Original Article

Efficacy and safety of adrenal arterial embolization for primary aldosteronism: a systematic review and meta-analysis

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Background: Primary aldosteronism (PA) is related with resistant hypertension and cardiovascular events. Adrenal artery embolization (AAE) is a choice for patients who refused surgery and medical therapy. However, whether AAE can effectively and safely treat PA is unclear. We performed this meta-analysis to determine the efficacy and safety of AAE for patients with PA.

Methods: Databases including Cochrane Library, Embase, PubMed and Web of Science were used to obtain relevant articles published before July 30, 2023. The primary outcome was blood pressure before and after AAE. The second outcomes included changes in plasma aldosterone level, serum potassium level, and plasma cortisol level.

Results: Finally, 7 prospective studies with 222 patients were included. The results showed that systolic and diastolic blood pressure was reduced by 21.68 mmHg (P<0.001) and 10.54 mmHg (P=0.007) respectively after AAE. The change in plasma aldosterone and serum potassium level was −11.52 ng/dL and 0.61 mmol/L respectively (P<0.001), whereas the reduction in cortisol level was not apparent. Moreover, AAE is a relatively safe procedure which only causes some minor complications such as back pain and fever.

Conclusions: This meta-analysis indicated that AAE could effectively and safely treat PA. It is a good choice for patients that are not suitable for adrenalectomy or drug therapy.

Keywords: Primary aldosteronism (PA); adrenal artery embolization (AAE); blood pressure; aldosterone; complication

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Introduction

Primary aldosteronism (PA) is a condition characterized by excessive aldosterone production due to adrenal adenoma or hyperplasia. The two major manifestations of PA are hypertension and hypokalemia. PA is a major cause of secondary hypertension, accounting for 5–15% of the general hypertensive patients (1,2). Patients with PA have more cardiovascular and cerebrovascular events than blood pressure-matched hypertensive patients, and cardiovascular risk increases along with plasma aldosterone level (3,4).

Mineralocorticoid receptor antagonists (MRAs) and laparoscopic adrenalectomy are two major therapies for PA. Nevertheless, MRAs cannot reduce plasma aldosterone level and tend to cause undesirable adverse effects, which limiting their wide application (5-7).

For patients suffering from adrenal adenoma or obvious adrenal hyperplasia, laparoscopic adrenalectomy is a good choice. However, some patients may refuse surgery for fear of complications or respond poorly to adrenalectomy. Adrenal artery embolization (AAE) or superselective AAE has been used as an alternative for the treatment of PA in the past few years (8).

AAE was first introduced to treat aldosterone-producing adenoma in 1993 and was proven to lower blood pressure durably by some further studies after that (9). The procedure was conducted under local anesthesia through brachial or femoral access. After identifying the route of target adrenal artery via angiography, absolute ethanol was infused into vessels through a microcatheter to stop the blood supply of adenoma. Compared with adrenalectomy, AAE is a more minimally invasive procedure and has less surgical risks as well as postoperative complications.

However, no rigorous randomized controlled trial (RCT) has been conducted to verify the efficacy and safety of AAE. We performed this meta-analysis to ascertain the effect of AAE on plasma aldosterone level, blood pressure, serum potassium level, and cortisol level in PA patients. Side effects of AAE were also reviewed. To our knowledge, this is the first meta-analysis to assess the therapeutic efficacy and safety of AAE in PA. We present this article in accordance with the PRISMA reporting checklist (10) (available at https://gs.amegroups.com/article/view/10.21037/gs-23-523/rc).

Highlight box

Key findings

- This meta-analysis indicated that adrenal artery embolization (AAE) could effectively and safely treat primary aldosteronism (PA). It is a good choice for patients that are not suitable for adrenalectomy or drug therapy.

What is known and what is new?

- PA is related with resistant hypertension and cardiovascular events. AAE is a choice for patients who refused surgery and medical therapy. However, whether AAE can effectively and safely treat PA is unclear.
- We found that AAE can effectively reduce blood pressure and plasma aldosterone level of PA patients. Hypokalemia can also be improved via AAE. Moreover, AAE is a relatively safe procedure which only causes some minor complications such as back pain and fever, and it has no apparent influence on cortisol secretion.

What is the implication, and what should change now?

- As a minimally invasive operation, AAE might be beneficial for patients that are not suitable for adrenalectomy or drug therapy. Further randomized controlled trials are required to confirm our findings.

Methods

Literature search

This meta-analysis was registered at International Prospective Register of Systematic Reviews (registration number: CRD42022304003). Articles written in English and published before July 30, 2023 were searched in Cochrane Library, Web of Science, Embase, and PubMed. The search strategy was (adrenal artery embolization or adrenal arterial embolization) and (aldosteronism). References of retrieved articles were also examined to obtain relevant studies. Two authors performed the literature search independently.

Inclusion criteria and exclusion criteria

Studies were initially included when meeting following criteria: (I) clinical trials; (II) target population was patient with PA; (III) treatment method was AAE; (IV) outcome included blood pressure and plasma aldosterone level. Exclusion criteria included incomplete outcome data, duplicated data, or non-English language. Case reports, review articles or letters to the editor were also excluded.

Data extraction

Outcome data and basic characteristics such as the first author, publication year, study type, sample size, follow-up time, adverse events, and various outcome measures were extracted. The primary outcome was blood pressure before and after AAE. The secondary outcome was plasma aldosterone level, cortisol level and potassium level before and after AAE. If more than 1 follow-up time was reported, data of the last one was extracted. For studies with more than one group, only data of the AAE group was extracted. When data were displayed only with graphs and there were no respond from the authors, values were obtained quantitatively via GetData Graph Digitizer (S. Fedorov). Two authors performed data extraction independently.

Quality evaluation

Most of the included studies were non-randomized studies. We thereby assessed the quality of studies with the Methodological Index for Non-Randomized Studies (MINORS), which contained twelve items and the first eight items were specially for non-comparative studies (11). In our meta-analysis, we compared the postoperative data with baseline data of patients. Hence only the first eight

Table 1 Characteristics of included studies

Author, year	Study type	Sample size	Follow-up time	Adverse events	Outcome measures				MINORS score
					Blood pressure	Aldosterone	Potassium	Cortisol	
Inoue, 1994 (12)	Prospective	4	3–10 M	+	+	+	–	–	11
Nakajo, 1997 (13)	Prospective	10	2–3 W	–	+	+	–	–	12
Zhang, 2020 (14)	Prospective	36	6 M	+	+	+	+	+	13
Dong, 2021 (15)	Prospective	41	12 M	+	–	+	+	+	12
Zhao, 2021 (16)	RCT	26	6 M	+	+	+	+	+	12
Zhou, 2022 (17)	Prospective	74	12 M	+	–	–	+	–	12
Qiu, 2023 (18)	Prospective	31	12 M	+	+	+	+	+	12

RCT, randomized controlled trial; M, month; W, week; +, reported in the study; –, not reported in the study; MINORS, Methodological Index for Non-Randomized Studies.

items were utilized to evaluate study quality. The score of each item ranged from 0 to 2 according to whether it was reported or not and adequate or not. Two authors conducted the assessment independently and inconsistency was resolved by careful discussion.

Statistical analyses

Data were analyzed through Review Manager Version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark). Outcome data were displayed in the form of mean difference (MD) with 95% confidence intervals (CIs). I^2 test was used to evaluate the heterogeneity, and $I^2>50\%$ indicated a significant heterogeneity. We included limited number of studies in our meta-analysis, thereby subgroup analysis or meta regression could not be performed to seek the potential causes of heterogeneity. Data were analyzed with fixed effects model for comparisons with inapparent heterogeneity. Otherwise, random effects model was used. Inter-group difference was deemed to be significant with $P<0.05$.

Results

Characteristics and quality of included studies

A total of 7 studies with 222 patients were included in our meta-analysis (*Table 1*, *Figure 1*). All studies were prospective studies and only one of them was RCT (12-18). Five of included studies were single-arm studies with only one group of patients undergoing AAE. The other two studies were two-arm studies, comparing AAE with drug therapy. In these two studies, only measures from AAE group were extracted. In all studies, PA was diagnosed according to clinical symptoms, biochemical tests, and computed tomography. Before AAE, adrenal venous sampling (AVS) was conducted to identify the lateralization. Five studies measured blood pressure before and after the embolization. Aldosterone level was recorded in six studies, potassium in five studies, and cortisol in four studies. Six studies documented the incidence of adverse events. Follow-up time ranged from two weeks to 1 year. The average MINORS score of included studies was 12.

Blood pressure changes after AAE

In all studies, patients had high blood pressure at baseline and blood pressure was reduced after AAE treatment. Two studies did not record the final blood pressure value after AAE but only recorded reduction in blood pressure. The other five studies measured blood pressure both before and after AAE. The pooled data of these five studies revealed a mean reduction of −21.68 mmHg in systolic blood pressure (95% CI: −29.49 to −13.88; $I^2=54\%$; $P<0.001$) and −10.54 mmHg in diastolic blood pressure (95% CI: −18.18 to −2.90; $I^2=77\%$; $P=0.007$) (*Figure 2*).

Biochemical parameters changes after AAE

Aldosterone, potassium and cortisol are three most measured biochemical parameters. Other parameters like renin activity and aldosterone-to-renin ratio were only explored in one or two studies, and therefore were not suitable for aggregated analysis. The pooled data of six

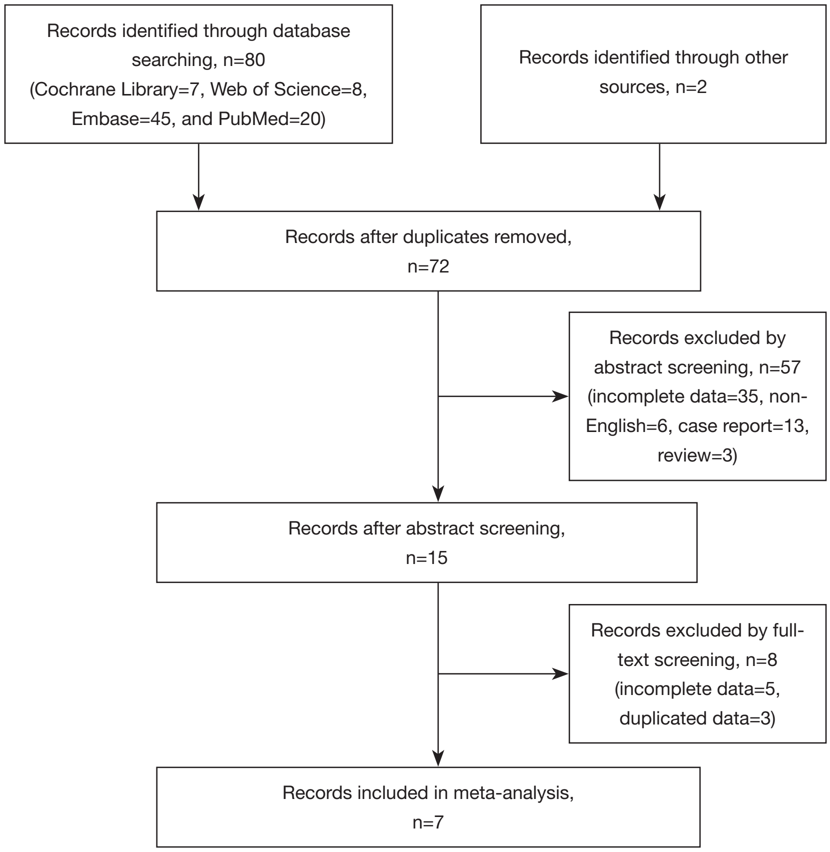

Figure 1 Flow diagram of the study selection process.

studies showed that the change in aldosterone level was −11.52 ng/dL (95% CI: −17.13 to −5.91; I^2=92%; P<0.001) after AAE (*Figure 3A*). Serum potassium level increased by 0.61 mmol/L (95% CI: 0.31 to 0.90; I^2=91%; P<0.001) after embolization (*Figure 3B*). In all included studies, mean potassium level returned to normal range after ablation. However, reduction in cortisol level was not apparent, with a mean change of −17.68 nmol/L (95% CI: −68.71 to 33.35; I^2=58%; P=0.50) (*Figure 3C*).

Adverse events

Six studies recorded the incidence of adverse events after AAE. No serious complications happened after the procedure in these studies. The most reported complication was minor flank or back pain, which occurred in 3–100% patients. Slight fever was another common complication which happened in 18.9–75% patients. Nausea, vomiting, abdominal distension, pleural effusion, and numbness of limbs also occurred in a few patients. These symptoms disappeared without special treatment within days.

Discussion

This meta-analysis assessed the efficacy and safety of AAE for PA. The pooled result from seven included studies indicated that AAE can effectively reduce blood pressure and plasma aldosterone level of PA patients. Hypokalemia can also be improved via AAE. Moreover, AAE is a relatively safe procedure which only causes some minor complications such as back pain and fever, and it has no apparent influence on cortisol secretion. These data verified preliminarily that AAE can treat PA effectively and safely.

MRAs and laparoscopic adrenalectomy are two main treatments for PA. For patients with lateralized secretion of aldosterone, adrenalectomy is usually recommended as therapeutic choice. Studies showed that unilateral adrenalectomy was superior to MRAs in attaining both biochemical and clinical success in PA patients (19,20). The underlying mechanism might be that adrenalectomy could

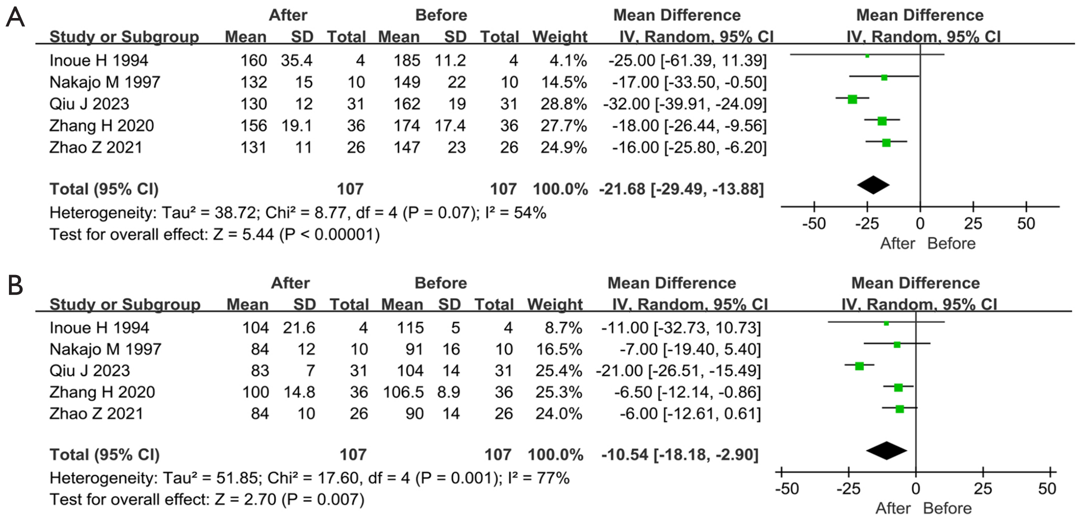

Figure 2 Forest plots of blood pressure changes after AAE. (A) Changes of systolic blood pressure. (B) Changes of diastolic blood pressure. SD, standard deviation; IV, inverse variance weighting method; CI, confidence interval; AEE, adrenal artery embolization.

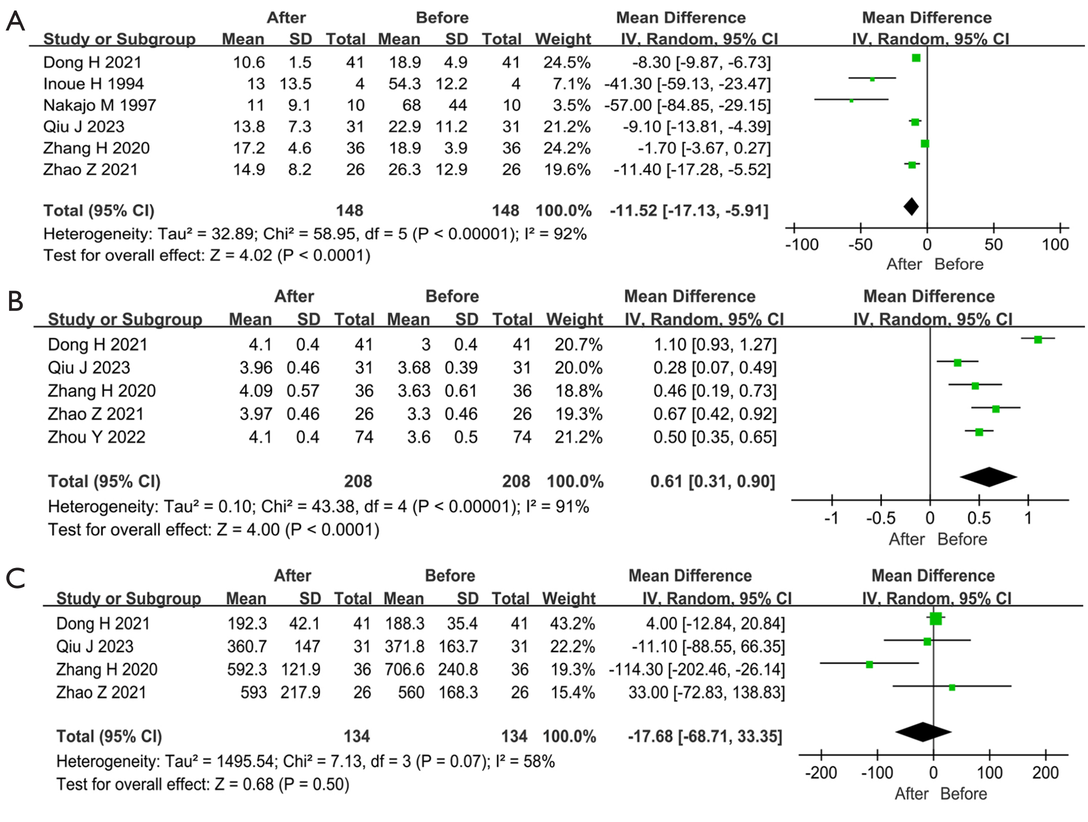

Figure 3 Forest plots of biochemical parameters changes after AAE. (A) Changes of aldosterone level. (B) Changes of serum potassium level. (C) Changes of cortisol level. SD, standard deviation; IV, inverse variance weighting method; CI, confidence interval; AEE, adrenal artery embolization.

reduce aldosterone level while MRAs could not. However, not all patients are suitable for adrenalectomy. For patients without lateralized secretion of aldosterone, MRAs might be a more appropriate choice (1). Nevertheless, MRAs treatment may cause various adverse events including cardiovascular events, gynecomastia, mastodynia, and hyperkalemia. It was estimated that nearly one third medically treated patients suffered from side effects caused by spironolactone (21). Therefore, many patients are reluctant to accept MRAs. On the other hand, they are worried about the surgical risks or unsuitable for adrenalectomy. For these patients, AAE can be considered as an alternative treatment.

Theoretically, AAE can lead to atrophy of the hyperplastic adrenal gland or adenoma, and the secretion of aldosterone should decrease accordingly. Some studies had been conducted to explore the therapeutic effect of AAE on PA. Nevertheless, most studies were prospective studies with limited number of patients. The conclusions of these studies were thus not compelling. Whether AAE was a suitable treatment for PA was unclear. In this situation, we performed the present meta-analysis to clarify the curative effect and safety of AAE in PA patients.

We found that both the systolic and the diastolic blood pressure were remarkably reduced after AAE. In Zhang's report (14), 25% patients with unilateral PA achieved complete clinical success, which means that blood pressure returns to normal range without antihypertensive medications (22). Similarly, hypertension of 24.3% patients in Zhou's study was cured by AAE (17). Qiu and colleagues explored the effect of AAE in patients suffering from bilateral PA (18). They found that hypertension disappeared in 12.9% of patients. These results were comparable to the result of adrenalectomy, which produced a 27% complete clinical success rate in unilateral PA and 15% in bilateral PA as reported previously (23,24). However, there is no study to compare AAE with adrenalectomy directly at present and therefore whether the efficacy of AAE is similar with adrenalectomy is unclear. Compared with MRAs, patients who underwent AAE attained a higher rate of complete clinical success and required less antihypertensive medications (17).

Excessive secretion of plasma aldosterone can not only cause hypertension, but also lead to other detrimental effects such as heart failure, cardiac hypertrophy and myocardial fibrosis (25). Thus, the reduction of aldosterone concentration is more beneficial than a simple drop in blood pressure for PA patients. In our meta-analysis, the level of aldosterone declined dramatically after AAE. As a result, the hypertension was improved in most patients. Moreover, 41.4% patients with complete biochemical success had a regression of left ventricle hypertrophy (18). By contrast, MRAs cannot inhibit the overproduction of aldosterone and thereby had no apparent benefit to cardiac remodeling (26). Moreover, Zhou's study indicated that AAE was superior to MRAs in obtaining complete biochemical success (17).

As a minimally invasive procedure, AAE led to no serious complications during or after the operation in our included studies. Slight pain or fever was reported in some patients, and these symptoms disappeared within days. Hypertensive crisis is a serious complication of adrenalectomy and its incidence rate was 4.9% (27). No intraoperative hypertensive crisis or severe arrhythmias was recorded during AAE procedure in these studies included in our meta-analysis. Nonetheless, it was recommended that intravenous antihypertensive medications, vasopressors, and antiarrhythmic medications should be routinely available when performing AAE (18). Moreover, our finding indicated that AAE had no apparent influence on the level of cortisol. No clinical manifestation of adrenal cortical dysfunction was observed in our included studies. These data implied that AAE was a relatively safe procedure.

As above mentioned, AAE was an effective and safe alternative for PA treatment. However, AAE has not been widely used for over 20 years. The reason may lie in that it is technically difficult and needs experienced operator to perform. Additionally, as a new technology, many clinicians were suspicious about its therapeutic effect. Thereby, studies comparing AAE and adrenalectomy are warranted.

Some limitations existed in our meta-analysis. Firstly, most of the included studies were not RCT and had small sample size, which might lower the level of evidence of this meta-analysis. More high-quality RCTs in the future are required to confirm our findings. Secondly, significant heterogeneity existed in some comparisons of this meta-analysis, and therefore the results and conclusion should be interpreted cautiously. In addition, the follow-up time was no more than 1 year in these included studies. Hence, the long-term therapeutic effect of AAE is unknown. We look forward to studies with longer follow-up time to clarify whether AAE has enduring effect. Data indicated renin >1 either on medication or following treatment with MRAs is a good prognostic factor (28). However, only two of our included studies provided data about renin changes, which is not enough for meta-analysis. In the future, we will update our findings with further relevant studies.

Conclusions

In conclusion, we found that AAE could lower blood pressure and plasma aldosterone level of PA patients. Serum potassium level was increased by AAE. In addition, AAE had no apparent influence on cortisol secretion and led to only a few complications such as minor back pain and fever. As a minimally invasive operation, AAE might be beneficial for patients that are not suitable for adrenalectomy or drug therapy. Further RCTs are required to confirm our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-523/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-523/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-523/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, including ensuring that any questions related to the accuracy or integrity of any part of the work have appropriately investigated and resolved.

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