Oral triiodothyronine in the perioperative management of central hypothyroidism

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ABSTRACT

Oral triiodothyronine (T3) has never been described in literature as a major form of perioperative therapy. This series highlights the role of oral triiodothyronine in the perioperative management of patients with overt hypothyroidism for semi-urgent surgeries. We describe 12 patients with central hypothyroidism occurring secondary to pituitary tumours manifesting with severe neurological symptoms that required early surgical intervention. These patients were managed without any significant complications by administering perioperative oral triiodothyronine.

Keywords: central hypothyroidism, hypothyroidism, oral triiodothyronine, perioperative management, pituitary surgery

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INTRODUCTION

The literature on emergent perioperative management of patients with overt hypothyroidism and myxoedema coma recommends the use of either intravenous (IV) triiodothyronine (T_3) or tetraiodothyronine (T_4), or a combination of both these agents.[1-3] It is unusual to encounter patients with myxoedema coma in the perioperative period. However, patients with overt hypothyroidism may at times present for semi-urgent surgeries; for example, pituitary tumours with rapid visual deterioration and uterine fibroids with profuse bleeding. Literature regarding the use of oral T_3 in this clinical setting is limited. The management strategy practised in our institution for these patients includes perioperative administration of oral T_3. The rate of absorption of ingested triiodothyronine approaches 100 percent[4] and it is the most biologically active form of thyroid hormone (five times more active than T_4).[2] Peak T_3 concentrations are achieved within 2–4 hours after oral administration.[5] Doses as little as 20 μg result in an elevation of serum T_3 concentrations for 6–8 hours as penetration into its large volume of distribution is slow.[5] Hence, eight-hourly oral administration of T_3 is effective in maintaining an adequate concentration of serum T_3 in the perioperative period. Patients with central hypothyroidism requiring urgent neurosurgical intervention constitute a majority of such patients in our institution. Based on this, we conducted a retrospective analysis of patients who had pituitary surgeries over a period of two years and who needed to be treated with oral T_3 during the perioperative period. We present 12 cases of central hypothyroidism which were managed perioperatively with oral T_3 without complications.

CASE SERIES

Over a two-year period between 2002 and 2004, 158 patients presented for anaesthesia for pituitary surgeries in the Christian Medical College Hospital, Vellore, India. Out of these subjects, we encountered 12 patients with severe central hypothyroidism secondary to pituitary pathology. All these patients had severe neurological symptoms and were planned for semi-urgent neurosurgical procedures within a week of presentation. By definition, central hypothyroidism is a condition whereby the free and total T_4 concentrations are below the reference interval and the thyroid stimulating hormone (TSH) concentration may or may not be below the reference interval. A number of non-thyroidal conditions have profound effects on circulating concentrations of thyroxine binding globulin (TBG) and thus can affect the values of total thyroxine. Hence, free thyroxine concentration (FTc) values correlate better with the clinical status than total thyroxine values.

A reduction in FTc value was a consistent finding observed in our patients. In all the patients, FTc levels were reduced (Table I). Five patients had a reduction in both FTc and T_4 values. In two out of the 12 patients (first two patients in Table I), the levels of total thyroxine (T_4), FTc and TSH were grossly reduced. Both of them had features suggestive of pituitary apoplexy. Apart from these two patients, two other patients (fourth and fifth patients in Table I) had clinical features of pituitary apoplexy. Eight of the 12 patients had non-functioning pituitary adenomas with hypopituitarism. A growth hormone-secreting macroadenoma with central hypothyroidism was seen in four patients. Serum cortisol levels were measured in all patients at admission to rule out glucocorticoid insufficiency. Eight of the 12 patients had reduced cortisol levels. Of these, five had non-functioning pituitary adenomas while three had

Table I. Features of patients with central hypothyroidism.

No.	Age/gender	Hormone levels			Pathology	Predominant symptoms
		FTc (ng/dL)*	TT_4 (µg/dL)†	TSH (µIU/ml)‡		
1	48 M	0.51	2.71	0.12	Nonfunctioning adenoma	Headache, altered sensorium
2	56 M	0.40	2.83	0.17	Nonfunctioning adenoma	Headache, decreased vision
3	66 M	0.63	4.88	0.03	Nonfunctioning adenoma	Vomiting, ptosis
4	25 F	<0.30	2.3	1.60	GH secreting adenoma	Altered sensorium, decreased vision
5	37 M	0.61	4.01	0.31	GH secreting adenoma	Headache, altered sensorium
6	33 F	0.58	5.34	3.18	Nonfunctioning adenoma	Decreased vision
7	60 M	0.58	5.54	2.96	Nonfunctioning adenoma	Decreased vision
8	53 M	0.61	5.26	1.40	Nonfunctioning adenoma	Decreased vision
9	31 M	0.65	6.2	0.49	GH secreting adenoma	Decreased vision
10	53 F	0.59	4.78	0.83	Nonfunctioning adenoma	Decreased vision
11	16 F	0.67	4.88	1.07	GH secreting adenoma	Decreased vision
12	45 M	0.40	2.95	6.65	Nonfunctioning adenoma	Decreased vision

FTC: free thyroxine concentration; TT_4: total thyroxine; TSH: thyroid-stimulating hormone; GH: growth hormone.
* Reference interval 0.8–2.0 ng/dL; † Reference interval 4.5–12.5 µg/dL; ‡ Reference interval 0.3–4.5 µIU/ml

growth hormone-secreting macroadenomas. We do not routinely employ ACTH-stimulation test to detect glucocorticoid deficiency.

All patients had significant neurological symptoms. Visual deterioration was the predominant symptom in nine patients. Patients with apoplexy manifested with symptoms of headache, vomiting and altered sensorium. In all the patients, hypothyroidism was diagnosed only prior to surgery based on thyroid function tests. All of them were medicated with 100 μg oral thyroxine (T_4) once hypothyroidism was identified. The patients were managed perioperatively by administering oral T_3 in addition to oral T_4. Oral T_3 was administered at a dose of 20 μg three times a day five days prior to the surgery and the same dose was continued for three days after the surgery. Patients were discharged at an appropriate dose of oral thyroxine (T_4). Oral prednisolone was initiated at an appropriate dose in all the patients after admission before initiation of thyroxine supplementation. In addition, adequate intravenous hydrocortisone was administered intravenously during the perioperative period. We did not encounter any perioperative complications related to low thyroid hormone concentrations and all the patients were haemodynamically stable during the perioperative period. Moreover, some of the potential adverse effects of parenteral thyroid hormone supplementation such as excessive cardiovascular stimulation and angina were not observed in our patients.

DISCUSSION

In this series, there was a variable degree of hypothyroidism present. All patients manifested with significant neurological symptoms, the commonest of which was visual deterioration mandating urgent neurosurgical intervention. Urgent surgery is recommended to relieve compression on the optic chiasm and to reduce intracranial pressure in patients with pituitary apoplexy. Significant recovery and restoration of visual acuity are possible even after complete blindness, if surgery is performed within a week of the apoplectic episode.[6,7] All the patients described in the series underwent uneventful pituitary surgeries when given oral T_3 supplementation.

Hypothyroidism is a common endocrine disorder and may be encountered in the perioperative period. With regard to the anaesthetic management of those patients with chronic hypothyroidism, it is clear that while they receive thyroxine replacement therapy and when they are euthyroid at the time of surgery, there is no increase in the risk of perioperative morbidity.[2] These patients do not require special treatment other than continuation of thyroxine replacement. There is some difference in opinion as to whether or not surgery should be postponed in a mild or subclinical hypothyroid patient.[2,8] Elective surgery should be postponed for patients with moderate and severe hypothyroidism. Patients with severe hypothyroidism who require urgent or emergent surgery should be treated perioperatively with intravenous T_3 or T_4 along with glucocorticoids.[9] Definitions of varying grades of hypothyroidism, viz, mild, moderate and severe, are not clear and vary between studies. Patients who are at an increased risk of perioperative complications include those manifesting with severe clinical symptoms, with markedly reduced serum T_3 and T_4 levels, and those presenting with myxoedema coma.[2] Elective surgery in these patients should be postponed until they are rendered euthyroid,[2] which takes about six weeks to two months

of enteral thyroxine therapy.

This study demonstrated that there is a definite role for oral triiodothyronine in the perioperative management of severely hypothyroid patients presenting for semi-urgent surgeries. These patients can be taken up for surgery with adequate perioperative oral T_3 supplementation along with oral T_4. We have employed this method for many years and have not encountered perioperative complications pertaining to a low concentration of thyroid hormone in these patients. We employ the same method for patients with overt primary hypothyroidism with grossly reduced hormone levels when they present for semi-urgent surgeries. A dosage of 20 μg of oral T_3 is equivalent to 100 μg of oral T_4. The initial effect of the hormone (oral T_3) starts at 24–72 hours. The maximum effect is achieved by 72 hours and the therapeutic effect persists up to 72 hours after discontinuing the therapy.[10] The plasma half-life is 1–2 days.[10] The rationale for our dosage schedule of oral T_3 is based on the above-mentioned pharmacokinetics of the drug. Intestinal atony (paralytic ileus) and uncorrected adrenocortical insufficiency are few of the contraindications for the administration of oral T_3 as well as T_4. Thyroid hormone supplementation in the presence of untreated adrenocortical insufficiency might precipitate a crisis. Oral T_3 is most suited for surgeries where bowel handling is minimal.

Thyroid hormone function is the last of the hormonal functions to be affected secondary to pituitary lesions.[11] Hence, thyroid deficiency tends to be a little less common in patients with pituitary tumours. When hypothyroidism occurs, it should be corrected preoperatively since hypothyroid patients have a diminished tolerance for the cardiovascular depressant effects of anaesthetic agents.[11] Coexisting hypocortisolism, which is common in these patients, may add to the perioperative risk. All inhalational and intravenous anaesthetics reduce plasma T_3 concentration, which remains depressed for up to seven days postoperative state.[12] Total T_3 is decreased 30 minutes after induction of anaesthesia and remains low for at least the first 24 hours in the postoperative state.[4] It has been shown that even mild surgical stress in the form of laparoscopic cholecystectomy results in significantly low T_3 concentrations in the postoperative period.[13] Moreover, surgical stress can induce a "sick euthyroid syndrome" by inhibiting the peripheral conversion of T_4 to T_3. Studies have shown that both elective and urgent surgeries in normal patients are accompanied by a transient reduction in the extrathyroidal production of the most active hormone, T_3, and by a reciprocal increase in the concentrations of the virtually inactive reverse triiodothyronine (r T_3).[14,15]

It may be questioned that in the absence of oral T_3 supplementation, whether these patients would have been at an increase in perioperative risk. Considering the perioperative risks involved in these patients with low hormone concentrations, it may be prudent to permit them to undergo surgery under adequate thyroid hormone supplementation. Though these patients were started on replacement therapy with oral thyroxine soon after being diagnosed with hypothyroidism on admission, it takes a longer time to achieve euthyroid levels with oral thyroxine. Hence instituting T_3 therapy may help in reducing the risks pertaining to low hormone concentrations. The half-life of endogenously- or exogenously-administered T_4 is seven days, whereas that of T_3 is one and a half days.[2] A longer half-life and difficulty in achieving a satisfactory increase in T_3 are some of the limitations for the use of T_4 only (oral and parenteral) in urgent situations. Thus T_3 may be well suited in urgent situations. There are no known randomised, prospective studies looking at the surgical outcomes in hypothyroid patients.[9] Thus, for many years, the perioperative management of these patients was opinion- and consensus-based and not evidence-based.

This study has some limitations. We did not measure the values of T_3, T_4 or FTc after starting oral T_3 therapy, which may be criticised as a drawback on monitoring efficacy. However, a clinically-satisfactory endpoint in the form of no adverse events related to low thyroid hormone concentrations was reached. Besides, doing these tests at regular intervals is not a clinical practice. As in other case series, we do not have a control group for these patients. Since alternative interventions are limited, and considering the occasional occurrence of the condition, it may be difficult to do a prospective clinical trial on central hypothyroidism. In summary, oral or nasogastric administration of T_3 is an effective method in the perioperative management of severely hypothyroid patients for semi-urgent surgeries where surgery can be deferred for a few days. Patients with pituitary tumours with central hypothyroidism are some of the ideal candidates for this therapy.

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