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ORIGINAL ARTICLE

Retrospective Cohort Study

Analysis of the incidence and influencing factors of hyponatremia before ^{131}I treatment of differentiated thyroid carcinoma

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Abstract

BACKGROUND

Hyponatremia is a common clinical electrolyte disorder. However, the association between hyponatremia and acute hypothyroidism is unclear. Acute hypothyroidism is usually seen in patients who undergo preparation for radioactive iodine therapy.

AIM

To analyze the incidence and influencing factors of hyponatremia in a condition of iatrogenic acute hypothyroidism in patients with differentiated thyroid cancer (DTC) before ^{131}I treatment.

METHODS

The study group consisted of 903 DTC patients who received ^{131}I treatment. The clinical data before and after surgery, as well as on the day of ^{131}I treatment were analyzed. According to the blood sodium level before ^{131}I treatment, patients were divided into the non-hyponatremia group and hyponatremia group. Correlations between serum sodium levels before ^{131}I treatment and baseline data were analyzed. Univariate analysis and binary logistic regression were performed to identify the influencing factors of hyponatremia.

RESULTS

A total of 903 patients with DTC, including 283 (31.3%) males and 620 (68.7%) females, with an average age of 43.8 ± 12.7 years, were included in this study. The serum sodium levels before surgery and ^{131}I treatment were 141.3 ± 2.3 and 140.5 ± 2.1 mmol/L, respectively (P = 0.001). However, the serum sodium levels in males and females before ^{131}I treatment were lower than those before surgery. Patients aged more than 60 years and less than 60 years also showed decreased serum sodium levels before ^{131}I treatment. In addition, the estimated glomerular filtration rate (eGFR) in males and females decreased before ^{131}I treatment compared with

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those before surgery (P = 0.001). Moreover, eGFR in patients over 60 years and under 60 years decreased before ^{131}I treatment, when compared with that before surgery. There were no significant differences in serum potassium, calcium, albumin, hemoglobin, and blood glucose in patients before surgery and ^{131}I treatment (P > 0.05). Among the 903 patients, 23 (2.5%) were diagnosed with hyponatremia before ^{131}I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia. Clinical data showed that patients with mild hyponatremia had no specific clinical manifestations, while moderate hyponatremia cases were mainly characterized by fatigue and dizziness, which were similar to neurological symptoms caused by hypothyroidism and were difficult to distinguish. Correlation analysis showed a correlation between serum sodium before ^{131}I treatment and the preoperative level (r = 0.395, P = 0.001). There was no significant correlation between blood sodium and thyroid-stimulating hormone (TSH) levels and urine iodine before ^{131}I treatment (r = 0.045, P = 0.174; r = 0.013, P = 0.697). Univariate analysis showed that there were significant differences in age, sex, history of diuretic use, distant metastasis, preoperative blood sodium, blood urea nitrogen (BUN), eGFR, TSH and urinary iodine between the two groups (all P < 0.05). Logistic regression analysis showed that factors such as history of diuretic use, distant metastases, preoperative sodium and BUN were all influencing factors of hyponatremia. The Hosmer and Lemeshow test ($c2$ = 2.841, P = 0.944) suggested a high fit of the model. Omnibus tests of model coefficients indicated the overall significance of the model in this fitted model (P < 0.05). Preoperative serum sodium was a significant factor associated with pre-^{131}I therapy hyponatremia (OR = 0.763; 95%CI: 0.627-0.928; P = 0.007).

CONCLUSION
The incidence of hyponatremia induced by ^{131}I treatment preparation was not high. Preparation for radioactive iodine therapy was not a risk factor for the development of hyponatremia in thyroid cancer patients.

Key Words: Differentiated thyroid cancer; Hyponatremia; Incidence; Low iodine diet; Logistic regression analysis

Core Tip: We analyzed the incidence and influencing factors of hyponatremia in patients with differentiated thyroid cancer (DTC) before ^{131}I treatment. We evaluated 903 postoperative DTC patients who received ^{131}I treatment. The results suggest that the incidence of hyponatremia induced by ^{131}I treatment preparation was not high. The identified influencing factors of hyponatremia included history of diuretic use, distant metastases, preoperative sodium and blood urea nitrogen. Our findings may help to improve patient management during the preparation period for ^{131}I treatment.

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INTRODUCTION

Hyponatremia is a common clinical electrolyte disorder, with an incidence of about 15% to 30%[1]. Hyponatremia in chronic hypothyroidism is commonly seen in clinical practice. The main mechanism for the development of hyponatremia in patients with chronic hypothyroidism is the decreased capacity of free water excretion due to elevated antidiuretic hormone (ADH) levels, which are mainly attributed to the hypothyroidism-induced decrease in cardiac output[2].

However, the association between hyponatremia and acute hypothyroidism is unclear[3]. Acute hypothyroidism is usually seen in patients with differentiated thyroid cancer (DTC) who undergo preparation for radioactive iodine (RAI) therapy. Before RAI therapy, it is suggested that treatment with thyroid hormone should be stopped to stimulate the uptake of ^{131}I by thyroid follicular epithelium and DTC cells [4]. Moreover, a low iodine diet is usually associated with low solute intake that may contribute to the development of hyponatremia. Previous studies reported that severe hyponatremia occurred in patients before ^{131}I treatment[5,6]. On the contrary, other studies showed that iatrogenic acute hypothyroidism after discontinuation of thyroid hormone had little effect on blood sodium concentration, and that insufficient sodium intake and low-iodine diet were not important causes of hyponatremia[3,7].

The incidence and influencing factors of hyponatremia before ^{131}I treatment in China are still unclear. The purpose of this study is to investigate the incidence of hyponatremia and related influencing factors in patients after DTC surgery before ^{131}I treatment (in a condition of iatrogenic acute hypothyroidism), in order to improve patient management during the preparation period for ^{131}I treatment.

MATERIALS AND METHODS

Study subjects

A total of 1228 DTC patients treated with ^{131}I from June 2017 to April 2020 were analyzed. All patients were confirmed to have DTC by pathology. Patients with thyroid stimulating hormone (TSH) not rising to 30 mIU/L after 4 wk of withdrawal of levothyroxine (L-T4), and with serum sodium levels lower than 136 mmol/L before and after DTC surgery were excluded from the study. The Institutional Review Board of the Second Hospital, Cheeloo College of Medicine, Shandong University approved this study (KYLL-2018[LW]013). All procedures complied with the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from each patient.

Clinical data before ^{131}I treatment

All patients with DTC underwent L-T4 replacement therapy after surgery. After that, L-T4 was stopped 4 wk before ^{131}I treatment. Enhanced computed tomography and oral Chinese herbal medicine were avoided during the low iodine diet. Morning urine and fasting blood samples were collected for laboratory examination on the day of ^{131}I administration. The following indices were recorded, including serum sodium, potassium, calcium, free triiodothyronine (FT3), free thyroxine (FT4), TSH, urinary iodine, fasting glucose, hemoglobin, total protein, albumin, globulin, blood urea nitrogen (BUN), serum creatinine (SCR), and estimated glomerular filtration rate (eGFR). eGFR was calculated according to the simplified formula of MDRD. The data before and after surgery and before ^{131}I treatment were examined in the same laboratory. All laboratory tests were measured on the VISTA 1500 systems (Siemens Diagnostics). The reference values for serum sodium were 137-147 mmol/L. Other data, including age, sex, body mass index, and systolic blood pressure were also collected before and after thyroid surgery and on the day of ^{131}I administration. To minimize possible bias, patients with comorbid conditions (heart failure, acute and chronic kidney disease, and liver cirrhosis), or with intake of medications (such as diuretics) were strictly recorded.

Diagnosis of hyponatremia

Hyponatremia was defined as serum sodium level ≤ 135 mmol/L. The diagnostic ranges of mild, moderate, and severe hyponatremia were 130-135, 125-129 and < 125 mmol/L, respectively. According to the serum sodium level before ^{131}I treatment, the patients were divided into the non-hyponatremia group (blood sodium level > 135 mmol/L) and the hyponatremia group (blood sodium level ≤ 135 mmol/L).

Statistical analysis

SPSS 20.0 software was used for statistical analysis. The paired *t* test or Wilcoxon signed rank test was used for paired comparisons. Pearson or Spearman rank correlation was used for correlation analysis of data distribution. Descriptive analysis of the baseline characteristics of the hypothyroid patients were performed between the hyponatremia and non-hyponatremia groups. Univariate analysis was performed to evaluate the risk factors for hyponatremia. The binary logistic regression equation was

established, and the factors with $P < 0.05$ in univariate analysis were included in the equation to further explore the influencing factors of hyponatremia. A P value < 0.05 was considered statistically significant.

RESULTS

General information

A total of 903 patients with DTC, including 283 (31.3%) males and 620 (68.7%) females, with an average age of 43.8 ± 12.7 years, were included in this study. The serum sodium levels before surgery and ^{131}I treatment were 141.3 ± 2.3 and 140.5 ± 2.1 mmol/L, respectively ($P = 0.001$, Figure 1A). However, the serum sodium levels of males and females before ^{131}I treatment were lower than those before surgery. The patients aged more than 60 years and less than 60 years also showed a decrease before ^{131}I treatment (Figure 1B). In addition, eGFR in males and females decreased before ^{131}I treatment compared with those before surgery ($P = 0.001$, Figure 1C). Moreover, eGFR in patients over 60 years and under 60 years decreased before ^{131}I treatment, when compared with that before surgery (Figure 1D). There were no significant differences in serum potassium, calcium, albumin, hemoglobin, and blood glucose in patients before surgery and ^{131}I treatment ($P > 0.05$).

Incidence and clinical manifestations of hyponatremia

Among the 903 patients, 23 (2.5%) were diagnosed with hyponatremia before ^{131}I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia. Clinical data showed that patients with mild hyponatremia had no specific clinical manifestations, while moderate hyponatremia cases were mainly characterized by fatigue and dizziness, which were similar to neurological symptoms caused by hypothyroidism and were difficult to distinguish (Table 1).

Influencing factors of ^{131}I sodium in blood before treatment

Correlation analysis showed a correlation between serum sodium before ^{131}I treatment and the preoperative level ($r = 0.395$, $P = 0.001$). There was no significant correlation between blood sodium and TSH levels and urine iodine before ^{131}I treatment ($r = 0.045$, $P = 0.174$; $r = 0.013$, $P = 0.697$) (Table 2).

Univariate analysis showed that there were significant differences in age, sex, history of diuretic use, distant metastasis, preoperative blood sodium, BUN, eGFR, TSH and urinary iodine between the two groups (all $P < 0.05$) (Table 3).

Logistic regression analysis showed that factors such as a history of diuretic use, distant metastases, preoperative sodium and BUN were all influencing factors of hyponatremia (Table 4). The Hosmer and Lemeshow test ($c^2 = 2.841$, $P = 0.944$) suggested a high fit of the model. Omnibus tests of model coefficients indicated the overall significance of the model in this fitted model ($P < 0.05$). Preoperative serum sodium was significantly associated with pre-RAI therapy hyponatremia (OR = 0.763; 95%CI: 0.627-0.928; $P = 0.007$).

DISCUSSION

In this study, the incidence of hyponatremia before ^{131}I treatment was 2.5% (23/903). Among the 23 patients with hyponatremia, approximately 91% (21/23) had mild hyponatremia. In a prospective study of 212 patients after DTC surgery, the incidence of hyponatremia before ^{131}I treatment was only 1.4% (3/212)[7]. Vannucci *et al* included 101 DTC patients who continued to withdraw thyroid hormone for about 2 wk and had a low iodine diet and found that the incidence of hyponatremia was 4% (4/101), of which approximately 75% (3/4) had mild hyponatremia[8]. Therefore, the incidence of hyponatremia caused by ^{131}I treatment preparation is not high, and is mainly mild hyponatremia. Previous studies have reported that patients with severe hyponatremia during ^{131}I preparation have an average withdrawal time of 4 wk for thyroid hormone, and the duration of low iodine diet is also more than 3 wk[3,5-6]. This study had similar ^{131}I preparation before treatment. However, there were no severe hyponatremia patients in this study. Severe hyponatremia patients are reported to have different degrees of myxedema, which is combined with other underlying diseases, suggesting that the occurrence of severe hyponatremia may be due to other underlying diseases, rather than caused only by withdrawal of thyroid hormone or low iodine diet[5].

Table 1 Clinical data of the patients with hyponatremia before ^{131}I treatment

Patients	Age (yr)	Gender	Pre-operation sodium (mmol/L)	Pre-^{131}I therapy sodium (mmol/L)	Potentially hyponatremia-inducing drugs	Potentially hyponatremia-inducing comorbidities
1	75	Male	138	134	Diuretic, ACEI	DM, adenocarcinoma of lung
2	71	Male	140	135	Diuretic, ARB	None
3	71	Male	140	133	None	None
4	64	Male	141	134	Diuretic	None
5	64	Male	141	135	None	None
6	64	Male	144	133	None	None
7	63	Male	136	134	Diuretic, ACEI	None
8	53	Male	140	135	None	DM
9	52	Male	138	135	None	DM, coronary heart disease
10	47	Male	144	135	None	None
11	45	Male	138	135	None	Adrenocortical hypofunction
12	38	Male	136	131	None	None
13	31	Male	136	128	None	DM
14	69	Female	140	129	None	RI, CHD, old cerebral infarction
15	49	Female	136	135	None	None
16	47	Female	142	135	None	None
17	42	Female	140	135	None	None
18	42	Female	140	134	None	None
19	41	Female	137	132	None	DM, diabetic nephropathy
20	35	Female	145	135	None	None
21	35	Female	138	134	None	None
22	33	Female	142	135	None	Chronic hepatitis B
23	32	Female	138	133	None	None

DM: Diabetes mellitus; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CHD: Coronary heart disease; RI: Renal insufficiency.

Table 2 Factors associated with pre-^{131}I therapy serum sodium level

	Correlation *r*	*P* value
Age (yr)	0.087	0.009
TSH (mIU/L)	0.045	0.174
Tg (ng/mL)	-0.028	0.402
Urinary iodine (μg/L)	0.013	0.697
Pre-operation serum sodium (mmol/L)	0.395	0.001
Blood urea nitrogen (mmol/L)	0.028	0.401
eGFR (mL/min m^2)	-0.073	0.027

In terms of the relationship between the severity of hypothyroidism and serum sodium levels, the TSH levels in the hyponatremia group were significantly lower than those in the non-hyponatremia, which is consistent with the hypothesis that the higher the TSH level, the lower the blood sodium level. This result suggests that the occurrence of hyponatremia may not be related to the increase in TSH level. A previous study reported that serum sodium levels ranged from 132 to 144 mmol/L in

Table 3 Baseline characteristics of the hyponatremia group and non-hyponatremia group before ^{131}I treatment

Items	Hyponatremia group	Non-hyponatremia group	*P* value
Sex (*n*, %)			0.008
Male	13 (56.5)	270 (30.7)	
Female	10 (43.5)	610 (69.3)	
Age (yr)	50.5 ± 14.2	43.6 ± 12.7	0.01
Body mass index (kg/m^2)	22.2 ± 3.3	23.1 ± 4.3	0.348
Systolic blood pressure (mmHg)	129.9 ± 21.1	124.5 ± 18.1	0.161
History of ACEI or ARB (*n*, %)			0.42
Yes	3 (13.1)	69 (7.8)	
No	20 (86.9)	811 (2.2)	
History of diuretics (*n*, %)			0.015
Yes	4 (17.4)	35 (4.1)	
No	19 (82.6)	845 (95.9)	
Distant metastasis (*n*, %)			0.014
Yes	6 (26.1)	77 (8.8)	
No	17 (73.9)	803 (91.2)	
Hemoglobin (g/L)	141.1 ± 19.5	144.2 ± 18.4	0.52
Fasting blood glucose (mmol/L)	5.2 (4.6, 7.2)	5.1 (4.8, 5.6)	0.267
Pre-operation serum sodium (mmol/L)	139.5 ± 2.6	141.3 ± 2.3	0.001
Pre-^{131}I therapy serum sodium (mmol/L)	133.6 ± 1.9	140.6 ± 1.8	0.001
Serum potassium (mmol/L)	4.3 ± 0.3	4.2 ± 0.3	0.462
Serum calcium (mmol/L)	2.3 ± 0.1	2.2 ± 0.1	0.062
Blood urea nitrogen (mmol/L)	4.7 ± 2.1	3.8 ± 1.2	0.043
Serum creatinine (μmol/L)	78.7 ± 13.3	74.4 ± 16.4	0.271
Urinary iodine (μg/L)	83.1 (52.9, 100.3)	93.1 (54.5, 203.1)	0.037
Total protein (g/L)	77.1 ± 5.9	76.9 ± 4.4	0.865
Albumin (g/L)	46.6 ± 4.2	47.9 ± 2.8	0.155
Globulin (g/L)	30.5 ± 4.1	29.1 ± 3.7	0.077
eGFR (mL/min m^2)	81.8 ± 11.4	88.8 ± 15.3	0.029
TSH (mIU/L)	99.5 ± 28.5	130.6 ± 59.4	0.001
FT3 (pmol/L)	2.8 ± 0.4	2.9 ± 0.6	0.594
FT4 (pmol/L)	2.1 ± 1.2	1.8 ± 1.2	0.27

DM: Diabetes mellitus; ACEI: Angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

hypothyroid patients (*n* = 999 cases) and from 134 to 144 mmol/L in patients with TSH in the normal range (*n* = 4875 cases), respectively, and there was no statistically significant difference in serum sodium levels between these two groups[9]. Although there was a trend of a 1.4 mmol/L decrease in serum sodium for every 100 mIU/L increase in TSH, the clinical correlation between the two groups could not be determined. Hammami *et al*[7] also reported that there was no significant correlation between TSH level and serum sodium level even in severe hypothyroidism patients with TSH levels of 140 to 192 mU/L.

In addition, it was found that the duration of a low-iodine diet was negatively correlated with the serum sodium level before ^{131}I treatment, which indicates that the longer the duration of the low-iodine diet, the higher the serum sodium level. In this study, urinary iodine was used as an indicator of patients' iodine intake. However, we

Table 4 Logistic regression analysis of factors associated with hyponatremia development

Items	β	OR (95%CI)	*P* value
Gender (male)	-0.647	0.524 (0.203, 1.354)	0.182
Age (yr)	0.007	1.007 (0.965,1.050)	0.762
Distant metastasis (*n*)	1.193	3.296 (1.112, 9.770)	0.031
History of diuretics (*n*)	-1.212	0.298 (0.090,0.988)	0.048
TSH (mIU/L)	-0.009	0.991 (0.980,1.002)	0.101
Urinary iodine (μg/L)	-0.011	0.989 (0.98,0.998)	0.075
eGFR (mL/min m^2)	-0.032	0.969 (0.934,1.005)	0.09
Pre-operation Na (mmol/L)	-0.271	0.763 (0.627, 0.928)	0.007
Blood urea nitrogen (mmol/L)	0.420	1.521 (1.094, 2.115)	0.013

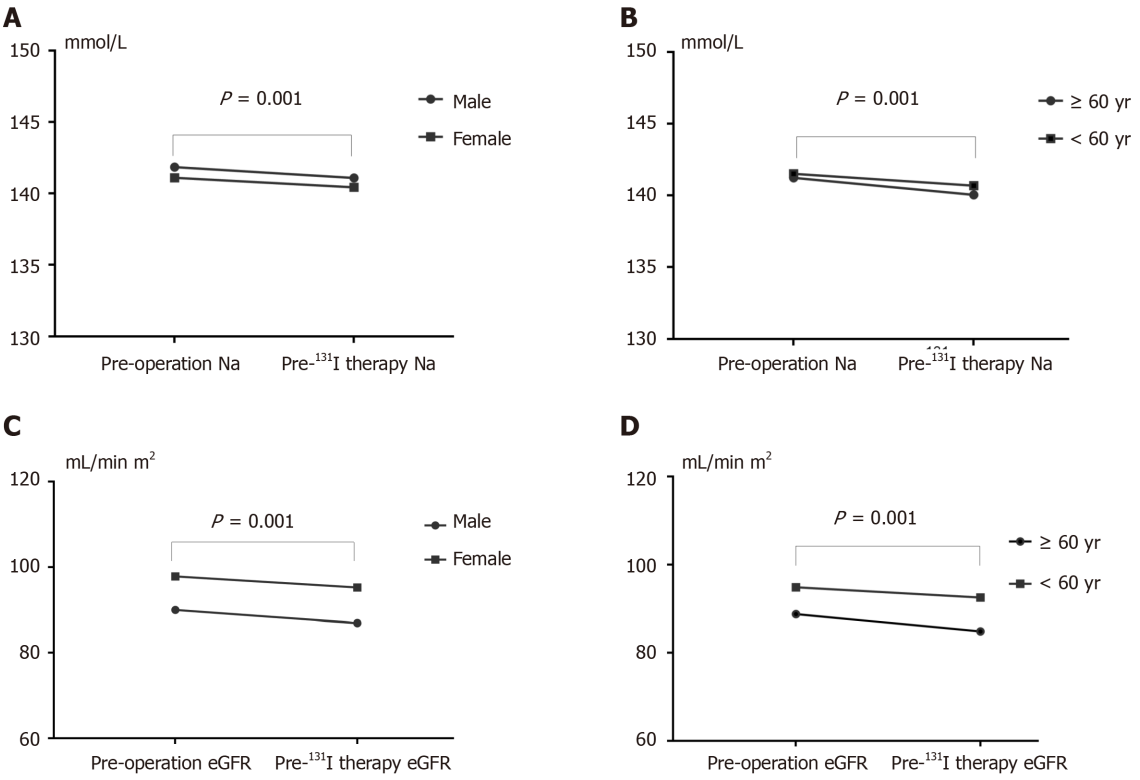

Figure 1 Comparison of serum sodium and eGFR levels before surgery and ^{131}I treatment. A: The serum sodium levels in males and females before ^{131}I treatment were lower than those before surgery; B: The serum sodium levels in patients aged more than 60 and less than 60 years showed a decrease before ^{131}I treatment; C: The eGFR in males and females decreased before ^{131}I treatment compared with that before surgery; D: The eGFR in patients over 60 and under 60 years decreased before ^{131}I treatment compared with that before surgery.

found that there was no correlation between urinary iodine and serum sodium level before ^{131}I treatment. It was also reported that low-iodine diet is a factor affecting the occurrence of hyponatremia, mainly based on the strict management of patients with low-iodine diet, which is often accompanied by low or no sodium intake[10]. Our results showed that as the urine iodine level decreased, the blood sodium level did not have a linear downward trend. In addition, although there was a statistical difference in urinary iodine levels between the two groups (P = 0.037), it has limited significance in clinic practice. This is because only when the median urinary iodine concentration is lower than 50 μg/L, it can reflect the severity of the body's iodine deficiency disorder. Therefore, serum sodium concentration may be affected only when a low iodine diet is accompanied by low sodium intake.

Our results showed that the preoperative serum sodium level was higher than before ^{131}I treatment, implying that ^{131}I treatment can cause a decrease in serum sodium

level. Theoretically, chronic hypothyroidism is one of the causes of hyponatremia, but the mechanism of its occurrence is unclear[11]. Liamis *et al*[2] believed that the decreased cardiac output in patients with chronic hypothyroidism could lead to increased secretion of ADH, reabsorption of water, and increased excretion of sodium in the urine, leading to hyponatremia. Bautista *et al*[12] believed that thyroid hormones could affect the expression of electrolyte reabsorption channels in kidney cells, and long-term hypothyroidism could reduce the kidney's ability to reabsorb electrolytes such as sodium, calcium, potassium and magnesium, leading to hyponatremia. Montenegro *et al*[13] suggested that short-term and transient hypothyroidism may lead to a decrease in GFR and renal blood flow, which may in turn affect electrolyte reabsorption. In this study, we did not detect abnormalities in the levels of ADH and other hormones, but the preoperative eGFR was higher than after ^{131}I treatment, indicating that the decrease in serum sodium level may be related to the decrease in eGFR.

Previous studies have suggested that age, sex, history of diuretic use and serum sodium level before surgery are all independent influencing factors of hyponatremia in DTC patients before ^{131}I treatment[14-15]. In this study, we found that age and history of diuretic use were significantly different between the hyponatremia and non-hyponatremia groups by univariate analysis, but they were not identified as independent influencing factors in the multivariate analysis. We believe that age may have a common relationship with renal function. In theory, the efficiency of GFR gradually decreases with age, leading to an increase in BUN and an increased risk of hyponatremia[14]. The data in this study were also consistent with this theory. A previous study suggested that diuretics directly induced the release of ADH or increased the response of collecting ducts to ADH, leading to the occurrence of hyponatremia, which was more common in hospitalized patients with other etiologies [2]. However, in this study, diuretics had a relatively small effect on the occurrence of hyponatremia, which might be related to the age of the population. We found distant metastasis was an independent influencing factor for the occurrence of hyponatremia. Patients with distant metastasis can lead to the syndrome of dysregulation of ADH secretion, which leads to hyponatremia[15]. The main mechanism may be that the increase in ADH secretion phosphorylates aquaporin-2 on the cell membrane and promotes water reabsorption[3].

However, this study has some limitations. For example, the sample size of patients with hyponatremia was small. Thus, the results of multivariate analysis may not be robust enough. However, considering that the incidence of hyponatremia was not high, the results still have a certain interpretability and reliability. In addition, the cause of hyponatremia was not further investigated in this study. Further studies with larger sample sizes, including prospective studies, are needed in the future to verify these results.

CONCLUSION

In conclusion, the incidence of hyponatremia was not high in patients with DTC. Preparation for radioactive iodine therapy was not a risk factor for the development of hyponatremia in thyroid cancer patients. Distant metastases, preoperative sodium and BUN were identified as influencing factors of hyponatremia.

ARTICLE HIGHLIGHTS

Research background

Hyponatremia in chronic hypothyroidism is commonly seen in clinical practice. However, the association between hyponatremia and acute hypothyroidism is unclear. Acute hypothyroidism is usually seen in patients who undergo preparation for radioactive iodine therapy.

Research motivation

The incidence and influencing factors of hyponatremia before ^{131}I treatment in China are still unclear. This article will offer our center's experience of the management of thyroid cancer patients prior to ^{131}I therapy.

Research objectives

To improve patient management during the preparation period for ^{131}I treatment. The cause of hyponatremia was not further investigated in this study. Thus, further studies with larger sample sizes, including prospective studies, are needed in the future to verify these results.

Research methods

An observational study design was used in this clinical study. Patients with and without hyponatremia were studied by univariate and multivariate analysis. The sample size in this study was larger than those reported in previous publications.

Research results

The incidence of hyponatremia induced by ^{131}I treatment preparation was not high (2.5%). Twenty-three (2.5%) patients were diagnosed with hyponatremia before ^{131}I treatment, including 21 cases (91.3%) of mild hyponatremia and 2 cases (8.7%) of moderate hyponatremia.

Research conclusions

This study indicates that preparation for radioactive iodine therapy is not a risk factor for the development of hyponatremia in thyroid cancer patients.

Research perspectives

Measurement of sodium post-radioactive iodine therapy should be considered in patients.

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