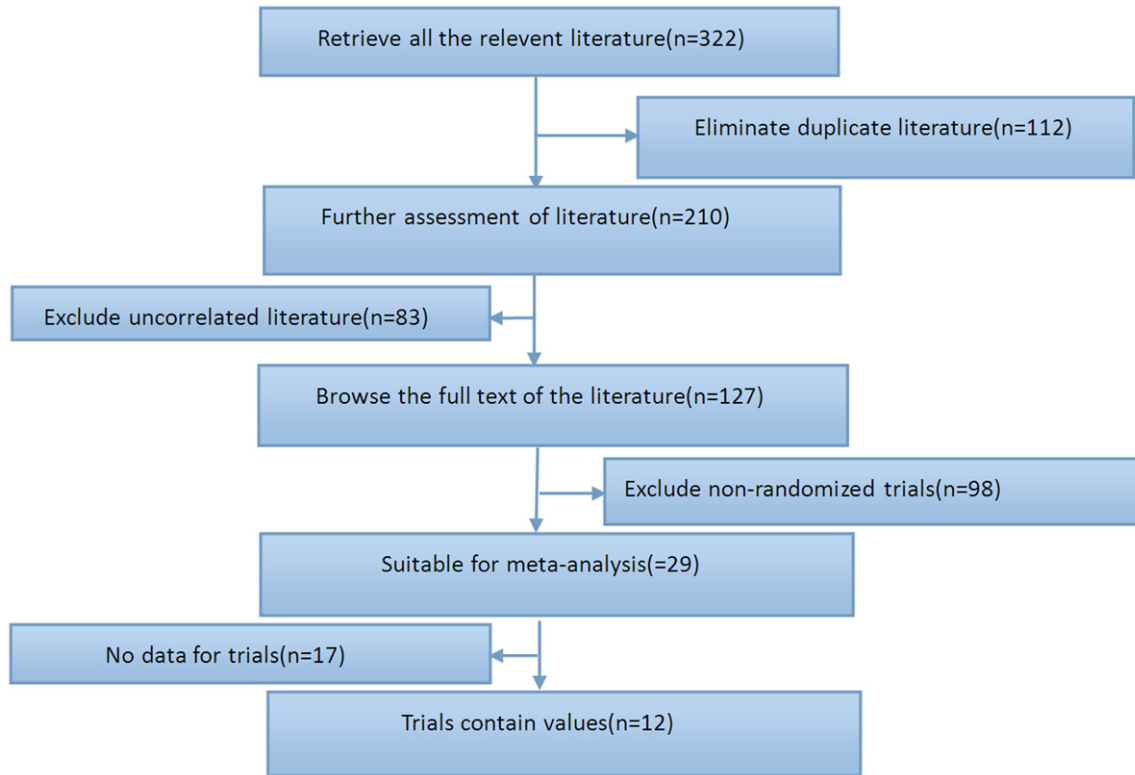


Figure 1. Search and screening studies about the efficacy and safety of lithium carbonate in combination with radioactive iodine therapy for hyperthyroidism.

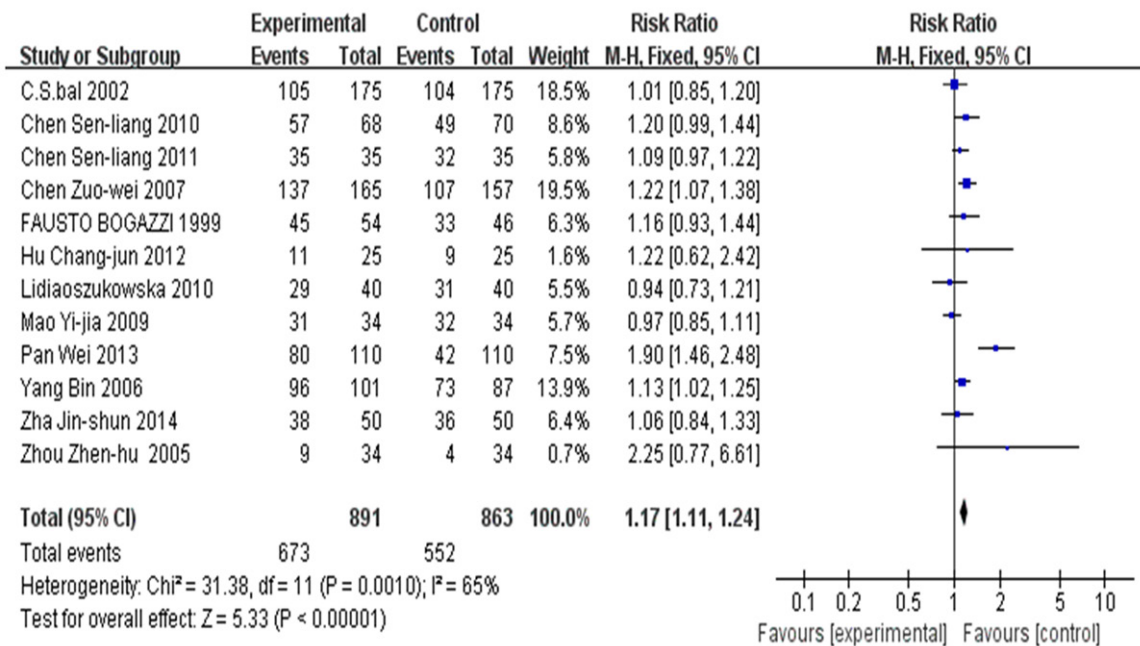


Figure 2. Forest plot of the number of people being cured.

reader or alkalis or notability) AND (hyperthyroidism or primary hyperthyroidism). We also

hand searched the references of all eligible articles and related previous review articles.

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Table 1. The basic characteristics of each study

Author	Published year	Country	Language	Male	Female	Mean age	131-iodine (NO.)	131-iodine plus lithium (NO.)	Total (NO.)	131-iodine cure	131-iodine plus lithium cure	Disease	Side effect	Invalid
Fausto [5]	1999	Italy	English	NA	NA	47.7	46	54	100	33 (72%)	45 (83%)	hyperthyroidism	bradycardia	NA
Bal C [6]	2002	India	English	132	218	41.8	175	175	350	104 (59%)	105 (60%)	hyperthyroidism	abdominal pain	0
Lidia [7]	2010	Poland	English	NA	NA	NA	40	40	80	31 (77%)	29 (72%)	hyperthyroidism	nausea	NA
Zha [8]	2014	China	Chinese	49	51	29.7	50	50	100	36 (72%)	38 (76%)	hyperthyroidism	diarrhoea	5
Yang [9]	2006	China	Chinese	75	113	37	87	101	188	73 (84%)	96 (95%)	hyperthyroidism	NA	0
Zhou [10]	2005	China	Chinese	20	48	41.5	34	34	68	4 (12%)	9 (26%)	hyperthyroidism	nausea	4
Chen [11]	2011	China	Chinese	62	6	39	35	35	68	32 (91%)	35 (100%)	hyperthyroidism with periodic paralysis	diarrhoea	0
Chen [12]	2007	China	Chinese	79	243	36.4	157	165	322	107 (68%)	137 (83%)	hyperthyroidism	Nausea, diarrhoea	NA
Mao [13]	2009	China	Chinese	28	40	(23-53)	34	34	68	32 (94%)	31 (91%)	hyperthyroidism	diarrhoea	0
Chen [14]	2010	China	Chinese	63	75	46.5	70	68	138	49 (70%)	57 (84%)	hyperthyroid heart disease	NA	7
Hu [15]	2012	China	Chinese	40	10	41.5	25	25	50	9 (36%)	11 (44%)	hyperthyroidism	abdominal pain and leukocytosis	20
Pan [16]	2013	China	Chinese	60	160	38.3	110	110	220	42 (38%)	80 (73%)	hyperthyroidism	NA	0

The cure rate of the test group was 75.53%. The cure rate of the control group was 63.69% (RR 1.17, 95% CI, 1.11-1.24; P<0.00001).

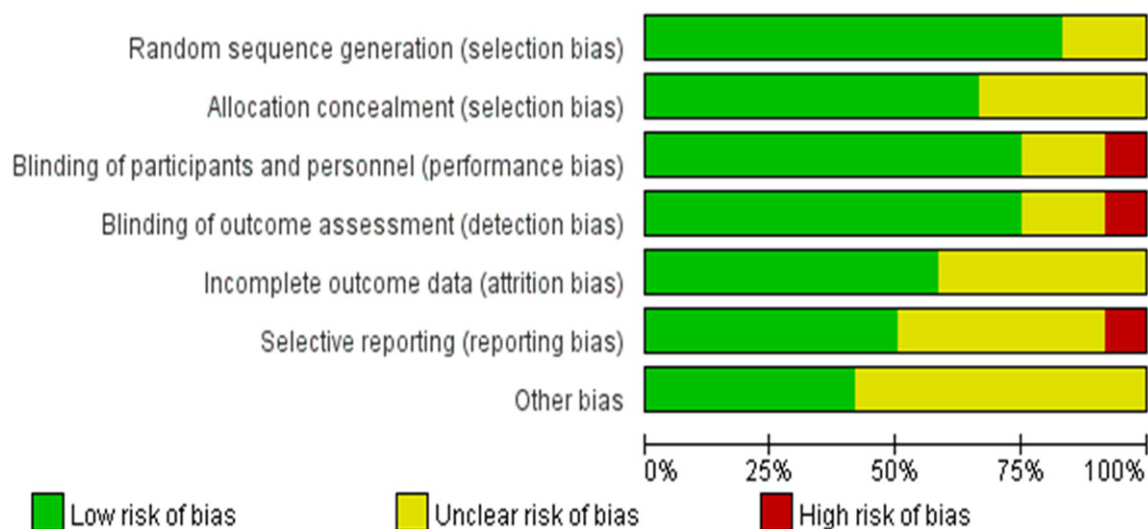


Figure 3. Methodological quality of the included studies The risk of bias of graph: review the judgments about each risk of bias item presented as percentages across all included studies.

Inclusion and exclusion criteria

Inclusion criteria: (i) Target population: individuals with hyperthyroidism; (ii) the Intervention of the test group: lithium carbonate with ¹³¹-iodine; (iii) the Intervention of the control group: ¹³¹-iodine; (iv) included the number of people being cured; (v) RCT design.

The exclusion criteria were as follows: (i) the population is not with hyperthyroidism; (ii) Studies without complete data; (iii) the test group and the control group are not clear; (iv) non-RCT design; (v) the intervention is not lithium carbonate with ¹³¹-iodine; the standard of cure: T3, T4, TSH is normal, clinical symptom is disappeared; Specific screening process are shown in **Figure 1**.

Data extraction and Statistical analysis

Two reviewers independently screened abstracts according to the inclusion criteria, and disagreements between reviewers were resolved by consensus. If an agreement could not be reached, a third reviewer would decide. The Basic study design characteristics were collected using a custom-designed data extraction form designed according to Cochrane review checklist 7.3 [4]. We pooled data across studies, and calculated relative risks (RR) and associated 95% confidence intervals (95% CI) for each outcome using the random effects

model. We used the Review Manager 5.2 for forest plot. The I^2 was calculated as an index of heterogeneity between studies. If I^2 was higher than 50%, the sensitive analysis should be performed to find out the source of heterogeneity and to assess whether the results could be significantly influenced. Detailed analysis was shown in **Figure 2**.

Quality assessment and risk of bias

Study quality was assessed via the following categories: randomization, quality of blinding (participants and personnel, and outcome assessment), withdrawal and loss and reporting bias. Two reviewers determined these items independently. The analyses were performed using Review Manager 5.2 (Cochrane Collaboration, United Kingdom). We assessed the bias of the study, We found that the bias is not almost existent.

Results

The initial search strategy found 322 potentially relevant publications, After rigorous screening, a total of twelve documents were enrolled in this meta-analysis [5-16]. Among the final studies, nine were conducted in china, one in india [6], one in itlay [5], one in poland [7]. The main characteristics of each study were shown in **Table 1**. The full-text reports were independently examined by both authors for compli-

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
C.S.bai 2002	+	+	+	+	+	?	+
Chen Sen-liang 2010	+	+	+	?	+	+	+
Chen Sen-liang 2011	+	+	?	+	+	+	+
Chen Zuo-wei 2007	?	?	-	+	+	?	?
FAUSTOBOGAZZI 1999	+	+	+	-	+	+	?
Hu Chang-jun 2012	+	+	+	+	?	+	+
lidia oszukowska 2010	?	+	+	?	+	+	+
Mao Yi-jia 2009	+	?	+	+	?	?	?
Pan Wei 2013	+	?	?	+	+	?	?
Yang Bin 2006	+	+	+	+	?	+	?
Zha Jin-shun 2014	+	+	+	+	?	-	?
Zhou Zhen-hu 2005	+	?	+	+	?	?	?

Figure 4. The risk of bias summary. Review the judgments about each risk of bias item for each included study.

ance with eligibility criteria; The patients of the study (Chen 2010) are hyperthyroid heart disease, the patients of the Study (Chen 2011) are hyperthyroidism with periodic paralysis, the patients of the remaining ten studies are hyperthyroidism. The methodological quality of the included studies was not very good. Detailed information was shown in **Figures 3 and 4.**

Efficacy

The number of people being cured: The twelve clinical trials randomized a total of 1754 patients. the number of patients with hyperthy-

roidism being cured in the test group was 673, the cure rate was 75.53%; while the control group was 552, the cure rate was 63.96% (RR-1.17; 95% CI, 1.11-1.24; P<0.00001). Because of the heterogeneity (heterozygosity test, Chi²=31.38, df=11 (P=0.0010), I²=65%), we conducted a subgroup analysis and sensitivity analysis. The analysis showed that the heterogeneity came from the studies of low qualities (Zhou 2005, Chen 2007, Mao 2009, Pan 2013). The heterogeneity was no longer existence after exclusion of these studies (**Figure 5**). The result of the subgroup analysis was Chi²=4.33, df=7 (P=0.74), I²=0%, the P=0.02 <0.05). The cure rate in the test group was 75.53%, The cure rate in the control group was 63.96%, which showed that the cure rate to be higher in the text group.

Safety and side effect

Among these studies, some side effects and toxicity of the lithium have been reported: bradycardia, nausea, diarrhoea, abdominal pain and leukocytosis. There were no serious adverse reactions and these side effects can not last for long time. No complications directly produced by lithium were observed in the present study. These studies showed that a relatively small dose of lithium and short-lasting pretreatment is safe for patients.

Discussion

Our systematic review with meta-analysis assessed the clinical efficacy and safety of lithium carbonate in combination with radioactive iodine therapy of hyperthyroidism from twelve published studies. Our analyses found that the combination therapy could increase the cure rate of hyperthyroidism. The cure rate of the

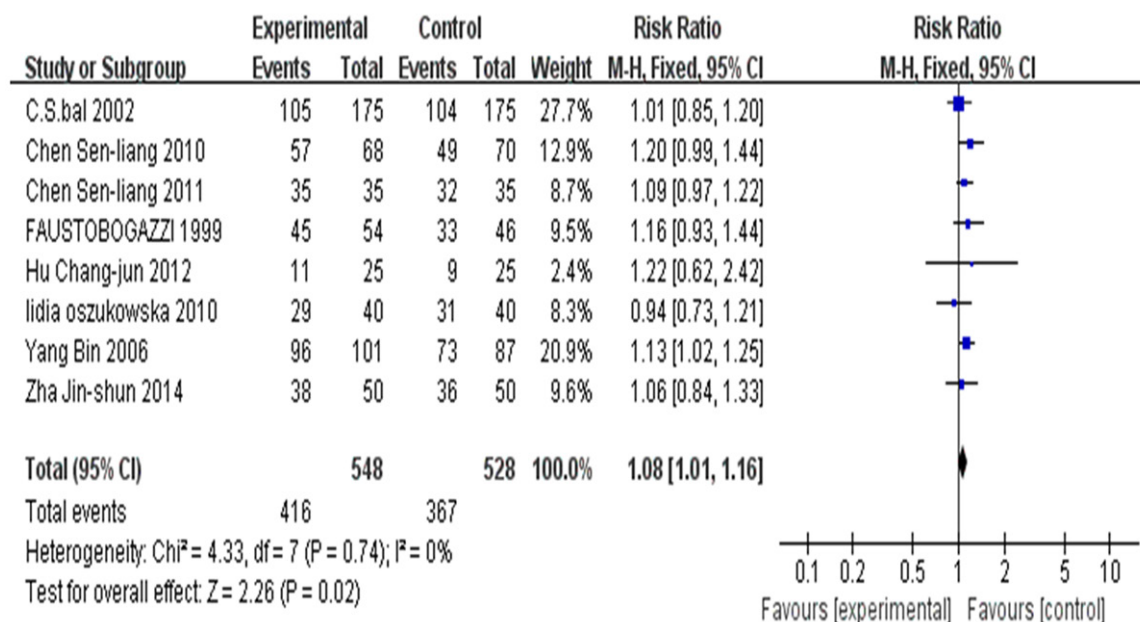


Figure 5. The forest plot of subgroup analysis.

test group was 75.53%. The cure rate of the control group was 63.69% (RR 1.17, 95% CI, 1.11-1.24; $P < 0.00001$), which indicated that the cure rate to be higher in the test group. Because of the heterogeneity, we conducted a subgroup analysis and sensitivity analysis. The heterogeneity was no longer existence after exclusion of these low qualities studies (Zhou 2005, Chen 2007, Mao 2009, Pan 2013) (RR, 1.08; 95% CI, 1.01-1.16; $I^2 = 0\%$; $P = 0.02$).

Side effects of short-term lithium therapy were not found, no serious side effects was observed in all the studies. So the safety of lithium carbonate in combination with radioactive iodine therapy of hyperthyroidism is undoubted. The short-term cure rate is relatively high, however, the long-term cure rate is unknown. Radioiodine therapy is an efficient therapy for hyperthyroidism [7]. But radioiodine is also rapidly discharged because of its turnover [17-19]. The efficacy of radioiodine therapy could be reduced by pretreatment with propylthiouracil but not with methimazole [20]. Previous study showed that radioactive iodine should not be used in patients with high concentrations of free thyroid hormone because of the risk of hyperthyroidism enhancement [7]. Lithium significantly affect the kinetics of iodine by reducing its release from the thyroid gland, thus increasing its retention [21]. This effect showed

that lithium may be useful as an adjunct to radioiodine therapy in thyrotoxicosis [5]. However, lithium is not widely used to potentiate the therapeutic action of radio iodine therapy. Favorable effect of lithium were reported in cases of thyroid carcinoma [22-24]. However, in cases of hyperthyroidism, few such studies have been conducted. The indications for the use of lithium carbonate have not been properly established, probably because of the effectiveness of regular antithyroid drugs and the fear of possible complications of lithium carbonate treatment. However, serious complications rarely occur [25]. The results of our analysis showed that radioiodine in combination with lithium allowed a quick control of hyperthyroidism than radioiodine alone. It also showed several beneficial effects of lithium carbonate treatment in most patients with low baseline thyroidal radioactive iodine uptake: a obvious increase in radioiodine retention, faster stabilization of the thyroid hormones. According to the analysis, we found that lithium carbonate treatment influenced the dynamic of T3 and T4 concentrations in the serum as compared with the control group. The effect of lithium carbonate on thyroid hormones level was previously found by others. One study [26] showed that this effect above mentioned is not only presented in patients with hyperthyroidism but also observed in patients with autonomous tumor

and multinodular goiter. Another study [27] showed that individuals with large goiters but contraindications to thyroidectomy, lithium carbonate treatment possibly represents an adjunct to radioiodide to achieve a more rapid control of hyperthyroidism. In this respect, an additional effect of the addition of lithium carbonate was the lack of serum free thyroxine and free triiodothyronine surge which was observed after radioiodide therapy. This effect may be related to radioiodide-induced destruction.

Several limitations to the present study should be considered. All trials included are termed as double-blinded and randomized, but the methodological quality of the included studies was not very good. Due to lack of information, our study did not analyse the long-term remission rate.

Conclusion

In short, the current evidence shows that the lithium carbonate has a high efficacy and safety of in the treatment of hyperthyroidism. It can improve the cure rate of hyperthyroidism, decrease the incidence of hypothyroidism and relapse of hyperthyroidism. But if the lithium carbonate is commonly used in clinical treatment of hyperthyroidism, it also requires a lot of further clinical trials to prove its efficacy. Further studies should be performed to rule out the confounding factors before arriving at conclusions.

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Disclosure of conflict of interest

None.

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