

## Original Article



# The role of hypothyroidism in weaning patients from mechanical ventilation: a randomized clinical trial

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### Abstract

**Introduction:** Hypothyroidism is a relatively common disease around the world in which the production of thyroid hormone is diminished due to some structural and/or functional disorders. The purpose of this study was to investigate the problems regarding mechanical ventilation caused by hypothyroidism in hospitalized patients.

**Methods:** In this clinical trial, 80 patients admitted to the ICU ward and intubated for more than one week were studied. Patients were classified into two 40-patient groups. Levothyroxine was prescribed for the patients in case group in the dosage of 0.1 mg while no levothyroxine was prescribed to the patients in the control group. Differences in the time of weaning was evaluated between the two groups.

**Results:** There was a significant difference between two groups regarding TSH, T3, and T4. There was also a significant difference between final outcome of the patients and time of weaning from the mechanical ventilation between the two groups; which can be attributed to the effect of levothyroxine on the recovery of patients and the reduction of weaning from mechanical ventilation.

**Conclusion:** The thyroid function of intubated patients should be monitored to be kept in normal levels to accelerate their recovery or prevent some of them from deterioration.

### Introduction

Prolonged hospital stay in patients admitted to the ICU is currently one of the common problems in hospitals. Some of these patients are often difficultly weaned from the mechanical ventilation due to weaning challenges.<sup>1</sup> There is an increasing body of evidence that delayed weaning can cause undesirable complications and cost of treatment. Mortality and ventilator-dependent pneumonia occur more frequently with prolonged ventilation.<sup>2</sup> Severe hypothyroidism is associated with muscle relaxation due to respiratory muscle depression and sleep apnea syndrome. Thyroid hormone secretion may be deteriorated in patients with primary hypothyroidism due to surgery stress that might be followed by prolonged recovery process and cardiac dysfunction. Hypothyroidism may often not be diagnosed; as its manifestation is very similar to that of heart failure. Hypothyroidism is one of the known causes of respiratory failure. Furthermore, cardiac failure, sedation, kidney failure, and malnutrition are the conditions that might also result in prolonged mechanical ventilation (PMV). Respiratory complications occur in patients with

hypothyroidism. Symptoms such as dyspnea, sleep apnea, diaphragmatic dysfunction, hypoxia, hypercapnia, and muscle dysfunction have been broadly reported. Rarely, severe hypothyroidism may cause respiratory failure and can be life-threatening. The mechanisms of respiratory failure caused by hypothyroidism include: 1) respiratory disturbance in response to hypoxia and hypercarbia; 2) hypercapnia leading to respiratory muscle disorder; 3) obstructive sleep apnea syndrome (OSAS). Hypotension caused by myxedema coma reduces respiratory responses to hypoxia and hypercapnia. Diaphragmatic weakness might be caused by hypothyroidism.<sup>3</sup> Hypothyroidism is an unpredictable cause of weaning failure in patients with PMV. However, hypothyroidism is curable and should be considered in all patients who suffer from weaning failure. Notwithstanding, serum TSH levels do not seem to affect the success of weaning. In critically ill patients, respiratory failure often occurs following neuroendocrine activation by altered serum T4, T3, and TSH levels. Abnormal thyroid function tests are seen in 10%-50% of these patients. Nevertheless, in the absence of a true

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thyroid disease, the disease is referred to as euthyroid sick syndrome. Long-term mechanical ventilation is defined as mechanical ventilation for more than 3 weeks. PMV is defined as having no ventilation support for more than 1 week.<sup>4</sup> Diagnosis of hypothyroidism in severely ill patients can be difficult, especially in old patients, especially when signs and symptoms of hypothyroidism are often absent in this group of patients.<sup>1</sup> The aim of this study was to investigate problems of mechanical ventilation weaning in patients with hypothyroidism admitted to the ICU.

## Methods

In this randomized double blind clinical trial, patients of the surgical ICU of Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran were admitted for various indications such as multiple trauma, traffic accidents, surgery, burns, stroke, and etc.<sup>5</sup> Among them, 80 patients who were intubated for more than one week and without previous known thyroid disease were included. Patients with myocardial infarction, history of using medications interfering with thyroid hormones such as lithium, history of heart disease, unexplained erythema, patients with previous history of hypothyroidism and patients without informed consent from their guardians were excluded from this study. Regarding the high rate of ICU patients undergoing surgery and undergoing intubation, assessment of all weaning issues especially thyroid hormone and other affecting causes is mandatory. A week after intubation following the routine tests (CBC, TSH, free T3, and free T4), the patients were classified into two 40-patient groups based on block randomization: (A) receiving routine and standard care for weaning, (B) receiving routine standard care for weaning plus one daily dose of levothyroxine. Case group received levothyroxine tablet (sodium levothyroxine tablet, Iran hormone product) 0.1 mg orally through nasogastric tube or feeding jejunostomy daily; while the control group did not receive any further medication other than their routine medications. Patients were weaned from the ventilator based on the principles of weaning by gradual discontinuation method and management. These weaning methods include gradual reduction in mandatory ventilation, gradual reduction in pressure support, spontaneous awakening trials, and spontaneous breathing trials. After stabilizing the respiratory state with regard to the arterial blood gas control, weaning of mechanical ventilator was performed. The respiratory rate of the patients was reduced based on the patient tolerance. Afterwards, the ventilatory support pressure was reduced. Patients tolerating this condition were placed on normal spontaneously ventilation state. After evaluating the patients' respiratory compliance, they were placed on the T-piece and extubated. In addition, patients with thyroid disease were also treated with levothyroxine as required. The clinical and laboratory findings were used to evaluate the presence of hypothyroidism or subclinical

hypothyroidism in study subjects. Improvement in ventilation and weaning parameters were considered as response to levothyroxine treatment in these patients.

The difference regarding weaning time between groups was evaluated. Data were analyzed using SPSS software version 22 and descriptive parameters were expressed in terms of mean, standard deviation and frequency. In this study, we considered  $P < 0.05$  as statistically significant.

## Results

In this study, 80 patients admitted to the ICU were studied. Of them, 45 (56.3%) were male and 35 (43.7%) were female. The mean age of the patients was  $59.8 \pm 16.13$  years. The mean body mass index (BMI) of patients was  $21.51 \pm 3.24$ . The average intubation frequency during the admission was  $1.10 \pm 0.30$   $0.30 \pm 1.10$ , so that 90% of the patients were intubated one time and 10% were intubated 2 times. The mean TSH level was  $3.8 \pm 9.71$   $9.71 \pm 3.8$   $\mu\text{IU}/\text{mL}$ . The mean of free T3 level was  $3.65 \pm 2.09$   $\text{ng}/\text{dL}$ . The mean T4 level was  $4.35 \pm 2.43$   $\text{ng}/\text{dL}$ . There was history of smoking in 28 patients and alcohol consumption in 12 patients. A history of diabetes was reported in 30 patients. Of 40 patients of levothyroxine (case) group, 22 were male (55%) and 18 were female (45%). The mean age of patients was  $63.17 \pm 13.80$  years. The mean BMI of patients was  $21.56 \pm 1.98$ . The mean number of intubations during the admission was one to two times, so 90% of the patients were intubated one time and 10% of the patients were intubated two times. The mean TSH level was  $4.74 \pm 1.25$   $\mu\text{IU}/\text{mL}$ . The mean free T3 level was  $2.38 \pm 3.38$   $\text{ng}/\text{dL}$ . The mean T4 level was  $2.33 \pm 4.65$   $\text{ng}/\text{dL}$ . Seven patients died and 33 were extubated. The awareness of patients in case group after levothyroxine administration was increased in all 40 patients (Table 1). The mean time of weaning from the ventilator after the start of levothyroxine was  $10.42 \pm 4.87$  days. Of 40 patients of control group, 23 were male (57.5%) and 17 were female (42.5%). The mean age of patients was  $56.45 \pm 17.71$  years. The mean BMI of patients was  $21.46 \pm 2.31$ . The mean number of intubations during the admission was one to two times, so that 90% of the patients were intubated one time and 10% of the patients were intubated 2 times. The mean TSH level was  $5.55 \pm 0.30$   $\mu\text{IU}/\text{mL}$ . The mean free T3 level was  $3.91 \pm 1.74$   $\text{ng}/\text{dL}$ . The mean T4 level was  $2.51 \pm 4.05$   $\text{ng}/\text{dL}$ . Fifteen patients died in the control group and 25 were extubated. There was a significant difference between two groups regarding TSH, T3 and T4, respectively ( $P < 0.005$ ). There was also a significant difference between final outcome of the patients and time of weaning from the mechanical ventilation between the two groups ( $P < 0.005$ ); which can be attributed to the effect of levothyroxine on the recovery of patients and the reduction of weaning from mechanical ventilation (Table 1).

## Discussion

Hypothyroidism is a known but unusual reason of

**Table 1.** Sociodemographic and clinical characteristics of patients

	Case group (n=40)	Control group (n=40)	P value
Sex, n			
Male	22	23	0.66
Female	18	17	
Age, mean±SD	63.17±13.80	56.45±17.71	0.56
BMI (kg/m <sup>2</sup> ), mean±SD	21.56±1.98	21.46±2.31	0.07
Number of intubation, mean±SD			
1	40	36	0.85
2	0	4	
More	0	0	
TSH (μIU/mL), mean±SD	4.74±1.25	5.55±0.30	0.0002
T3 (ng/dL), mean±SD	2.38±3.38	3.91±1.74	0.033
T4 (ng/dL)	2.33±4.65	2.51±4.05	0.001
Mean days of weaning after levothyroxine intake, mean±SD	10.42±4.87	13.14±3.11	0.003
Level of consciousness increasing (n)	35	11	0.000
Level of consciousness decreasing (n)	5	29	
Extubated (n)	33	25	0.000
Death (n)	7	15	

BMI: body mass index, TSH: thyroid stimulating hormone.

respiratory failure. Hypothyroidism may have variety of undesirable effects that can affect patients' weaning from mechanical ventilation. This is associated with muscle weakness and diaphragmatic dysfunction.<sup>6</sup> It can also change the ventilation drive with obstruction of the airways as well as obstructive and central apnea. Datta and Scalise reported a 3% significant clinical hypothyroidism in PMV patients. In addition, they reported that treatment with thyroid replacement leads to ventilation release in three out of four patients. They concluded that although hypothyroidism is unavoidable, treatment for hypothyroidism should be considered for all patients with failed weaning.<sup>4</sup> Hypotension and hypercapnia are serious complications of hypothyroidism. These alterations are due to respiratory muscle weakness and undesired respiratory response to hypoxemia and hypercapnia. Hypothyroidism may cause or deteriorate sleep apnea. Hypothyroidism symptoms include shortness of breath in exercising, exercise restrictions, sleep disturbance, air flow obstruction, reduced airway responses to hypoxia and hypercapnia, pleural effusion, decreased intra-abdominal pressure, and severe diaphragmatic dysfunction.<sup>7</sup> Hypothyroidism can cause respiratory distress through three mechanisms. The first mechanism is the central ventilation response to hypoxia and hypercapnia. Some researchers have reported that about half of the patients with hypothyroidism are exposed to reduced ventilation in response to increased CO<sub>2</sub>; and almost all of them have a similar disorder to reduce O<sub>2</sub> tensions. The second mechanism is hypoventilation due to diaphragmatic weakness and other respiratory muscles that occurs in

30 to 40% of cases of hypothyroidism.<sup>8</sup> Hypothyroidism leads to anemia, neural fibrosis, irreversible type II fibroid atrophy and muscle mass loss. The prognosis of respiratory muscle dysfunction depends on the severity of hypothyroidism and its duration. TSH levels above 90 μIU / mL is a poor prognostic factor, as found in our study.<sup>9</sup> The third mechanism is OSAS, occurring in 25% to 35% of people with hypothyroidism. The original OSAS pathophysiology is probably due to soft tissue infiltration by mucopolysaccharides and proteins, which limit the airway tract. Central sleep apnea may occur due to aerobic and neuromuscular reactions that cause hypoxia. After treatment, upper respiratory and hypoxic responses usually become normal within 7 to 14 days after the replacement of hormones. However, dysfunction of the respiratory muscles may be permanent or require a few months to recover.<sup>10</sup> Ventilation control in patients with acute hypothyroidism may be needed and may improve the quality of life of patients with chronic hypothyroidism as a palliative treatment. Nutrition and physiotherapy are also needed to prevent muscular atrophy.

## Conclusion

Hypothyroidism plays an important role in the outcome of comatose and intubated patients and can also affect the clinical course of the patients. It can be concluded that the thyroid function and the blood levels of the thyroid hormones should be monitored in these patients to be kept in normal levels to accelerate their recovery or prevent some of them from deterioration.

## Conflict of interest

The authors declare no conflict of interest.

## Ethical Approval

The study protocol was approved by the Research Ethics Committee of Tabriz University of Medical Sciences. Additionally, the study was registered at Iranian Registry of Clinical Trials (IR.TBZMED.REC.1395.1226)

## Study Highlights

### What is current knowledge?

- Hypothyroidism may have variety of undesirable effects that can affect patients' weaning from mechanical ventilation. Although hypothyroidism is unavoidable, treatment for hypothyroidism should be considered for all patients with failed weaning.

### What is new here?

- Hypothyroidism plays an important role in the outcome of comatose and intubated patients and can also affect the clinical course of the patients.

**Authors' contribution**

Study concept, design and supervision: MM and KS; drafting of the manuscript: AF and JF. KS is responsible and accountable for the accuracy or integrity of the work. All authors have read and approved the manuscript.

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