Original Article

Using Herbal and Traditional Medicinal Products is the Risk Factor of Adrenal Insufficiency in Thailand: The Retrospective Cohort Study

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Background: Herbal and traditional medicinal products (HTM) are widely used worldwide, particularly in the Asian region. Adulteration of undeclared glucocorticoids in these products may lead to adrenal insufficiency (AI).

Objective: To investigate the relationship between HTM usage and the risk of AI.

Materials and Methods: A 7-year retrospective study of 369 adult patients who had undergone the ACTH stimulation test was conducted in a tertiary care medical center in Thailand. An adjusted risk ratio was used to compare the incidence of AI between patients using HTM and those not using HTM.

Results: Overall, 44.7% of the patients who reported using HTM were diagnosed with AI with adjusted risk ratio of 1.71 (95% CI 1.01 to 2.94). Cushingoid appearance was found to be significantly related to AI.

Conclusion: There is a significantly higher incidence of AI in patients who use HTM. Healthcare professionals should be concerned about AI in the patients who have a history of HTM use.

Keywords: Adrenal insufficiency, Herbal medicine, Traditional medicine, ACTH stimulation test

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Herbal and traditional medicinal products (HTM) are increasingly used by people in many countries, especially in the Asian region. The prevalence of HTM use without prescription in Asia has been variously reported to be between 5% and 77%[1-4]. In Thailand, the range has been reported to be between 45% and 47.8%[1,5]. Patients most likely to use these products were over 70 years old, female, and individuals with illnesses not receiving any medical care, diabetes mellitus, cardiovascular diseases, chronic kidney diseases, and cancer[4,6]. HTM may contain material from a single plant or from a mixture of material from several plants in various recipes. It has been generally believed that because these products are prepared from natural material they must be safe, especially those herbal medicines that have been used by humans for many generations. However, frequently, products have been illegally marketed as HTM and have been adulterated with undeclared potent medicinal drug components. Corticosteroids are one of the most commonly found adulterants. Other adulterants include non-steroidal anti-inflammatory drugs, oral hypoglycemic drugs, and antihistamines[7,8].

Undeclared adulterating corticosteroids have been reported in HTM in both raw and finished form of the HTM, particularly in traditional Chinese medicines[9-12]. Many organizations in several countries, especially Western nations including USA

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and EU, have insured the safety of HTMs as a top priority. Governing regulations are strictly enforced. As a result, cases of adulterated HTM are rare in these countries. However, this problem continues in Asian countries including India, China, Singapore, and Thailand.

In Thailand, there are many forms of HTM including capsules, tablets, and powder packed in small plastic bags dispensed by local drugstores and Thai traditional medicine doctors. These products are variously known in Thai as "Ya Samun Prai", "Ya Moh", and "Ya Look Korn" depending on how the products are traditionally prepared. Corticosteroids are illegally added to these products to increase potency, e.g., a powerful analgesic or a strong anti-inflammatory effect. These adulterated undeclared corticosteroids are known to have a significant clinical impact including multiple adverse effects such as adrenal insufficiency (AI), which is potentially fatal.

Prolonged high intake of corticosteroids can result in a negative feedback inhibition on the hypothalamic pituitary adrenal (HPA) axis, decreasing the release of adrenocorticotropic hormone (ACTH). Reduction of corticosteroid synthesis and secretion from the adrenal gland can precipitate AI. Normally, recovery of the HPA axis can occur rapidly. However, the prolonged use of corticosteroids can delay HPA recovery. The reported dose and duration of corticosteroids that cause HPA suppression are approximately 40 mg of prednisolone for a period of more than two to three weeks[13]. As the amount of corticosteroid in adulterated HTM is unpredictable, an overdose leading to AI may easily occur.

Many studies have reported an association between the use of HTM and AI. The prevalence of the use of HTM was markedly higher in critically ill patients with low serum cortisol[14]. One study in Thailand reported that half of the inpatients diagnosed with adrenal crisis had a history of HTM use, suggesting that AI was the prime culprit[15]. There is, however, a paucity of information on outpatients. Patients with a history of HTM who have been screened for AI need to undergo ACTH stimulation testing to determine cortisol levels. Unfortunately, ACTH stimulation tests cannot be performed in some institutions due to a shortage of the necessary medication or specialists, resulting in difficulty in diagnosis. If the relationship between AI and HTM usage history were determined, HTM use could be a predictive diagnostic factor for AI, especially in individuals with indeterminate cortisol levels. Additionally, if specific characteristics of patients with a history of HTM usage who are at risk for AI could be identified, the need for ACTH stimulation tests could be reduced.

The objectives of the present study were first, to explore the relationship between a history of HTM usage and the prevalence of AI in both in- and out-patients with indeterminate cortisol levels and, second, to identify characteristics associated with AI in patients with indeterminate cortisol levels who have a history of HTM usage.

Materials and Methods

A 7-year retrospective study was conducted in a tertiary care center at the Faculty of Medicine, Chiang Mai University, Thailand. Data were obtained from the electronic medical records of all patients aged over 18 years old who had undergone either low dose (LDT) or high dose (HDT) ACTH stimulation testing between January 2010 and January 2017 in both the in-patient and out-patient departments. The study protocol was approved by the local ethical committee. When more than one test was conducted on a patient, only the first test was included in the study. According to the protocol of the institution, either LDT or HDT was performed on all patients who had 8 a.m. serum cortisol at the indeterminate levels of 3 to 18 μg per dL. Exclusion criteria were patients with other explainable causes of AI, i.e., a history of pituitary surgery, pituitary radiation, pituitary tumor, multiple pituitary hormonal deficiencies, adrenal gland diseases, a history of previous adrenalectomy, and incomplete ACTH stimulation test results. Women who were currently taking oral contraceptives were also excluded. Patients being treated with glucocorticoids or other HTMs suspected of containing corticosteroids were told to discontinue those substances for at least 24 hours before the ACTH stimulation tests. Serum cortisol levels were measured by an electrochemiluminescence immunoassay (ECLIA) method using an Electrosys Cortisol II platform (Cobas Roche Diagnostics). Intra- and inter-assay coefficients of variation for serum cortisol were less than 10%. Data on serum albumin, total cholesterol and serum creatinine within three months before or after the ACTH stimulation testing were also collected. The estimated glomerular filtration rate (eGFR) was calculated using the modified MDRD formula.

Six hundred thirty-two patients had undergone ACTH stimulation testing. Of these, 263 patients met the exclusion criteria. Consequently, 369 patients were included in the analyses. The study flow is

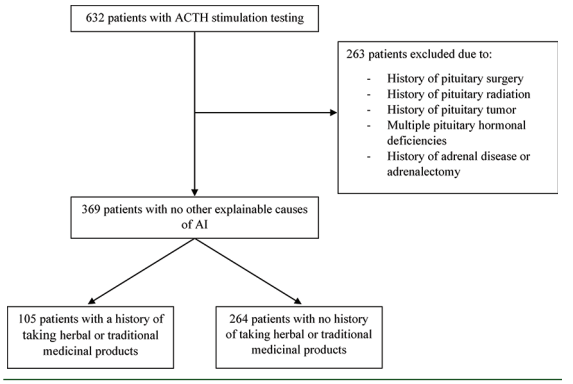

Figure 1. The scheme of the study flow.

shown in Figure 1.

The ACTH stimulation testing protocol

ACTH tests were conducted between 10 a.m. and 1 p.m. All tests were conducted by well-trained nurses and all patients had an indwelling catheter during the procedure. The total serum cortisol level was determined at 0, 30, and 60 minutes after the intravenous administration of either 1 µg or 250 µg ACTH (Synacthen®, Tetracosin®). Due to a shortage of ACTH in Thailand, between May 2010 and March 2014, only 1 µg ACTH was used instead of 250 µg (HDT). The 1 µg ACTH dose was prepared under sterile conditions as a 250 µg ampule of ACTH, which was diluted with normal saline and then packed in 1 ml ready-to-use syringes and stored at 2°C to 8°C.

Definitions

AI was defined as a peak serum cortisol level of less than 18 µg per dL at 30 or 60 minutes after LDT or HDT[16]. Patient with an autoimmune disease was defined as patients who had been documented with any underlying autoimmune disease, e.g., systemic lupus erythematosus, rheumatoid disease, or Hashimoto's thyroiditis. Malignancies included both solid tumors and hematologic malignancies. Orthopedic conditions included any joint pain, back pain, osteoarthritis, bursitis or a history of fracture. A history of HTM usage was defined as self-reported personal use of any type or form of HTM suspected of containing glucocorticoids (e.g., reported of rapidly resolved of concerning symptoms, increasing appetite, or gaining weight after HTM usage), which had not been prescribed by a conventional medical practitioner within three weeks prior to the ACTH stimulation test. The patients that used concomitant HTM and glucocorticoids prescribed by conventional medical practitioners were not categorized as patients in HTM group. The duration of HTM usage was retrieved from the medical record. Cushingoid appearance was defined as a constellation of at least one of the following signs of corticosteroid excess, e.g., moon face, facial plethora, easy bruising, purplish striae, proximal muscle weakness, buffalo hump, or and hirsutism documented in the patient's medical record by a treating physician. No medical record regarding Cushingoid appearance was marked as "no Cushingoid appearance". Symptoms of AI were characterized as any symptom of fatigue, weight loss, syncope, intractable nausea, and vomiting or orthostatic hypotension documented in their medical record.

Statistical analysis

Data were analyzed using the Stata Statistical Software (StataCorp., College Station, TX, USA). The statistical significance level was set as two-tailed with a p-value less than 0.05. Categorical variables were presented as a number or percentage and continuous variables are presented as means and standard deviations (SDs). For inferential statistics, categorical variables were analyzed using the Fisher's exact test, while continuous variables were analyzed using the t-test or Mann-Whitney U test as appropriate. The 95% confidence interval (CI) was calculated. The relationship between AI and a history of HTM usage was analyzed using a risk regression model and was presented as both the crude and adjusted risk ratios. Variables including age, gender, body weight, serum albumin, cholesterol, creatinine, and history of prednisolone and dexamethasone use were used to adjust the model. Differences between subgroups were demonstrated by the p-value for interaction. Imputation method was employed for missing values.

Results

Baseline characteristics

Of the 369 patients (166 males and 203 females) suspected of having AI who had undergone ACTH stimulation testing, 105 patients (28.5%) had reported a history of HTM usage, while 264 (71.5%) denied using these products. Baseline characteristics are shown in Table 1. Among the patients, 29.8% (n=110/369) had a definite diagnosis of AI. Of those with a history of taking HTM, 44.7% had AI (n=47/105). Overall, the mean age of participants was 56.4±17.2 years, but the mean age of those with a history of HTM usage was significantly higher than those that did not use any. A history of hypertension

Table 1. Baseline characteristics of patients with and without history of traditional medicine used

Characteristics	Total (n=369)	History of traditional medicine used (n=105)	No history of traditional medicine used (n=264)	p-value
	n (%)	n (%)	n (%)	
Sex				0.21
Male	166 (45.0)	43 (41.0)	123 (46.6)	
Female	203 (55.0)	62 (59.0)	141 (53.4)	
Age (year); mean±SD	56.4±17.2	62.1±14.5	54.1±18.9	<0.001
Body weight (kg); mean±SD	57.4±18.1	58.3±17.4	57.1±14.5	0.51
Underlying disease				
Autoimmune diseases	81 (21.9)	21 (20.0)	60 (22.7)	0.34
Malignancy	32 (8.7)	5 (4.8)	27 (10.2)	0.06
Diabetes mellitus	56 (15.2)	20 (19.1)	36 (13.7)	0.13
Hypertension	107 (29.1)	45 (42.9)	62 (23.6)	<0.001
Coronary artery disease	40 (10.9)	18 (17.1)	22 (8.37)	0.01
Orthopedics condition	28 (7.6)	12 (11.4)	16 (6.1)	0.06
Adrenal insufficiency	110 (29.8)	47 (44.7)	63 (23.8)	<0.001
ACTH stimulation dose				0.01
• 1 µg	41 (37.3)	26 (55.3)	15 (23.8)	
• 250 µg	69 (62.7)	21 (44.7)	48 (76.2)	
Cushingoid appearance	84 (22.8)	52 (49.5)	32 (12.1)	<0.001
Signs and symptoms of AI				
Fatigue	117 (31.7)	27 (25.7)	90 (34.1)	0.12
Weight loss	31 (8.4)	4 (3.8)	27 (10.2)	0.04
Dizziness or syncope	72 (19.5)	21 (20.0)	51 (19.3)	0.88
Hypoglycemia	23 (6.2)	7 (6.7)	16 (6.1)	0.82
Hypotension	99 (26.8)	23 (21.9)	76 (28.7)	0.11
Department				0.26
Inpatient department	113 (30.6)	29 (27.6)	84 (31.8)	
Outpatient department	256 (69.4)	76 (72.48)	180 (68.2)	
Baseline SBP (mmHg); mean±SD	119.5±19.2	120.1±21.9	119.2±21.7	0.72
Baseline DBP (mmHg); mean±SD	70.9±19.2	71.5±13.3	70.7±13.9	0.63
ACTH stimulation dose				0.03
1 µg	163 (47.2)	55 (52.3)	108 (40.9)	
250 µg	182 (52.7)	50 (47.6)	156 (59.1)	
Serum morning cortisol (µg/dL); mean±SD	9.29±3.3	8.8±3.4	9.5±3.4	0.07
Serum basal cortisol (µg/dL); mean±SD	10.0±5.7	8.3±4.5	10.7±6.3	<0.001
Cortisol at 30 minutes (µg/dL); mean±SD	20.1±8.1	17.1±7.5	21.3±7.9	<0.001
Cortisol at 60 minutes (µg/dL); mean±SD	22.2±8.6	19.1±8.3	23.4±8.6	<0.001
Serum albumin (g/dL); mean±SD	3.5±0.96	3.4±0.8	3.6±1.1	0.18
Serum cholesterol (mg/dL); mean±SD	167.6±59.7	169.8±5.1	166.6±4.3	0.67
Serum creatinine (mg/dL); mean±SD	1.1±1.2	1.2±1.5	1.1±1.1	0.52
Serum sodium (mmol/L); mean±SD	137.2±0.2	138.3±4.8	136.7±10.7	0.18
eGFR (mL/min/1.73 m^2); mean±SD	90.7 48.7	85.4 49.2	92.8 48.4	0.21

ACTH=adrenocorticotropic hormone; AI=adrenal insufficiency; SBP=systolic blood pressure; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; SD=standard deviation

Table 2. Characteristics of patients in the herbal or traditional medicinal product user group (n=105)

Characteristic	n (%)
Indications of use	
Fatigue and loss of appetite	38 (36.2)
Joint pain	22 (20.9)
Malignancy	1 (0.9)
Skin diseases	4 (3.8)
Other	6 (5.7)
Unknown	34 (32.5)
Duration of use	
<3 months	27 (25.8)
3 to 6 months	12 (11.4)
>6 months	64 (60.9)
Unknown	2 (1.9)
Frequency of use	
Persistent	28 (26.7)
Intermittent	77 (73.3)
Withdrawal period before ACTH stimulation testing	
<1 month	86 (81.9)
1 to 6 months	12 (11.5)
>6 to 12 months	4 (3.8)
>12 months	1 (0.9)
Unknown	2 (1.9)

ACTH=adrenocorticotropic hormone

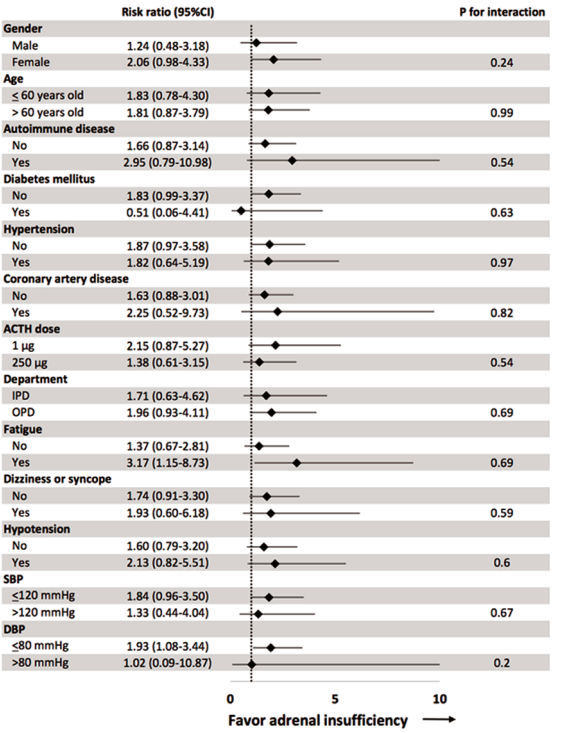

Figure 2. Subgroup analysis of AI risk ratios of patients with and without a history of using herbal or traditional medicinal products.

and coronary artery disease and the presence of Cushingoid appearance were significantly higher in the HTM user group than the non-user group. Patients in the HTM user group were more likely to receive LDT.

Characteristics of patients in the HTM user group are shown in Table 2. The primary reasons for undergoing ACTH stimulation testing as specified in the medical records of this group included reports of fatigue and loss of appetite. Most of the patients in this group had used HTM intermittently for more than six months.

Relationship between AI and the use of HTM

The relationship between AI and HTM use is shown in Table 3. Risk regression analysis revealed that patients with a history of HTM use exhibited a significantly higher risk of AI than those without this history with an adjusted risk ratio of 1.71 (95% CI 1.01 to 2.94, p=0.04).

In both patients with and without a history of HTM usage, there was no difference in the risk of AI within the subgroups, e.g., age, gender, underlying diseases, symptom presentation, ACTH dose, and baseline blood pressure (Figure 2).

Analysis of patients who had a history of using HTM revealed that patients with Cushingoid

Table 3. Risk ratios for adrenal insufficiency of the patients with a history of taking herbal or traditional medicinal products

Characteristics	Risk ratios for AI (95% CI)			
	Crude	p-value	Adjusted*	p-value
History of herbal, dietary supplement, or traditional medicine use	1.87 (1.28 to 2.73)	0.001	1.71 (1.00 to 2.94)	0.04
Control	1.00		1.00	

AI=adrenal insufficiency; CI=confidence interval

* Adjusted for age, gender, body weight, serum albumin, cholesterol, creatinine, history of taking prednisolone, and dexamethasone

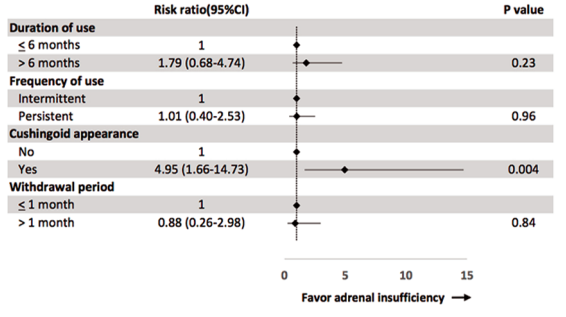

Figure 3. Subgroup analysis in patients with a history of herbal, dietary supplement or traditional medicine use.

appearance had a significantly higher incidence of AI than those without this characteristic with an adjusted risk ratio of 4.95 (95% CI 1.66 to 14.73, p=0.004). Within the subgroups of users of HTM, the duration and frequency of use and withdrawal time were not significantly different (Figure 3).

Discussion

The present study highlights the important relationship between the use of HTM and the occurrence of AI as indicated by a high risk ratio of 1.71, a result comparable to previous studies[15,17] such as a study in Taiwan that reported 61.5% of inpatients diagnosed with adrenal crisis had a history of HTM use. In Thailand, roughly 50% of patients with AI reported a history of ingesting unprescribed over-the-counter substances, a result in concordance with the present study's finding of 44.7%[15]. The minor differences in the incidence of AI may be due to divergent definitions of HTM ingestion as well as differences in laboratory cortisol assay techniques. Previous studies have not included quantitative measurements of effects of AI resulting from the use of HTM. Additionally, previous studies did not include adjustment for confounding variables that could potentially affect outcomes such as age, gender, body weight, and other laboratory tests that could cause serum cortisol interference. In the present study, the risk ratio of AI occurrence based on a history of using HTM was adjusted for those variables. Finally, neither of the previous studies confirmed the AI diagnosis by the ACTH stimulation test. Diagnosis in those studies was based solely on basal serum cortisol levels.

Cushingoid appearance has been noted as one of the physical characteristics that is significantly associated with AI, with an adjusted-risk ratio of 4.95 in patients who have a history of taking HTM. However, Kamrat reported no association between Cushingoid appearance and the incidence of AI in patients taking unprescribed over-the-counter medicines suspected of containing corticosteroids[15]. That may be due to the very low number of cases where only one patient in the study was characterized as having the Cushingoid appearance[15]. In the present study, almost 50% of the patients with a history of using HTM had the Cushingoid appearance as documented by a physician. This significant correlation indicates that Cushingoid appearance could be employed as one of the diagnostic factors of AI. Physicians treating patients with both the Cushingoid characteristic and a history of using HTM should consider HTM as a possible underlying factor for the AI. However, mischaracterization of Cushingoid appearance can easily occur as diagnosis of this characteristic is subjective. Additionally, Cushingoid appearance can have other causes such as people with obesity or a history of chronic alcohol drinking[18]. In the present study, the reported timing of use was not significantly linked to AI. The longer the use of glucocorticoids, the higher the risk of HPA axis suppression and the occurrence of AI could be explained from the physiologic alteration of HPA axis[19]. The explanation for the authors' negative association could be presumed from the recall bias of the patients and the incomplete data.

Several studies have documented that some widely distributed HTM medications have been deliberately adulterated with corticosteroids or contain the main components of corticosteroid-like substances originating from the plant itself[20-22]. For example, one study reported that chronic topical application of an herbal cream containing the ethanol extract of the plant *Cardiospermum halicacabum* resulted in iatrogenic Cushing syndrome caused by the corticosteroid-like substances contained in the plant extract[21]. That indicates undesirable clinical effects can be caused both by undeclared corticosteroidal drug adulterants as well as by naturally occurring corticosteroid-like substances in the plant. Both can result in unexpected clinical side effects due to the uncontrolled high corticosteroidal dosage.

Based on all of the above-mentioned data, prolonged ingestion of HTM medication containing corticosteroids, whether adulterated or naturally occurring, can lead to AI, a potentially fatal complication resulting from chronic use and abrupt withdrawal. In treating AI, the consulting physician should be aware of the patient's history of using HTM, particularly patients from the Asian region. Recently,

however, several sources of HTM adulterated with corticosteroid have recently been reported to be available through drugstores, health food stores, and via the internet in Western regions[14,23,24].

The present study demonstrates the key strengths and the major finding of a significant relationship between a history of HTM usage and the occurrence of AI in both in- and out-patients. This discovery suggests a need to increase public awareness and to establish stringent regulations regarding the dispensing of HTM. A Cushingoid appearance has been shown to be strongly related to the incidence of AI in patients with a history of using HTM. In institutions where access to the ACTH stimulation test is limited or unavailable, patients with the Cushingoid appearance should be suspected of having AI and treatment with corticosteroids should begin immediately if symptoms of AI were present.

One strength of the present study is that the diagnoses of AI were definitively confirmed by the standard ACTH stimulation test using the endorsed cut-off point. The statistical accuracy and thus, the value of the study was augmented by the inclusion of potential confounding factors that might affect cortisol measurement results. The high number of patients in the present study provides an adequate power of analysis (power 98%) with the very small missing value. Thus, this result can be widely applicable to the usual practice.

There are some limitations in the present study. First, the study did not know whether the HTM used by the patients was adulterated with corticosteroid. Additionally, the amount of adulterating corticosteroid in the HTM used by each patient was not available. The lack of these information potentially affects the accuracy to estimate the correlation between HTM usage and the incidence of AI. However, the authors presumed from the side effects of HTM, which are increased appetite, cushingoid appearance, rapidly resolution of symptoms, that they may contained glucocorticoids. Further research is needed to address this issue. Second, the present study included only patients with indeterminate serum morning cortisol levels (3 to 18 µg per dL). This can alter the actual prevalence of patients with AI as some patients with serum cortisol levels below three µg per dL would have been definitively diagnosed with AI without an ACTH stimulation test. It is presumed that a higher prevalence of AI in patients taking HTM would have been found if the study had included the entire population that had been tested for serum morning cortisol. A third limitation is that both LDT and HDT were included in the present study, which could have resulted in a lack of uniformity in the test procedures. However, previous report stated that performing LDT demonstrated higher sensitivity in detecting AI than HDT[25]. In addition, the current guideline from the Endocrine Society has recommended the same cut-off levels of peak serum cortisol for both LDT and HDT[16]. Therefore, this limitation may have only slight interference to the present study. Finally, the retrospective nature of the present study could be considered a limitation.

Conclusion

There is a significantly higher incidence of AI, which is nearly two-fold, in patients who use HTM. Healthcare professionals should be alert for AI in the patients who have a history of HTM usage. Cushingoid appearance could be employed as one of the diagnostic factors for AI. Ensuring the safety of HTM marketed in Thailand by monitoring adulteration with corticosteroids in Thailand should be a national priority.

What is already known on this topic?

Undeclared adulteration of corticosteroids in traditional or herbal medicine is commonly found in the Asian region, particularly in Thailand. Prolonged use of the substances contaminated with corticosteroids may lead to secondary AI. The risk of AI related to traditional or herbal medicine ingestion in Thailand has not been reported yet.

What this study adds?

Almost two-fold increase in risk of AI has been observed in those who use traditional or herbal medicinal products. This finding should alert the health care professionals in terms of increasing awareness of AI in patients reported using traditional or herbal medicine. In addition, the safety of these medicinal products marketed in Thailand should be restricted by national policy and regulations.

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Authors' contributions

Manosroi W designed the study, analyzed the data, wrote and edited the manuscript. Buranapin S edited the manuscript. Atthakomol P analyzed the

data. Manosroi A discussed and edited the manuscript. Manosroi J discussed and edited the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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