Oral Levothyroxine is an Effective Option for Myxedema Coma: A Single-Centre Experience

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Keywords

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Abstract

Introduction: Myxedema coma is an endocrine emergency with a very high mortality rate. As per the American Thyroid Association, initial thyroid hormone replacement for myxedema coma should be intravenous levothyroxine (LT4). However, in India, the availability of intravenous LT4 is limited. Often, crushed LT4 tablets are given through the enteral route when parenteral therapy is unavailable. No data or protocol is available for the administration of oral LT4 in myxedema coma. The aim of this study was to assess the effectiveness of oral LT4 in patients diagnosed with myxedema coma and to formulate a protocol for oral LT4 that can be used to guide the treatment of patients when intravenous LT4 is unavailable. **Methods:** This retrospective observational study included patients diagnosed with myxedema coma between January 2010 and December 2019. The diagnosis of myxedema coma was based on the diagnostic scoring system for myxedema coma proposed by Popoveniuc et al. [Endocr Pract. 2014 Aug;20(8):808–17]. Dosing of oral LT4 was decided as per our institutional protocol. **Results:** Fourteen patients (11 males and 3 females) with a median age of 67.5 years (range 11–82) with myxedema coma were included. All

patients had central nervous system manifestations, and sepsis was the most common precipitating factor. The median myxedema score was 72.5 (normal ≤ 25), and the median length of hospital stay was 12 days (range 3–18). The oral LT4 regimen consisted of a loading dose of 300–500 µg, followed by taper over the next 3–5 days. With this regimen, 13 patients survived, and only 1 patient died. **Conclusion:** Oral LT4 is an effective treatment option for myxedema coma when intravenous LT4 is unavailable.

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Introduction

Myxedema coma is an endocrine emergency resulting from severe insufficiency of thyroid hormones and associated with a very high mortality rate. It was probably described first in 1879 by Ord in a report where 2 out of 12 patients with severe hypothyroidism appeared to have died in coma. Since then, around 300 cases have been reported in the literature [1], with the reported incidence rate being around 0.22 per million per year [2]. The diagnosis of myxedema coma is usually clinical and supported by laboratory parameters suggestive of hypothyroidism. Popoveniuc et al. [3] proposed a diagnostic scoring sys-

tem for myxedema coma that was based on data from retrospective cases from their institution and from selected case reports from the literature. The parameters assessed included evidence of thermoregulatory dysfunction, central nervous system effects, gastrointestinal symptoms, cardiovascular dysfunction, metabolic disturbances, and the presence of a precipitating event [3].

As per the American Thyroid Association task force recommendations, initial thyroid hormone replacement for myxedema coma should be intravenous levothyroxine (LT4) with or without liothyronine (LT3) [4]. The advantages of intravenous administration are early saturation of binding sites, predictable effect and rapid replenishment of thyroid hormone pool. Oral LT4 is generally not advised under the presumption that gastrointestinal absorption of oral formulations would be unpredictable in myxedema coma. Difficulties with the insertion of a nasogastric tube is another factor that may preclude the use of oral LT4 in myxedema coma.

Myxedema coma being a very rare condition, randomized clinical trials are not realistic or ethical, and so the recommendations regarding the type and route of replacement therapy are based on expert opinions and isolated case reports. However, in India, accessibility to intravenous preparations of LT4 or LT3 are limited. Most institutions give crushed LT4 tablets through the nasogastric tube when parenteral therapy is unavailable. No data or protocol is available for the administration of oral LT4 when intravenous LT4 is not available for the treatment of myxedema coma. Hence this study was planned to assess the effectiveness of oral LT4 in patients diagnosed with myxedema coma and to formulate a protocol for oral LT4 that can be used to guide the treatment of patients when intravenous LT4 is unavailable.

Materials and Methods

This retrospective observational study included all patients diagnosed with myxedema coma who presented to a tertiary referral university teaching hospital between January 2010 and December 2019. Diagnosis of myxedema coma was based on diagnostic scoring system for myxedema coma proposed by Popoveniuc et al. [3]. A score of more than or equal to 60 is suggestive/diagnostic of myxedema coma; a score of 25–59 indicates a high risk for myxedema coma, and with a score less than 25 myxedema coma is unlikely. Maximum possible score is 230. In their series, the area under the ROC curve was 0.88 (95% CI, 0.65–1.00), and the score of 60 had 100% sensitivity and 85.71% specificity for the diagnosis of myxedema coma [3]. Thyroid function tests (TFT) which included thyroid stimulating hormone (TSH), free thyroxine (FT4), and free thyronine (FT3), random cortisol, hemogram, biochemistry,

cultures, and arterial blood gas analysis were done in all patients with scores more than 25 prior to therapy. TFT and cortisol measurements were done by electrochemiluminescence immunoassay (ECLIA). All patients underwent evaluation with electrocardiography, echocardiography, and chest X-ray.

Patients were categorized into 3 groups: (a) no coronary artery disease (CAD); (b) CAD with normal left ventricular ejection fraction (LVEF); and (c) CAD with low LVEF based on cardiac status to avoid unwanted cardiac morbidity and mortality with excessive LT4 doses in those with coexisting cardiac diseases. All patients were treated with oral LT4 administered through a nasogastric tube as per the institutional protocol (Fig. 1). FT4 levels were measured every alternate day until discharge to ensure there was adequate absorption of thyroxine. Sepsis was based on systemic inflammatory response and/or quick sequential organ failure assessment criteria. All patients with evidence of sepsis received initial empirical antibiotics followed by culture-specific antibiotics. Patients received 50–100 mg intravenous bolus dose of hydrocortisone before the start of LT4 therapy until the result of plasma cortisol was available, based on which further doses were decided. Standard intensive supportive care was provided to all when required.

Statistical Analysis

The SPSS (Statistical Program for Social Sciences) package, version 20.0 for PC Windows (SPSS Inc., Chicago, IL, USA), was used for data analysis. Continuous variables are reported as mean $\pm$ standard deviation or median values and ranges, whereas categorical variables are reported as absolute numbers and percentages. Spearman's Rank correlation was applied to find a correlation between TFT and the myxedema score. *p* values of <0.05 were considered statistically significant.

Results

Fourteen patients including 10 males, 3 females, and an eleven-year-old boy were included in the present study. The median age was 67.5 years (range 11–82). Nine patients had pre-existing hypothyroidism. The median length of hospital stay was 12 days (range 3–18). Ten out of fourteen patients required intensive care treatment. The clinical profile of the patients is described in Table 1. All 14 patients had central nervous system manifestations. Sepsis was the most common precipitating factor. Cultures were positive in six patients (2 blood cultures, 2 bronchoalveolar lavage cultures and 2 urine cultures). *Pseudomonas aeruginosa* was the most common organism causing sepsis. In four patients, use of benzodiazepine drugs precipitated the illness. In one patient, no obvious precipitating factor could be identified. Myxedema score, precipitating factors, associated comorbidities, TFT, and outcomes are summarized in Table 2. The oral LT4 protocol for myxedema coma proposed by us is elaborated in Figure 1.

Fig. 1. Protocol for oral LT4 in myxedema coma.

Subject 5 had hypothyroidism and calcific pancreatitis, and at presentation with abdominal pain she had a very low myxedema score. Subsequently, she developed acute-onset altered sensorium with hyponatremia when given benzodiazepines for her pain. At that time, her myxedema score was found to be high, and she recovered when she was treated according to the protocol. All except one patient in this series had primary hypothyroidism. Subject 6 had central hypothyroidism as part of hypopituitarism secondary to excision of pituitary macroadenoma. He came with myxedema coma following omission of LT4. The sole pediatric patient in this series was suffering from Down's syndrome and autoimmune hypothyroidism. The child was admitted with severe sepsis secondary to urinary tract infection and had a very high myxedema

score. The child was treated with appropriate intensive care, intravenous antibiotics, and oral LT4 starting at a dose of 10 µg/kg and gradually tapered off according to the protocol.

Median pretreatment TSH, FT4, and FT3 were 67.5 µIU/mL, 0.40 ng/dL, and 0.97 pg/mL, respectively. There was no correlation between the myxedema score and TSH ($p = 0.199$) or FT4 ($p = 0.059$). Serial rise in FT4 levels done to ensure adequate oral absorption is shown in Figure 2. The median loading dose of oral LT4 was 500 µg, 300 µg, 275 µg in the groups without CAD, CAD with normal LVEF, and CAD with low LVEF, respectively. With the oral LT4 regimen, 13 patients survived. The only patient who died had a delayed presentation to our institution and a very high myxedema score (>100). Eleven of the 13 patients who survived had at least one follow-up

Table 1. Summary of clinical features

Thermoregulatory dysfunction (temperature <35°C)	10/14 (71.4)
Central nervous system effects	14/14 (100) Somnolent/lethargic 8/14 (57.1) Stupor 4/14 (28.5) Coma 2/14 (14.2)
Gastrointestinal findings	12/14 (85.7) Anorexia/constipation/abdominal pain 9/12 (75) Decreased intestinal motility 3/12 (25)
Bradycardia (heart rate ≤60 beats per minute)	7/14 (50)
Other ECG changes	9/14 (64.2) Low-voltage complexes 6/9 (66.6) Bundle branch block 2/9 (22.2) QT prolongation 1/9 (11.2)
Pericardial effusion	3/14 (21.4)
Pleural effusion	4/14 (28.5)
Pulmonary edema	2/14 (14.2)
Hypotension (SBP <100 mm Hg or MAP <65 mm Hg)	1/14 (7.1)
Hyponatremia (serum Na <135 mEq/L)	11/14 (78.5)
Hypoglycemia (venous plasma glucose <50 mg/dL)	4/14 (28.5)
Hypoxemia (SpO ₂ in room air <90% or pO ₂ <60 mm Hg)	1/14 (7.1)
Hypercarbia (pCO ₂ >50 mm Hg)	2/14 (14.2)
Decrease in GFR (eGFR <90 mL/min/1.73 m ²)	8/14 (57.1)
Coagulopathy	1/14 (7.1)
Required steroids at discharge	4/14 (28.5)
Sepsis	10/14 (71.4)
Precipitating drugs	4/14 (28.5) (midazolam 2, alprazolam 1, zolpidem 1)

ECG, electrocardiogram; eGFR, estimated glomerular filtration rate (Cockcroft-Gault formula); GFR, glomerular filtration rate; MAP, mean arterial pressure; Na, sodium; pO₂, partial pressure of oxygen; pCO₂, partial pressure of carbon dioxide; SBP, systolic blood pressure; SpO₂, saturation of peripheral oxygen.

visit following discharge, and 2 patients were telephonically contacted.

Four patients required steroid replacement as their pre-LT4 random cortisol was low. Of these, 3 patients were continued on steroids for other medical indications (asthma exacerbation, multiple myeloma, and hypopituitarism). The fourth patient could stop steroids at first review 2 weeks after discharge following a normal response to ACTH stimulation. None of the patients had evidence of coexisting permanent hypocortisolism.

Discussion

This observational study on 14 patients with myxedema coma showed that oral LT4 is an effective option when an intravenous preparation is unavailable for the treatment of myxedema coma. Myxedema coma is most commonly described in elderly women, but in this study, 78.6% of subjects were males. This may reflect the gender disparity in healthcare-seeking behavior in our population. Various Indian studies have shown that women are a lot less likely to seek medical attention unless it is an

Fig. 2. FT4 response to the treatment with oral LT4.

Table 2. Myxedema score, precipitating factors, associated comorbidities, thyroid function test, and outcomes

Patient	Age, years	Gender	Myxedema score	Precipitating factors	Associated comorbidities	TSH, μ IU/mL	FT4, ng/dL	Outcome
1	77	M	55	Sepsis	CKD, DM, HTN, myeloma	100.00	0.04	Survived
2	68	M	85	Withdrawal of T4	CAD, CKD, DM, HTN	95.00	0.09	Survived
3	56	M	85	Sepsis	CAD, CKD, DM, HTN, CLD	33.37	0.67	Survived
4	76	M	85	Sepsis, drugs (midazolam)	CAD, DM, HTN	10.02	0.42	Survived
5	51	F	35	Drugs (alprazolam)	DM	99.00	0.08	Survived
6	54	M	55	Withdrawal of T4	CAD, DM, hypopituitarism	11.45	0.40	Survived
7	71	M	55	–	CKD, CLD	100.00	0.19	Survived
8	67	F	85	Sepsis	CAD, CKD, DM, CVA, RA	62.40	0.49	Survived
9	64	M	90	Sepsis, drugs (zolpidem)	CAD, CKD, DM, HTN	13.80	1.50	Survived
10	82	M	65	Sepsis	CAD, CKD, DM, HTN	67.00	0.40	Survived
11	80	M	60	Sepsis	COPD, BPH	34.00	0.40	Survived
12	51	F	70	Sepsis, drugs (midazolam)	Seizure disorder	100.00	0.54	Survived
13	11	M	75	Sepsis, withdrawal of T4	Down's syndrome	100.00	0.18	Survived
14	77	M	115	Sepsis, alcohol	DM, HTN	68.00	0.28	Expired

BPH, benign prostatic hypertrophy; CAD, coronary artery disease; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HTN, hypertension; RA, rheumatoid arthritis.

emergency [5]. In agreement with the published literature, sepsis was the most common precipitating factor in our study.

The present study did not show a correlation between myxedema scoring [3] and TFT, which highlights the importance of scoring all patients with a clinical suspicion of myxedema as TFT alone may not aid in early diagnosis. The clinical course of Subject 5, in whom the scoring was initially very low and subsequently increased on exposure

to benzodiazepines, highlights the importance of rescoring when clinically indicated. Nasogastric tube insertion can be a problem in myxedema coma patients because of the upper airway obstruction from the myxedema. However, no such difficulties were encountered in any of the patients.

The vascular endothelium and myocardium have thyroid hormone receptors and are sensitive to changes in circulating thyroid hormone concentration necessitating

lower doses in cardiac patients. The proposed loading dose in cardiac patients was decided based on the median doses administered in the three groups in our case series. An oral dose of 500 µg was chosen as maximum loading dose, since a dose of more than 500 µg of oral LT4 was associated with fatal outcomes in a previously published study [6]. Further tapering doses were based on alternate day FT4 values to ensure an upward trend with oral LT4 treatment.

The prognosis of patients with myxedema coma is difficult to predict due to the rarity of the condition. The reported mortality rate ranged from 80% in the last century to 52%, 36%, and 25% in recent small case series [7–9]. A large, retrospective observational study using a national database in Japan showed that the overall in-hospital mortality of myxedema coma was 29.5% [10]. The fact that only 1 out of 14 patients expired in the current series indicates that oral LT4 along with intensive supportive care is an effective option in myxedema coma when intravenous LT4 is unavailable. It could be argued that the low mortality rate in this cohort is due to the possibility that the patients were not extremely unwell at presentation, and only 2 patients were comatose at presentation. However, we attribute it to the diagnostic approach in our institution in which all patients with suspected myxedema coma are subjected to early application of the diagnostic scoring system proposed [3] and therefore are offered early effective treatment for this serious endocrine emergency.

The advantages of intravenous LT4 is well accepted in the setting of myxedema coma, and oral LT4 has never been proposed as an option even though its oral bioavailability is 80%, given the unpredictable pharmacokinetics of oral LT4 due to impaired gastrointestinal absorption [11]. However, still many centers end up using oral LT4 in myxedema coma because of the unavailability of parenteral LT4. So, deriving a protocol for oral LT4 is extremely important for resource-poor settings. Previously, there have also been case reports and small series, which showed that the outcome of myxedema coma was not influenced by the route of LT4 administration [6, 7]. In one such study, oral administration of 200 µg LT4 every 8th hourly in five consecutive doses (total dose of 1 mg) resulted in significant restoration of depleted thyroid status and clinical improvement within 48 h after treatment initiation. However, it was administered only to 1 patient [6].

The proposed protocol was based on our institutional protocol for the treatment of myxedema coma derived from data of retrospective cases diagnosed at our institu-

tion as well as from selected case reports. However, we suggest this oral protocol is to be used to treat patients with myxedema coma only when parenteral LT4 is unavailable and/or is not affordable to the patient.

Conclusion

Oral LT4 is an effective treatment option for myxedema coma when intravenous LT4 is unavailable.

The mortality rate in our series of myxedema coma was only 7.1%, indicating that early diagnosis with the myxedema scoring system and management with the suggested oral LT4 protocol along with intensive supportive care seems to be an effective management strategy.

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Statement of Ethics

The study protocol has been approved by the Research Institute's Committee on Human Research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Arjun Rajendran was in charge of data collection, analysis, and writing up the article. Dr. Nisha Bhavani was responsible for overseeing the project and editing the protocol of oral T4 in myxedema coma. Dr. Vasantha Nair of the Thyroid Cancer Clinic was responsible for patient follow-up. Dr. Praveen V. Pavithran was also involved in the follow-up of the patients. Dr. V. Usha Menon was involved in statistical analysis, and Dr. Harish Kumar was the overall coordinator of the entire study.

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