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ORIGINAL ARTICLE

The safety of withholding hydrocortisone during preoperative periods in pituitary adenomas patients with an intact HPA axis: A meta-analysis of randomized controlled trials.

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Abstract

OBJECTIVES: For patients with pituitary adenomas with an intact hypothalamus-pituitary-adrenal axis before surgery, whether routine steroid therapy is needed is still controversial. We conducted a meta-analysis to assess the safety of withholding hydrocortisone compared with hydrocortisone in pituitary adenoma patients during preoperative periods.

MATERIAL AND METHODS: We searched PubMed, Embase, Web of Science, and Cochrane Library databases up to November 2022 using inclusion and exclusion criteria. We employed either a fixed-effect or random-effect model for the analysis and assessed heterogeneity using the I^2 statistic.

RESULTS: Three studies involving 512 patients out of 400 studies were conducted. The pooled data revealed a higher incidence of postoperative transient diabetes insipidus in the no-hydrocortisone group than in the hydrocortisone group (RR, 1.88; 95% CI, 1.13 to 3.12; $p = 0.02$). The cortisol level in the no-hydrocortisone group was lower than in the hydrocortisone group after tumor removal (mean difference, -36.82; 95% CI, -44.27 to -29.38; $p < 0.00001$) but higher on the second day after surgery (mean difference, 4.04; 95% CI, 2.38 to 5.71; $p < 0.00001$). No significant differences were observed in early adrenal insufficiency (RR, 1.04; 95% CI, 0.37 to 2.96; $p = 0.93$), adrenal insufficiency in the third month after surgery (RR, 1.56; 95% CI, 0.70 to 3.48; $p = 0.28$), cortisol level on the first day after surgery (mean difference, 0.24; 95% CI, -11.25 to 11.73; $p = 0.97$), postoperative permanent diabetes insipidus (RR, 1.61; 95% CI, 0.43 to 6.07; $p = 0.48$), postoperative delayed hyponatremia (RR, 1.06; 95% CI, 0.41 to 2.74; $p = 0.91$), or postoperative blood glucose level (mean difference, -0.41; 95% CI, -1.19 to 0.37; $p = 0.31$) between the no-hydrocortisone and hydrocortisone groups.

CONCLUSION: Withholding preoperative steroid therapy is safe for pituitary adenomas patients with an intact hypothalamus-pituitary-adrenal axis.

Abbreviations:

TSS	- transsphenoidal surgery
AI	- adrenal insufficiency
HPA	- hypothalamus-pituitary-adrenal
RCT	- randomized controlled trials
NH	- no-hydrocortisone
H	- hydrocortisone
DI	- diabetes insipidus
DH	- delayed hyponatremia
RR	- risk ratio
OR	- odds ratio
95%CI	- 95% confidence interval

INTRODUCTION

Pituitary adenomas is a common intracranial tumor with an incidence of 10-20% (Ciric *et al.* 1997; Melmed 2011; Halvorsen *et al.* 2014). Transsphenoidal surgery (TSS) for pituitary adenoma removal has become a standard surgical approach due to its numerous advantages, including rapid symptom relief, improved patient health, and minimal impact on overall quality of life (Ciric *et al.* 1997; Sunil *et al.* 2022). However, postoperative endocrine disease occurs in 10-30% of patients undergoing surgery for pituitary adenomas (Webb *et al.* 1999; Little *et al.* 2019; Buttan & Mamelak 2019). Among these complications, postoperative adrenal insufficiency (AI) is one of the most life-threatening, leading to lethargy, fever, vomiting, tachycardia, hypotension, circulatory failure, and even death. Historically, it was believed that preoperative steroid therapy was necessary for all patients with pituitary adenomas, regardless of whether their hypothalamic-pituitary-adrenal (HPA) axis was intact before surgery, to prevent postoperative AI (Salem *et al.* 1994; Yeh & Chen 1997; Borg *et al.* 2018). However,indiscriminate use of steroids can affect osteopenia, cardiovascular disease, weight gain, and potentially increased mortality (Peacey *et al.* 1997; Sholter & Armstrong 2000; Okinaga *et al.* 2005; Zueger *et al.* 2012; Mizutani *et al.* 2015; Buckley & Humphrey 2018). Some experts believe that preoperative steroid therapy does not affect the postoperative prognosis of patients with pituitary adenomas (Marko *et al.* 2010; Tohti *et al.* 2015; Alexander *et al.* 2022). The necessity of preoperative steroid therapy in pituitary adenoma patients, particularly those with an intact HPA axis, remains controversial.

Consequently, in order to evaluate the safety of withholding preoperative steroid therapy in pituitary adenoma patients with an intact HPA axis, we performed a meta-analysis of all randomized controlled trials (RCT).

METHODS

This meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer *et al.* 2015).

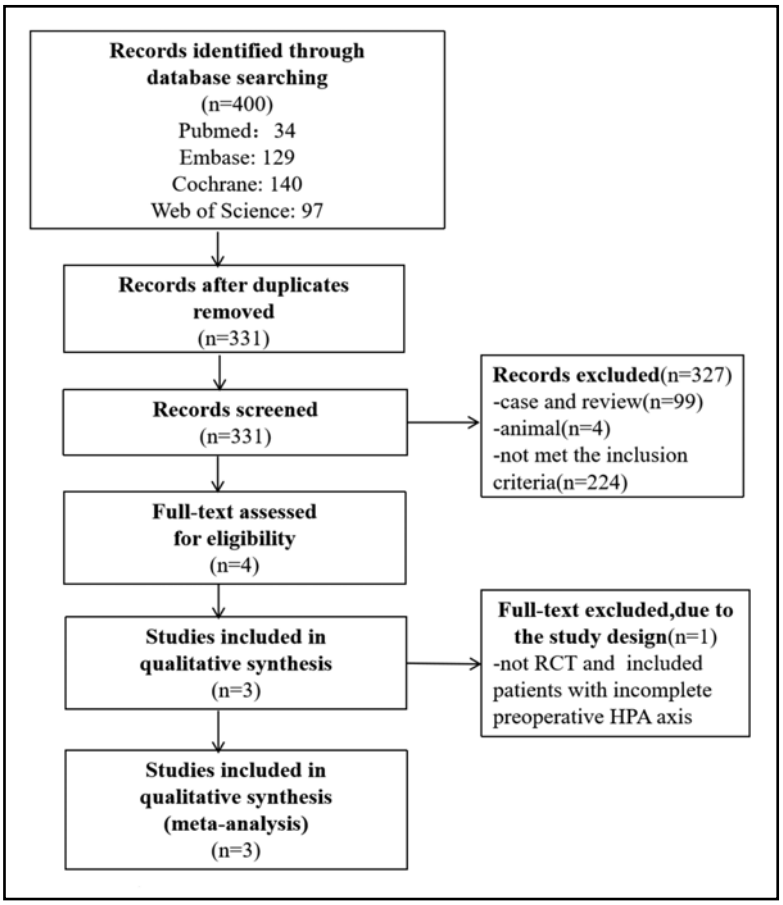

Fig. 1. Flow charts for PRISMA search, HPA, hypothalamus-pituitary-adrenal

Tab. 1. Characteristics of Included Studies

	Study design	Patients NH/H	Age (years) NH/H*	Number of males (%) NH/H	Type of tumor	Follow-up duration
Sterl,2019	RCT	17/19	47 ± 15/55± 15	10(58.8)/7(36.8)	Pituitary adenoma, acromegaly, prolactinoma, other	6 weeks
Lee,2020	RCT	20/20	50 ± 14/48 ±16	8(40)/9(45)	Nonfunctioning	3 months
Guo,2022	RCT	218/218	44.5 ± 13.8/45.4 ± 13.0	90(41.2)/82(37.6)	Nonfunctioning, functioning, growth hormone, prolactin, thyroid stimulating hormone, plurihormonal	3 months

H, hydrocortisone; NH, no-hydrocortisone; RCT, randomized controlled trials.
*Age was reported as mean standard deviation in all of the studies.

Search strategy and selection criteria

A comprehensive search was carried out on four electronic databases, including PubMed (Medline), Web of Science, Embase, and the Cochrane Library, from their inception to November 2022. We utilized the following keywords: 'Pituitary Neoplasms' and 'Hydrocortisone'. Two authors independently reviewed and summarized the search results, with disagreements resolved by consensus.

We considered all articles that potentially met the following inclusion criteria: 1) an RCT with quantitative data on clinical outcomes of interest, comparing no-hydrocortisone (NH) vs hydrocortisone (H); 2) all included patients are adults (≥18 years old); and 3) all included adults suffered from pituitary adenomas with an intact HPA axis which is fully defined as a peak cortisol level>18μg/dl (497 nmol/L) in an insulin resistance test or rapid ACTH test. Exclusion criteria were conducted as follows: 1) review articles, letters, case reports, and any studies in languages other than English; 2) articles enrolled pediatrics; 3) not an RCT; 4) patients with cushing disease, patients who had already developed AI before TSS, patients with pituitary apoplexy or other acute pituitary lesions that needed emergency surgery, patients who needed permanent glucocorticoid replacement therapy owing to other diseases, and patients who were pregnant or had a previous history of brain or adrenal surgery.

In this study, we defined postoperative AI as postoperative serum morning cortisol concentration < 5μg/dl (Jackanich *et al.* 2019). Hormone therapy was used if AI occurred after TSS in both groups of the study.

Data extraction and outcomes

Data extraction was performed from eligible studies by two authors independently. Relevant variables included authors, year of publication, number of patients per group, design of study, type of tumor, age, gender, follow-up duration, primary outcome as number of early AI (within three days after surgery), secondary outcome as number of AI in the third month after surgery, other outcomes as postoperative cortisol level including after tumor removal, the first day and the second day after surgery, postoperative blood glucose level, number of complications included transient diabetes insipidus (DI), permanent DI, delayed hyponatremia (DH), hypocalcemia, hypokalemia, bone mineral density loss, hypernatremia.

Risk of bias assessment

Based on the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, two authors independently assessed the risk of bias in the enrolled RCTs (Higgins *et al.* 2011).

Statistical synthesis and analysis

We utilized the risk ratio (RR) or odds ratio (OR) for dichotomous variables and mean difference for continuous variables to represent the probability or level of an event occurring with a 95% confidence interval (CI). To evaluate the degree of heterogeneity, we employed the I^2 test metric. When I^2 was less than 50%, no significant heterogeneity was observed, and a fixed-effect model was implemented (Higgins *et al.* 2003). Conversely, a random-effect model was utilized (Higgins *et al.* 2003). Additionally, if continuous variables were documented using interquartile spacing in the paper, we employed the conversion formula to convert mean and standard deviation (Higgins & Green 2009; Luo *et al.* 2018). Rev-Man software (version 5.3) was used in all our statistical analysis. When a p value is less than 0.05, it was considered statistically different.

RESULTS

Search results

After screening and assessing 400 potentiallly relevant studies , three RCTs (Sterl *et al.* 2019; Lee *et al.* 2020; Guo *et al.* 2022) were selected in our meta-analysis (Fig.1).

Characteristics of the included studies and quality assessment

The characteristics of the included studies (Guo *et al.* 2022; Lee *et al.* 2020; Sterl *et al.* 2019) are shown in Table 1. A total of 512 participants were enrolled, with 255 in NH group and 257 in the H group.

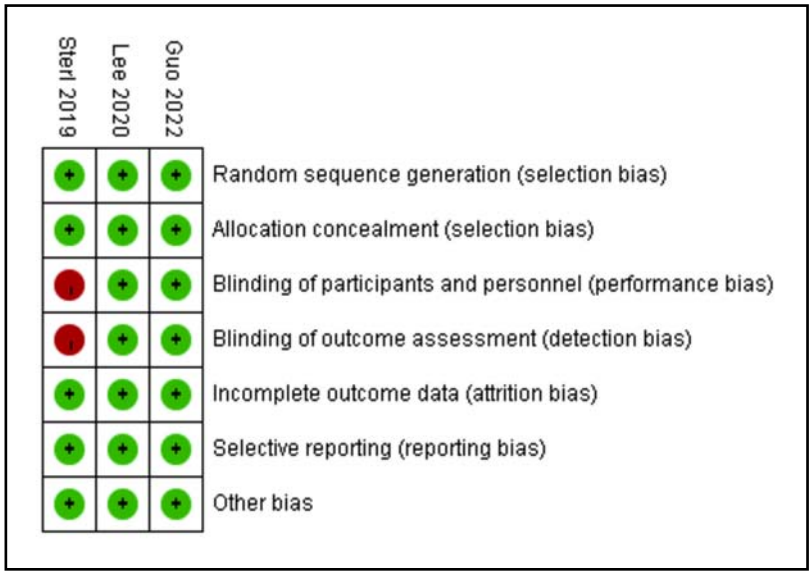

Fig. 2. Risk of bias summary

The bias risk of enrolled studies was evaluated using the "risk of bias" assessment tool, according to the Cochrane Handbook for Systematic Reviews of Intervention (version 5.0.2). All studies described the randomization methods and allocation. Two studies (Guo *et al.* 2022; Lee *et al.* 2020) were considered high-quality with low risk of biases across all domains, while one study (Sterl *et al.* 2019) was considered high risk due to the lack of blinding. Fig.2 displays the quality assessments for the included studies.

Meta-analysis results

Early AI and AI in the third month after surgery rate

Three studies reported the number of early AI cases, with a total of 56 out of 512 (10.9%). According to the pooled data, there was no significant difference between the NH and the H groups regarding the rate of early AI (RR, 1.04; 95% CI, 0.37 to 2.96; $p = 0.93$) (Fig. 3A). Additionally, there was no significant difference in the rate of AI in the third month after surgery between the NH group and the H group (RR, 1.56; 95% CI, 0.70 to 3.48; $p = 0.28$) (Fig. 3B).

Postoperative cortisol level (after tumor removal, the first day and the second day after surgery)

Based on the pooled data, the NH group had lower cortisol level than the H group after tumor resection (Mean difference, -36.82; 95% CI, -44.27 to -29.38; $p < 0.00001$) (Fig. 4A). However, no significant difference was observed on the first day after surgery (Mean

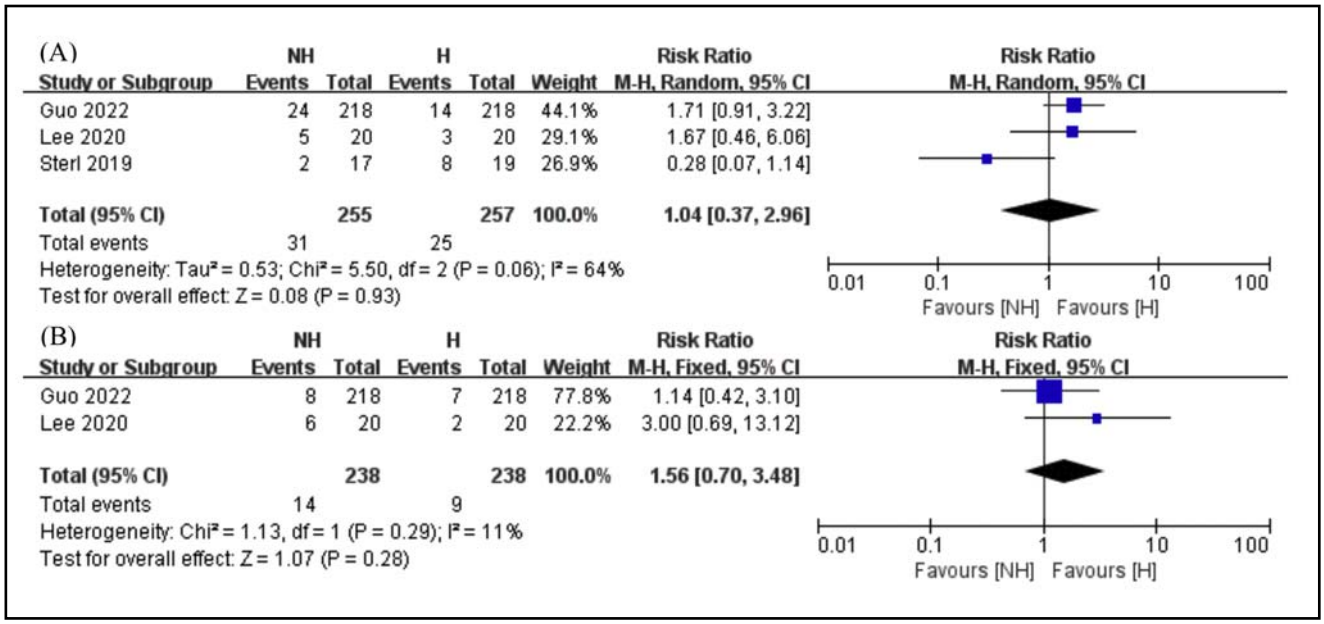

Fig. 3. (A) Forest plot for early AI between no-hydrocortisone and hydrocortisone groups. (B) Forest plot for AI in the third month after surgery between no-hydrocortisone and hydrocortisone groups.

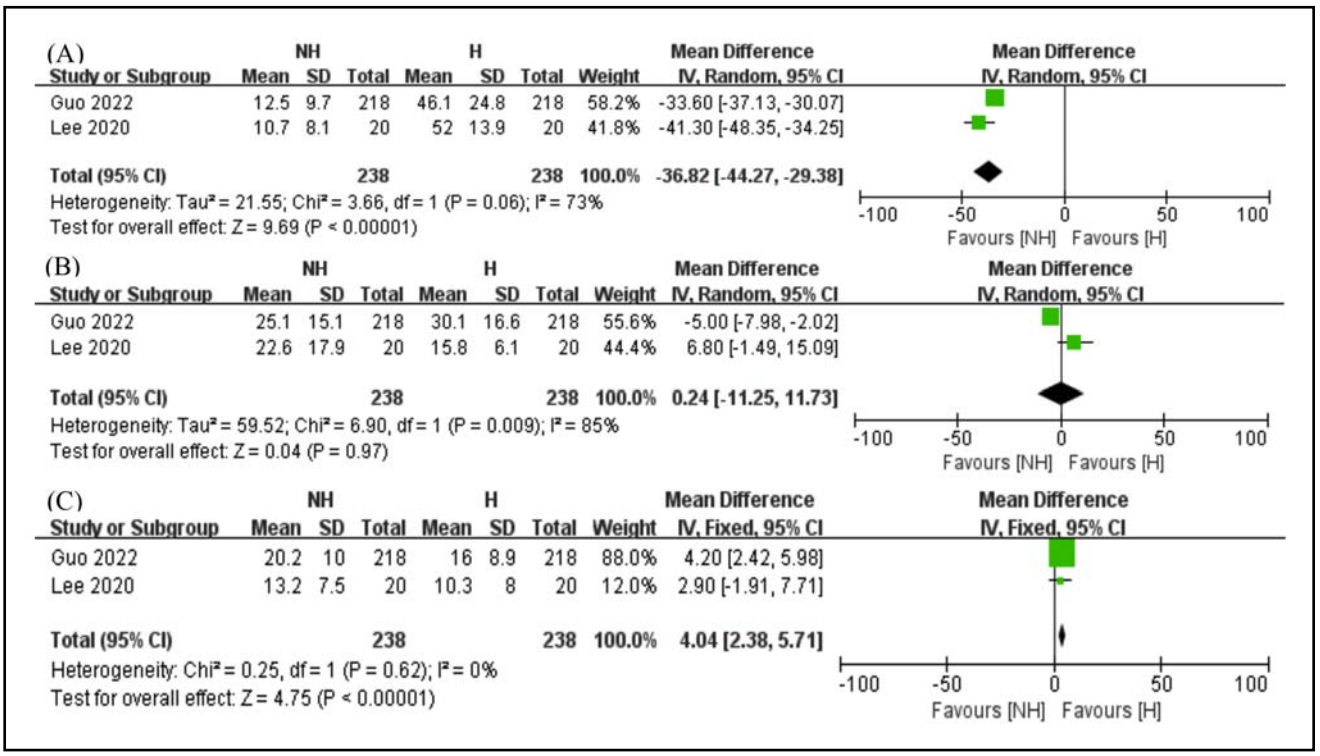

Fig. 4. (A) Forest plot for cortisol level after tumor removal between no-hydrocortisone and hydrocortisone groups. (B) Forest plot for cortisol level on the first day after surgery between no-hydrocortisone and hydrocortisone groups. (C) Forest plot for cortisol level on the second day after surgery between no-hydrocortisone and hydrocortisone groups.

difference, 0.24; 95% CI, -11.25 to 11.73; $p = 0.97$) (Fig. 4B). In contrast, the cortisol level in the NH group was higher than that in the H group on the second day after surgery (Mean difference, 4.04; 95% CI, 2.38 to 5.71; $p < 0.00001$) (Fig. 4C).

Postoperative transient DI and permanent DI rate

According to the studies included in the analysis, the incidence rates of both postoperative transient DI and permanent DI were reported. The pooled data revealed that the NH group had a higher incidence of postoperative transient DI compared to the H group (RR, 1.88; 95% CI, 1.13 to 3.12; $p = 0.02$) (Fig. 5A). However, no significant difference was observed in the rate of permanent DI between the NH group and the H group (RR, 1.61; 95% CI, 0.43 to 6.07; $p = 0.48$) (Fig. 5B).

Postoperative DH rate

The combined data showed no statistically significant difference between the two groups regarding postoperative DH incidence (RR, 1.06; 95% CI, 0.41 to 2.74; $p = 0.91$) (Fig. 6).

Postoperative blood glucose level

Upon pooling the data, we observed no significant difference between the NH and H groups in postoperative blood glucose levels (Mean difference, -0.41; 95% CI, -1.19 to 0.37; $p = 0.31$) (Fig. 7).

DISCUSSION

Secondary AI occurs in 4% to 9% of patients when adrenal function is intact before surgery, and up to 18% of patients may experience early transient AI (Fatemi *et al.* 2008; Burgers *et al.* 2011). Fewer studies have detailed the incidence of early and late AI, with reports of early and late AI ranging from 10% to 51% and 2.3% to 36% (Jane *et al.* 2011; McLaughlin *et al.* 2013; Dallapiazza *et al.* 2015; Bondugulapati *et al.* 2016). In our study,the incidence of early AI was 12.2% in the NH group and 9% in the H group. The incidence of AI in the third month after surgery was 5.9% in the NH group and 3.8% in the H group with no statistically significant difference. Compared with previous studies, the incidence of AI in the NH group did not increase, indicating that for pituitary adenomas patients with an intact HPA axis, preoperative non-routine use of hormone therapy did not increase the occurrence of postoperative AI and preoperative retention of hormone drugs was safe. The possible explanation is that the risk of developing AI when the patient's preoperative HPA axis is intact may also reflected by tumor size, expansion to surrounding structures, tumor aggressiveness, and the experience of the surgeon. In addition, there is also literature suggesting that early postoperative hyponatremia may also be an indicator of endogenous cortisol deficiency, which should be suspected of potential secondary AI (Liamis *et al.* 2011). Therefore, we considered

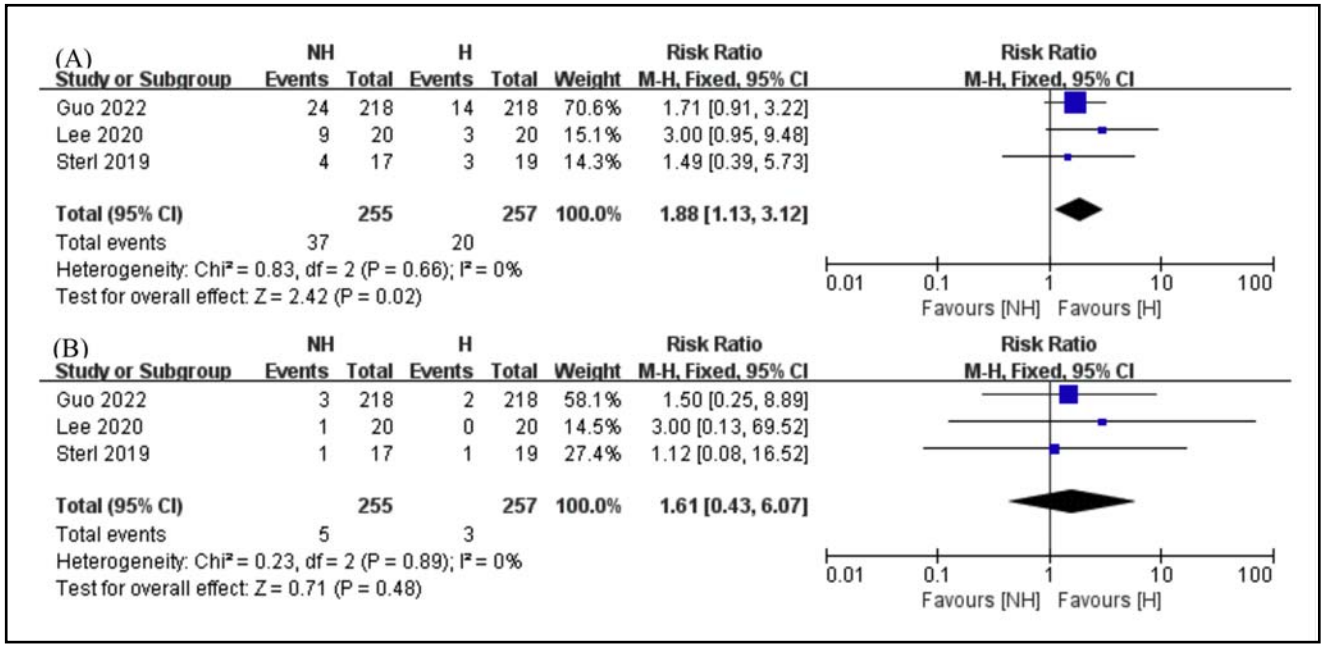

Fig. 5. (A) Forest plot for postoperative transient DI between no-hydrocortisone and hydrocortisone groups. (B) Forest plot for postoperative permanent DI between no-hydrocortisone and hydrocortisone groups.

that post-operative testing is more important aspect. Replacement is given if a patient is symptomatic and tests low cortisol levels following surgery. It is not necessary to use hormone replacement therapy before surgery to prevent AI in all patients.

Our study found that after tumor resection, the blood cortisol level in the NH group was lower than in the H group, with a statistically significant difference. We believed that this was because hydrocortisone was used 30 minutes before surgery in the H group, which caused an exogenous increase in blood cortisol. Interestingly, we found that on the first day after surgery, blood cortisol level was still lower in the NH group than in the H group, with no statistically significant difference. However, on the second day after surgery, the blood cortisol level of the NH group was higher than the H group, with statistically significant difference. The possible explanation is that when patients with an intact HPA cycle were treated with exogenous steroids, the negative feedback mechanism of the HPA axis is activated, thus reducing cortisol secretion, which can also explain why the blood cortisol level of the H group was lower than that of the NH group on the second day after surgery. Another explanation is that the stress tolerance of pituitary surgery in the first and second day after surgery subsequently leads to a strong intrinsic response in patients, resulting in increased cortisol rebound in patients with pituitary adenomas after surgery without steroid use (Borg *et al.* 2018; Miller & O'Callaghan 2002; Regan & Watson 2013; Tohti *et al.* 2015). Intrinsic reactivity increases blood cortisol, keeping blood cortisol level at a lower threshold. Studies have shown that a lower cortisol threshold after surgery may prevent more patients from receiving unnecessary steroid therapy (McLaughlin *et al.* 2013). In addition,studies have shown that in patients with intact HPA axis, cortisol level may be normal or elevated after surgery, demonstrating that the body has demonstrated an appropriate physiological response to the stress of surgery and that preoperative hormone supplementation may not necessarily be necessary (Rajaratnam *et al.* 2003; Wentworth *et al.* 2008).

Although there has been evidence that the use of steroid drugs after surgery may cause potential DI, or the incidence of DI after surgery does not seem to increase in patients who do not receive steroid supplement therapy during the perioperative period (Rajaratnam *et al.* 2003; Regan & Watson 2013). But the incidence of transient DI in the NH group was higher than that in the H group in our study, and the difference was statistically significant. The data showed that HPA function was strongly activated during perioperative period (El-Sibai *et al.* 2017). We considered that the increase of endogenous cortisol or ACTH after surgery in the NH group, which is higher than that in the H group in our data, might activate the negative feedback mechanism and lead to the temporary inhibition of vasopressin, resulting in the occurrence of transient DI that was more obvious than that in the H group. However, we also found no statistical significance in the difference in permanent DI between the two groups. Most patients could recover from transient DI, while only a few developed permanent DI. We considered that failure to recover pituitary function after surgery might be related to insufficient secretion of anti-urea hormone. It showed no difference in the incidence of DI between the two groups, which is consistent with the previous study (Tohti *et al.* 2015).

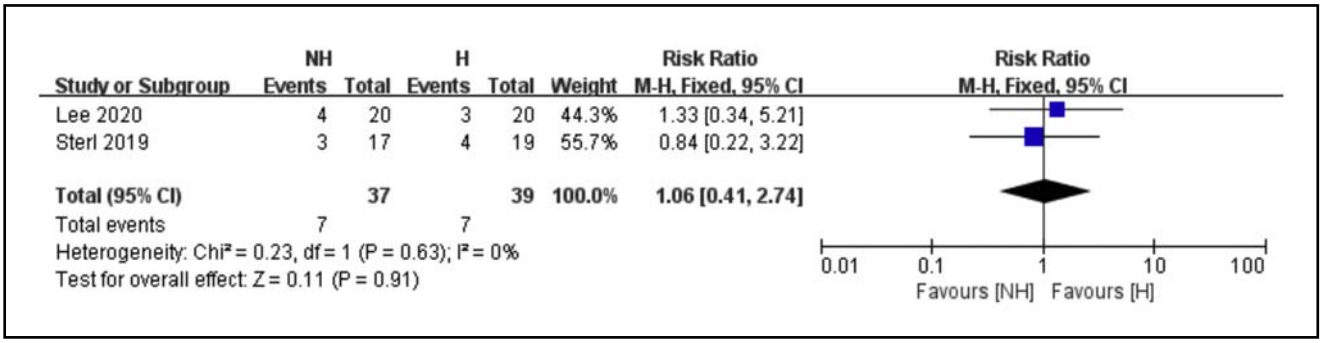

Fig. 6. Forest plot for postoperative delayed hyponatremia, DH between no-hydrocortisone and hydrocortisone groups.

Study have shown that the occurrence of DH is related to the operation of the pituitary manipulation and relocation of the pituitary gland (Kristof *et al.* 2009). Our study found no statistically significant difference in the incidence of DH between the two groups, which was also consistent with the previous study (Tohti *et al.* 2015).

In our data, no significant difference in postoperative blood glucose levels was observed between the two groups. However, considering the large heterogeneity and the fact that most of the patients were not diabetic patients, the influence of hormone use on blood glucose and body complications was difficult to assess at present.

In addition, a study by Guo *et al.* reported the results of hypernatremia, hypokalemia, and hypocalcemia in two groups, all of which showed that the incidence of the NH group were lower than that of the H group.

Despite its strengths, this meta-analysis has several limitations: 1) only 3 RCTs were included and there were two of the three RCTs with small number in our analysis,which may affect the extensibility of the results,so more RCT with large sample size are needed for validation; 2) although all the included articles adopted TSS surgery, the methods of hormone administration were slightly different, which may have some influence on the level of blood cortisol after surgery, and further studies are needed; 3) study have shown that anesthetic drugs can have an effect on postoperative hormone secretion, but the effects of anesthetic drugs were not studied in the included articles,which need further verification by more prospective studies. In spite of these limitations, we believe that the results of our meta-analysis are rigorous and can be used as guidance for future research.

CONCLUSION

In conclusion, this meta-analysis demonstrates no significant differences between the NH group and the H group in terms of postoperative AI and other complications. Omitting preoperative hormone therapy before TSS does not increase the incidence of postoperative AI. Thus, withholding preoperative steroid treatment is safe for pituitary adenoma patients with an intact HPA axis. In patients with pituitary tumors and an intact HPA axis, hormone replacement therapy should not be routinely administered prior to TSS.

COMPLIANCT WITH ETHICAL STANDARDS

Research involving human participants and/or animals: None.

SOURCE OF FUNDING

None.

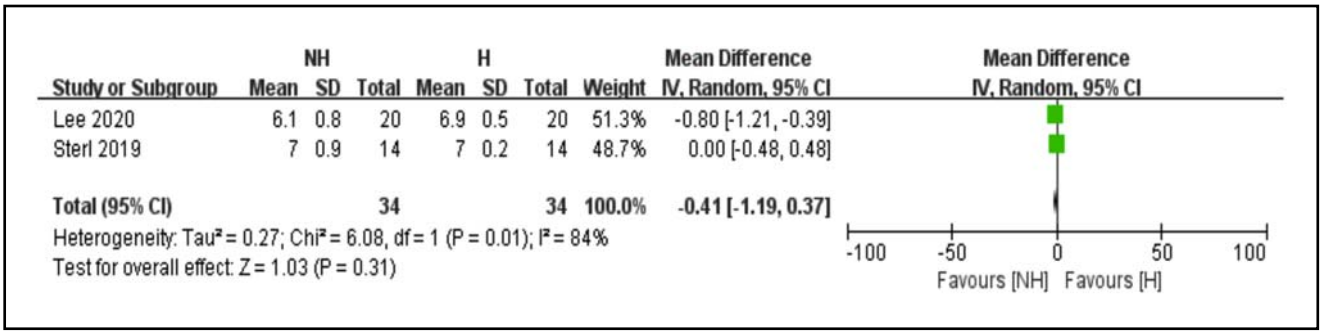

Fig. 7. Forest plot for postoperative blood glucose level between no-hydrocortisone and hydrocortisone groups.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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